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Impact of daily anxiety and depressive symptoms on sexual desire and arousal: individual differences across women with vulvovaginal pain

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INTRODUCTION

Why this thesis?

As the title suggests, the present thesis deals with the topic of female genital pain, specifically vulvovaginal pain. Before I begin to discuss the topic and outline the scientific study we conducted, I feel it is important to digress a little in order to explain why this topic was chosen and why it is relevant now. Since the dawn of scientific research, humans have always been fascinated by their bodies. This interest, initially aimed at ensuring the survival of the species, has led to increasingly surprising results over the years. However, when examining research in both medicine (body's health) and psychology (mind's health) from a broad perspective, it becomes evident that most scientific research has been based on a single sample: a male, heterosexual, cisgender person weighing about 70 kilograms (Viola, 2022). This bias has had deleterious consequences for people and bodies considered nonconforming to such standards, including women, who have been viewed as a "mirror" of the standard body (Viola, 2022).

For years, women's bodies have been poorly studied, poorly considered and consequently poorly treated, partly due to the taboo that has historically surrounded them, which has its roots in discriminations existing since ancient times (Viola, 2022; Cantarella, 2022). To understand and hopefully overcome such discrimination, it is essential to trace its origins: since the beginning of Western society, the female figure has been linked to evil (Cantarella, 2022). For an example, consider Eve, the first woman according to biblical tradition, blamed for the original sin and responsible for the expulsion from paradise, or Pandora, the first woman in ancient Greek mythology, sent to earth to punish men for a sin committed by another man (Cantarella, 2022). Firstly

philosophers, interested in the nature of human life, then medical doctors, investigating the human body, shaped their theories influenced by popular culture (Cantarella, 2022). Hence the numerous postulations about women's bodies, which very often take their basis from the attempt to "explain" an element considered the ultimate feminine: the menstrual cycle. Always considered a taboo, not only has the female sexual apparatus been little studied, but scientific study has also undeniably mixed with cultural practices based on social discrimination. To cite an example, Hippocrates, the father of Western medicine, in his work *De natura mulierum*, described women's problems as arising from a wandering uterus, with treatments closely linked to the social roles of the affected women, mainly widows and "late virgins": for the former, the solution proposed was to get pregnant again; for the latter, to marry (Cantarella, 2022).

Although this male-centered paradigm has been largely predominant, recent focus has shifted to different and nonstandard bodies in medicine and various health disciplines. Nevertheless, it would not be until the 20th century that academic and scientific interest in female sexuality would increase, first in the 1950s with Kinsey's sociological reports, until 1966 with the publication of Masters and Johnson's *Human Sexual Response*. Beginning in the 1960s and 1970s, in conjunction with women's rights movement and the sexual revolution, people began to think of women's emancipation as also stemming from specialized medical care and attention, for a medicine that accurately treats not only 50%, but 100% of the world's population, namely, a gender medicine. Thus, gender medicine takes the form of a medicine that is attentive to physiological differences related to sex but also to the health consequences of gender inequalities (Viola, 2022).

Among women's conditions that have been overlooked over time, a significant role is played by vulvar and genitopelvic pain. Although it affects nearly 1 in 7

premenopausal women, this condition is often misdiagnosed, leading to diagnostic delays that severely impact patients' quality of life (Graziottin, 2006). The scarcity of scientific studies on these diseases is problematic not only at the scientific level but also at clinical and institutional levels (Ferritti, 2023). To date, those facing a vulvar or genitopelvic pain condition face an extremely high diagnostic delay, on top of which is the economic burden, since most of these conditions are still not recognized by the Italian National Health System (Ferritti, 2023).

Given this background, the present thesis, resulting from an investigation carried out within the Padova Sex Lab, aims to shed light on this pain, specifically vulvodynia, and its significant impact on the psychological and sexual lives of affected women. Indeed, previous literature has highlighted how vulvodynia is closely related to sexual dysfunction, acting as both its cause and consequence (Bergeron, 2020). Within this context, the choice to focus on sexual desire and arousal seeks to address the lack of scientific studies on the subject and acknowledges the discomfort reported by women in their sexual lives. Additionally, I chose to investigate the impact of psychological variables such as anxiety and depression, which are correlated with both the presence and persistence of genitopelvic pain and sexual dysfunction (Bergeron, 2020).

Therefore, the first chapter of this thesis reviews vulvodynia in terms of classification, diagnosis, etiology, and differential diagnosis. The second chapter discusses the impact of anxiety and depression on vulvar pain, their impact on sexual functioning, and the interrelationship between anxiety, depression, and sexual functioning. Starting from the third chapter, we will illustrate the research study we conducted, beginning with the methodology (Chapter 3), followed by the results (Chapter 4), and finally discussing these results in the context of existing literature (Chapter 5).

CHAPTER 1. VULVOVAGINAL PAIN AND VULVODYNIA

1.1 Definition and classification

Chronic vulvar pain is a multifaceted condition affecting up to 16% of the general population, and it can be described as recurrent and persistent pain localized in the vulvar area lasting at least 3 months (Harlow and Stewart, 2005; Bornstein et al., 2016). The term "vulva" refers to external female genitalia, and it comprises the anatomical areas of the labia (majora and minora), the clitoris, and the vaginal and urethral opening (Yeung and Pauls, 2016). Nevertheless, this anatomical part is often misunderstood with the vagina, which on the other hand refers to the channel extending from the cervix of the uterus to the external genital opening (Yeung and Pauls, 2016). The vulva is a highly sensitive area, and it can be affected by several factors that lead to discomfort and pain: conditions such as infections (e.g., yeast infections, bacterial vaginosis), dermatological disorders (e.g., lichen sclerosus), hormonal imbalances, pelvic floor dysfunction, musculoskeletal issues, nervous system disorders, and sexually transmitted infections can all contribute to vulvar pain (Goldstein et al., 2020). Additionally, traumatic injuries, surgical interventions, psychological factors, and systemic diseases may also play a role in exacerbating vulvar discomfort (Goldstein et al., 2020). When vulvar pain doesn't come from an acknowledged cause it is called idiopathic, such as the case of vulvodynia (Goldstein et al., 2020).

In 2015, the International Society for the Study of Vulvovaginal Disease (ISSVD), the Boards of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the International Pelvic Pain Society (IPPS) divided vulvar pain into two types (Bornstein et al., 2016). The first is vulvar pain caused by a specific, clearly

identifiable disorder, such as infection (e.g., recurrent candidiasis, herpes), inflammation (e.g., lichen sclerosus), neoplastic or neurologic disorder, trauma (psychological or obstetrical), hormonal deficiency or iatrogenic cause (Bornstein et al., 2016). The second is vulvodynia, newly defined as "vulvar pain of at least 3 months" duration, without clear identifiable cause, which may have potential associated factors" (Bornstein et al., 2016). Vulvodynia often presents with symptoms such as burning, stinging, itching, or rawness, significantly impacting the quality of life and sexual function of affected individuals (Bornstein et al., 2016).

The American consensus terminology further categorized vulvodynia based on its localization, ranging from the most prevalent vestibulodynia, affecting the vestibule area, to more specific conditions like clitorodynia, where the pain focuses on the clitoris (Bornstein et al., 2016). On the other hand, if pain and/or discomfort is spread across the entire vulvar region we talk about generalized vulvodynia, and mixed when combining both localized and generalized sensations (Bornstein et al., 2016). Furthermore, sometimes the pain can be triggered by specific activities, such as inserting a tampon or riding a bike, in which case we talk about "provoked" vulvodynia, and some other times the pain arises without a specific trigger, a condition called spontaneous vulvodynia (Bornstein et al., 2016). Another critical aspect of vulvodynia is its onset, which can be classified as either primary or secondary depending on whether there did (secondary) or did not (primary) exist a pain-free period (Bornstein et al., 2016). Lastly, temporal patterns of symptoms define if the pain is intermittent, persistent, constant, immediate or delayed (Bornstein et al., 2016).

Although vulvodynia is statistically significant among vulvovaginal diseases, it falls under the broader category of "genitopelvic pain". Suffering from chronic genital

pain is very common in the female population and can manifest in various disorders affecting the vulva, vagina, cervix, uterus, adnexa, pelvic floor muscles, and the entire innervation system of these structures (Goldstein et al., 2020). These clinical conditions are generally referred to as “genitopelvic pain”, an umbrella term that encompasses multiple disorders. More specifically, chronic pelvic pain is defined as “localized pain in the pelvis, specifically in the lower abdomen, typically lasting longer than three months” (Goldstein et al., 2020). Genital pain, on the other hand, affects the external or internal genital apparatus, or both, and can manifest in diverse and multifactorial clinical conditions (Dewitte et al., 2018). The two forms of pain are closely related, often being referred to as a single entity, as what many women describe as pain associated with the vulvovaginal area may actually originate from the bladder, intestines, or another pelvic structure.

This overlap highlights the complexity of diagnosing and treating these conditions, underscoring the importance of a comprehensive approach to understanding and managing genitopelvic pain. For this reason, in the next paragraphs I will firstly outline the chronic pain conditions that most often overlap with vulvodynia. Then, I will discuss three of the most frequently reported diagnoses in the field of genitopelvic pain, aiming to elucidate their differences and nuances. These diagnoses include vulvodynia, dyspareunia, and vaginismus. As these three diagnoses are often conflated, it becomes crucial to elucidate their distinctions, providing a comprehensive explanation to clarify the differences. Moreover, while the focus of the thesis will primarily be on vulvodynia, it’s important to acknowledge that symptoms can overlap among these conditions, underscoring the need for accurate diagnosis and tailored treatment approaches.

1.2 Chronic overlapping pain conditions

Discussing vulvodynia, its differential diagnoses, and resulting complications requires highlighting the frequent occurrence of vulvodynia alongside various other chronic diseases (Bergeron et al., 2020). These syndromes encompass chronic fatigue syndrome, chronic migraine, chronic low back pain, chronic tension-type headaches, endometriosis, fibromyalgia, interstitial cystitis (also known as painful bladder syndrome), irritable bowel syndrome, temporomandibular disorders, and of course, vulvodynia (Bergeron et al., 2020). These chronic pain conditions share overarching etiological mechanisms, notably central sensitization (Bergeron et al., 2020), which often leads to diagnostic challenges for healthcare professionals. Moreover, individual differences play a significant role: not all individuals with one of these conditions will develop others, and the combination and number of conditions vary. Some individuals experience multiple conditions concurrently, while others develop them successively over many years. Recognizing the overlap among common chronic pain conditions, including vulvodynia, has led to the introduction of the term “chronic overlapping pain conditions” and has prompted innovative approaches in clinical research, trial design, and practice (Bergeron et al., 2020).

1.3 Vulvodynia, dyspareunia and vaginismus: differential diagnosis

As previously said, this thesis will primarily focus on vulvar pain, more specifically on vulvodynia. Nevertheless, the terms “genitopelvic” and “vulvar” pain can comprehend a wide range of disorders affecting the same anatomical locations (vulva, vagina, cervix, uterus, pelvic floor muscles, and nerves radiating this area) (Rowen and Goldstein, 2020). Alongside vulvodynia, two of the most frequently cited vulvovaginal pain conditions are

"dyspareunia" and "vaginismus". Although frequently interchanged, these three present themselves clinically as different disorders and are linked by the fact that they affect the female sexual sphere, leading to feelings of pain and discomfort during or after intercourse and severely limiting the ability to enjoy a satisfying sex life (Rowen and Goldstein, 2020). For this reason, vulvodynia, dyspareunia and vaginismus are often confused and mistakenly used as synonyms, but they are actually distinct problems that require a differentiated understanding (Rowen and Goldstein, 2020). As a result of their new and greater understanding achieved over the years, the definitions of these syndromes have undergone a number of variations over time: presenting the current definitions, emphasizing their mutual differences at the symptomatologic and etiologic levels, is therefore essential to avoid the formulation of incorrect diagnoses and the administration of ineffective treatments.

To start with, the evolution of terminology concerning female genital pain conditions is chronologically and substantially different. The origin of the term "vulvodynia", denoting persistent vulvar pain, can be traced to the fusion of "vulva" (the external female genitalia) and "Odyne", the Greek deity symbolizing pain (Amalraj et al., 2009). However, it wasn't until the nineteenth century that Robert Barnes introduced the term "dyspareunia", in his work *A clinical history of the medical and surgical diseases of women* in 1878, referring to pain during sexual intercourse (Barnes, 1878). Finally, the term "vaginismus" was coined by J. Marion Sims in 1862 to describe involuntary vaginal muscle contractions impeding intercourse (Sims, 1862).

Dyspareunia refers to genital pain experienced during intercourse (Bergeron et al., 2020). It is defined as recurrent or persistent pain during sexual activity or otherwise during any attempt at vaginal penetration (Lewis et al., 2004; Seehusen et al., 2014).

Dyspareunia can be further classified as superficial or deep, depending on the site of discomfort: the former refers to pain localized in the area of the vaginal introitus or the first part of the vagina and appears immediately with the first attempts at penetration, while the latter refers to pain that occurs with deep vaginal penetration (Seehusen, et al., 2014). It is also possible to distinguish primary dyspareunia, which occurs from the very first sexual intercourse, from secondary dyspareunia, if it begins after previous non-painful sexual activity (Seehusen, et al., 2014). The prevalence of dyspareunia ranges approximately from 12-15% of women of reproductive age and up to 45.3% of postmenopausal women (Graziottin and Rovei, 2007), although estimates vary widely (from 3% to 43%) depending on the culture, the population considered, and the definition used by researchers to analyze it (Bergeron et al., 2020; Boardman and Stockdale, 2009). The underlying causes can be multiple and are generally divided into biological, psychosexual, and relational and can include both vaginismus and vulvodynia (Seehusen, et al., 2014; Graziottin and Rovei, 2007).

The term "vaginismus" refers to an involuntary contraction of the muscles of the vagina that interferes with sexual intercourse (Basson et al., 2004). The latest published consensus definition integrates the psychic and physical dimensions by defining vaginismus as follows: "The persistent or recurrent difficulties of the woman to allow vaginal entry of a penis, a finger, and/or any object, despite the woman's expressed wish to do so. There is often (phobic) avoidance and anticipation/fear/experience of pain, along with variable involuntary pelvic muscle contraction. Structural or other physical abnormalities must be ruled out/addressed" (Basson et al., 2004). From this definition it follows that vaginismus is indeed characterized by fear and anxiety of penetration, but also by a defensive and involuntary contraction of the muscles surrounding the vagina.

Vaginismus involves recurrent or persistent involuntary spasms of the perineum and the outer third of the vagina that prevent penetration (American Psychiatric Association, 2013). Vaginismus can further be defined as "situational" if present only with certain partners or with certain types of penetration (for example, penis but not fingers or tampons) or "complete" if the attempt is impossible in any situation and with any form of vaginal penetration (Crowley et al., 2009). Although many patients report how attempting intercourse seems to "hit a wall", most of the times the muscles of the vagina relax and the pain disappears as soon as the attempt at penetration ends (Pacik, 2014). This led clinicians and researches to focus on the cognitive and emotional meanings underlying the physical symptom, considering that the causes of vaginal spasm will be unique to each person (McEvoy et al., 2021).

Finally, the term "vulvodynia" refers to chronic vulvar pain, more specifically to "vulvar pain lasting at least 3 months, without a clearly identifiable cause, which may have potential associated factors" (Bornstein et al., 2016). It is a condition characterized by vulvar hypersensitivity accompanied by pain and burning with no clinically discernible cause and differs from vaginismus in both symptomatology and triggers (Rowen and Goldstein, 2020). While vaginismus manifests with pain exclusively upon introduction of foreign bodies into the vagina, and the person experiences severe distress and involuntarily contracts muscles even at the idea of such introduction, the symptoms of vulvodynia occur in a variety of situations, not only during attempts at penetration (Rowen and Goldstein, 2020). Because of its multifaceted nature, vulvodynia can correspond to very different symptoms, which can present very differently depending on the person (Galizia, 2022). These symptoms comprehend itching, burning (which may extend to the clitoris and anus), frequently reported at the end of urination, pinprick

sensation, swelling of the labia minora and labia majora, profuse vaginal discharge (leukorrhea), sensation of abrasions, sensation of electric shocks, abrasions at the vaginal entrance, urinary discomfort (frequent urination, urgency), stabbing pain (like a "stab wound"), constricting pain (like a "bruise"), and foreign body sensation (Galizia, 2022). Moreover, they can be triggered by a wide variety of situations: wearing clothing that is too tight, using intimate cleansers that are not appropriate for one's needs, riding a bicycle or horseback, falls on the coccyx (even many years before), pelvic surgeries, complicated deliveries, and many others (Galizia, 2022). In severe cases, patients struggle to sit or walk comfortably and only find relief when lying down with legs apart and without tight underwear. Symptoms of vulvodynia can vary throughout the day and may improve or worsen, often linked to hormonal changes during the menstrual cycle (Galizia, 2022).

Following the description of these three pathologies in detail, it can be inferred that dyspareunia can be, but not necessarily is, a symptom of vulvodynia, whereas vaginismus represents a completely different disorder than the latter. Those suffering from vaginismus experience pain exclusively during penetrative intercourse or attempts at penetration, which they fear and consequently avoid. In contrast, vulvodynia symptomatology occurs as a result of a variety of stimuli, not necessarily sexual, and any fear of penetrative intercourse would represent a consequence of the pain rather than its cause. Finally, it is important to note that it is also possible for people with vulvodynia to develop a strong fear of intercourse (characteristic of vaginismus), but this becomes a consequence of vulvar pain and not a cause of it (Desrochers, 2009). Understanding the distinctions between these conditions is crucial for accurate diagnosis, appropriate treatment planning, and providing effective support for individuals experiencing sexual pain disorders.

Although these three conditions are different from each other in terms of nature and symptoms, dyspareunia and vaginismus were typically classified as separate sexual pain disorders until the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; American Psychiatric Association, 2013). In the DSM-V they all appear combined in the section on Sexual Dysfunctions, under the diagnosis of genitopelvic pain/penetration disorder (American Psychiatric Association, 2013). To this regard, an interesting proposal is that of Lahaie and colleagues (2015), which emphasizes fear as a discriminant factor in the classification. Starting from the difficulty in finding a differential diagnosis factor highlighted both in research and clinical field, the authors conducted a comprehensive study involving women with vaginismus, dyspareunia/provoked vestibulodynia, and controls, hypothesizing that fear could actually represent a valid distinguishing factor (Lahaie et al., 2015). Participants of this study underwent a comprehensive experimental session involving structured interviews, pain sensitivity testing, and a filmed gynecological examination (Lahaie et al., 2015). While genital pain did not show significant differences between vaginismus and dyspareunia/PVD, it successfully discriminated both clinical groups from controls (Lahaie et al., 2015). When trying to differentiate between the groups using only fear as a discriminant (including its self-report, behavioral and psychophysiological components), the authors found that this could be done through two different functions: function 1 being behavioral and self-report measures of fear, and function 2 being psychophysiological measures of fear (Lahaie et al., 2015). Through these functions, 74% of women with vaginismus, 78 % of women with dyspareunia PVD, and 90.7 % of women in the control groups were correctly classified (Lahaie et al., 2015). When trying to differentiate between the three clinical categories, 78 % of women in the vaginismus

group and 86 % of women in the dyspareunia/PVD group were correctly classified, with behavioral measures of fear and vaginal muscle tension having the highest weight (0.58 and 0.55 respectively) on the discriminant function, underscoring the clinical relevance of fear in these conditions (Lahaie et al., 2015). Moreover, such emphasis on fear as a discriminant factor in vulvar pain disorders not only enhances diagnostic precision but also offers valuable insights for tailored treatment approaches and improved clinical outcomes in individuals experiencing genito-pelvic pain (Lahaie et al., 2015).

In conclusion, despite the similarities and partial overlaps, vulvodynia is a distinct diagnostic entity from dyspareunia and vaginismus. Understanding its unique aspects is crucial for expediting and refining the diagnostic process and identifying the most suitable therapy to enhance the quality of daily, sexual, and relational life for affected individuals.

1.4 Epidemiology

Although it is still a very under-recognized condition, vulvodynia is reported to have very high incidence and prevalence rates. Pukall et al. (2016) estimated that globally vulvodynia affects 10% to 28% of women of reproductive age. Although there have been no global epidemiological studies assessing the incidence of vulvodynia, evidence from country-specific studies reveals that this condition can occur in women of all ages. In Italy, the largest epidemiologic study was conducted in 2016 by gynecologists Graziottin and Murina, who performed a cross-sectional study of consecutive female patients with chronic vulvar pain who attended 21 Italian medical centers over a time span of nearly 2 years, in a project called “Vu-Net”. Of a total of 1183 subjects diagnosed with chronic vulvar pain, vestibulodynia was diagnosed in 837 of 1183 patients (70.8%) and

generalized vulvodynia in 323 (27.3%), together with an overall prevalence of 15% with a mean age of 31 years (Graziottin and Murina, 2016).

Similar results can be found in other European studies, recently conducted in Spain and Portugal. Gómez et al. (2019) administered a survey asking participants whether they currently suffered from vulvodynia or had suffered from it in the past, with results ranging from 6.% in the former case to 13% in the latter case. These estimates almost identically mirror earlier work done by Vieira-Baptista's team in 2014 in Portugal, which reported a prevalence of 6.5% at the time of the survey, with estimates as high as 16% over the participants' lifetime. In the United States, however, Harlow and colleagues (2014) conducted a survey to assess the prevalence of symptoms consistent with a diagnosis of vulvodynia in the Boston and Minneapolis/Saint Paul metropolitan areas. From analysis of self-report questionnaires administered to more than 5,000 women - aged 18 to 40 years - the authors found an 8% prevalence rate of symptoms associated with vulvar burning and pain that persisted for more than 3 months. This finding was later corroborated by the study by Reed et al. (2012), who estimated a prevalence of vulvodynia of 8.3% in a sample of about 2000 women in Michigan.

Moreover, epidemiological surveys allow us to observe how prevalence estimates vary according to the age groups of women considered, including older and postmenopausal women (Reed et al., 2012). Counterintuitively, the incidence of vulvodynia appears to be higher in younger women than in older women (Bergeron, et al. 2020). The incidence appears to be higher among younger women, with a mean age of onset around 25 to 30 years (Vieira-Baptista et al., 2014; Harlow et al., 2014) and a higher prevalence at childbearing age. In fact, according to estimates by Reed et al. (2014), it reaches an annual incidence of up to 7.6% at the age of 20 years, and drops to 3.3% at the

age of 60 years. In addition, other factors to be mentioned in the epidemiological context are sociocultural factors. Interestingly, unlike in Europe and the United States, a completely different result was found in Nepal: in a hospital study of a sample of 5521 female patients who reported symptoms commonly associated with vulvodynia, participants were diagnosed on the basis of clinical examination and/or laboratory findings, but only <1% were diagnosed vulvodynia (Pathak et al., 2011). According to Bergeron et al. (2020), the lack of knowledge of vulvodynia or among women and health care providers in Nepal may contribute to the relatively low prevalence rate, potentially resulting in underestimation and underdiagnosis of the condition.

Furthermore, a similar scenario can be seen in African American women in the United States. In fact, Reed and colleagues (2012) observed that African American women are less likely (approximately 43% less likely) to meet the criteria for vulvodynia than white women, but the prevalence of the condition in this population remains significant (4.2%). Nevertheless, the diagnosis on vulvodynia was given by the authors depending on survey-based criteria, which could have had an impact on prevalence rates found in this study (Reed et al., 2012). Such drastically different results among different ethnic groups could also be determined by social norms, which would effectively prevent these women from talking openly about their pain and sexuality (Reed et al., 2014). In contrast to African-American women, Hispanic women in the United States are found to have 40%-80% higher rates of vulvodynia than non-Hispanic white women (Harlow et al., 2014; Reed et al., 2014) and 47% more likely to report primary vulvodynia (Reed et al., 2014). Nevertheless, as epidemiological studies in non-westernized countries are lacking, the reason for such different results remains open.

In conclusion, an epidemiological analysis of vulvodynia becomes necessary to highlight how this syndrome is far from invisible, if observed with the right eyes. The data presented highlight how this condition isn't rare and/or uncommon, but rather is part of women's lives in a large global percentage. Of note, it also becomes clear how the prevalence and incidence data currently found in the literature probably do not fully represent the real situation. Such different statistics among social groups and geographic locations underscore the importance of having data that are accurate and free from bias, to help the progress of the scientific community, incentivizing health professionals to get closer to the study of the condition, as well as to be of help to women suffering from this pain to get out of deep feelings of loneliness and encourage them to seek help.

1.5 Etiology

As previously said, vulvodynia often manifests with initial symptoms localized in the vulvar area such as itching sensations, burning, a sensation of needles stinging, and pain upon penetration (Goldstein et al., 2020). Given the absence of obvious biological causes at an initial gynecological examination, this syndrome has historically been interpreted as a psychogenic pain, to the point that in 1978, Dodson and Friedrich called it psychosomatic vulvovaginitis (Dodson and Friedrich, 1978). The term "psychosomatic", referring to an illness caused by anxiety and worry and not by any infection or injury, when applied to vulvodynia resulted in a general overlooking or dismiss of the symptoms reported by women seeking medical assistance (Shallcross et al., 2019; Graziottin et al., 2020). However, contrary to what is expected from the presumed psychosomatic origin of vulvodynia, several studies support a multifactorial nature of this syndrome, highlighting how it can result from biological, psychological and/or social causes

(Goldstein et al., 2020; Graziottin et al., 2020). Reading vulvodynia from a biopsychosocial perspective is thus essential to better understand this condition and develop a treatment that is suitable for the patient and her individual characteristics and needs (Shallcross et al., 2019). According to the biopsychosocial model, in fact, the person is seen as a system with unique characteristics and dynamics that not only is maintained by the coordination of a complicated network of internal dynamics, but is also strongly influenced by the characteristics of the larger system of which it is a part (Engel, 1980). Given the cross-sectional nature of studies on the etiology of vulvodynia, it is impossible to find a single cause for this syndrome with certainty of a causal direction (Pukall et al., 2016; Goldstein et al., 2020; Sadownik, 2014). As a result, nowadays there is still no single, agreed upon cause, but rather we talk about factors that may play a role in its onset and maintenance (Pukall et al., 2016; Goldstein et al., 2020). The main etiological factors will be discussed below, first divided into biological, social, and finally psychological factors with a special focus on the role of anxiety and depression in the genesis and maintenance of symptoms.

1.5.1 Neurobiological factors

Peripheral and central pain mechanisms. Vulvodynia is a syndrome characterized by allodynia and hyperalgesia (Goldstein et al., 2020). The former is defined as pain in response to a non-noxious stimulus, while the latter refers to an increased response for a normally painful stimulus and, in non-pathological situations, they both may be useful adaptations to protect vulnerable tissues (Sandkühler, 2009). However, in vulvodynia as in other chronic pain conditions, these symptoms persist long after the initial cause for pain has disappeared, making pain no longer a symptom but rather a disease in its own

right (Sandkühler, 2009). Most of the time, this is due to mechanisms within the nervous system, such as peripheral and central sensitization (Zhang et al., 2011; Rubal et al., 2023). Peripheral sensitization occurs when sensory signals travel backward along the nerve fibers and cause inflammation in the area where the pain receptors are located (Rubal et al., 2023). This involves the release of chemical inflammatory mediators into the tissue, and is frequently observed in some of the comorbid conditions of vulvodynia, such as irritable bowel syndrome or interstitial cystitis (Rubal et al., 2023). To this respect, Tympanidis et al. (2003) found an increase of C nociceptive nerve fiber density in the vulvar vestibule in vulvodynia patients, which positively correlated with the level of local inflammation but did not correlate with an increase in allodynia in the vestibular mucosa. As previously said, the nature of these correlational studies makes it impossible to draw causal conclusions: the etiology of these increased nerve fiber density and its role in vulvodynia pathogenesis remains an open question (Rubal et al., 2023; Tympanidis et al., 2003). Interestingly, the increase observed in vulvodynia patients within Tympanidis's study is in contrast with results from Lauria and Lombardi (2007), who conducted a study on skin biopsies of patients with peripheral neuropathies and found reduction in intra-epidermal nerve fiber density, suggesting a substantial biological difference between chronic pain conditions.

Peripheral sensitization mechanisms can be the beginning of central sensitization, a condition in which the nervous system is increasingly excited, which results in normal inputs evoking exaggerated responses (Rubal et al., 2023). Alterations in the central processing of nociceptive signals might persist beyond their initial stimuli, spanning days, months, or even years, and could extend to somatotopically distant areas from the original source of pain, constituting one of the main causes of chronicity of vulvar pain (Bergeron,

2020). Central sensitization is largely found and studied in chronic pain patients, and it is a phenomenon of synaptic neuroplasticity based on altered sensory processing in the brain and resulting in hyperalgesia, dysfunction in descending pain inhibitory mechanisms, increased activity in pain pathways, and long-term potentiation of synapses in the anterior cingulate cortex (Woolf, 2007; Ji et al., 2018). As explained in Rubal et al. (2023), when the pelvic organs tissue is damaged, it sets off special nociceptors, which send impulses quickly through some nerve fibers (A delta) and slowly through others (C), via the hypogastrius plexus and pudendal nerves. Moreover, the rostral ventromedial medulla and periaqueductal gray descending pathway then play a key role in modulating these pain messages, making the patient feel these symptoms in a stronger or weaker manner (Rubal et al., 2023). This process is key in making pain feel more intense, previously referred to as hyperalgesia (Goldstein et al., 2021; Rubal et al., 2023). Moreover, the abnormal nociceptive signal amplification in the central nervous system occurring in central sensitization would also explain increased sensitivity to touch and pain found in women with vulvodynia not only in the urogenital area, but also in extragenital ones (Wesselmann et al., 2014; Sutton et al., 2015; Foster et al., 2005; Giesecke, 2004).

It is important to note that vulvodynia isn't the only syndrome where pain occurs in the absence of clinically obvious pathology, but it is part of a group of conditions called "central sensitivity syndromes'" (Torres-Cueco et al., 2021; Jones, 2016). These conditions include fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and temporomandibular joint disorder, and they all exhibit heightened sensory processing within the central nervous system in neuroimaging studies (Jones, 2016). However, it's still uncertain whether this observed correlation is a result of the conditions or a contributing factor to their development (Walitt et al., 2016).

Embryologic and congenital factors. The hypothesis of vulvodynia possibly arising from congenital factors took its start from several studies demonstrating its coexistence with interstitial cystitis and painful bladder syndrome (Bergeron et al., 2020). First Fitzpatrick et al. (1993) analyzed the case study of three patients where vulvodynia and interstitial cystitis coexisted, and, because both the vestibule of the vulva and the bladder are derived from the urogenital sinus, proposed that the coexistence of "vulvar vestibulitis" and interstitial cystitis in some patients represents a generalized disorder of urogenital sinus-derived epithelium. Later, a case study by Tarr et al. (2003) of a young 4-years-old girl contributed to supporting this hypothesis of a congenital origin. Because both the umbilicus and vulvar vestibule are derived from primitive urogenital sinus, the authors suggest that women with vulvodynia may have a congenital abnormality in urogenital sinus–derived epithelium (Tarr et al., 2003).

Genetic aspects. With regard to genetic predisposition for vestibulodynia, a familiarity analysis operated by Morgan in 2016 on 183 women who underwent vestibulectomy revealed that the risk was elevated in first-degree, second-degree and third-degree female relatives. Furthermore, the potential genetic predisposition to vulvodynia was investigated by examining its impact on the likelihood of experiencing recurring Candida or bacterial vaginosis infections or a prolonged reaction to infection or inflammation (Farmer et al., 2011), changes in the body's inflammatory response (Kalfon et al., 2019), or an elevated susceptibility to hormonal changes linked with oral contraceptive use (Goldstein et al., 2016). Babula et al. (2008) also added a further distinction between primary and secondary provoked vestibulodynia, whereby the contribution of genetic

factors would be greater in women who always experienced pain rather than for women whose pain started after some time.

Hormonal factors. It has been largely accepted that vaginal tissue as well as other regions of the reproductive tract are regulated by levels of sex steroids, namely estrogen, progesterone and testosterone (Pukall et al., 2016). This results in anatomic and physiologic changes in the vulva and vagina according to variations of such steroids, which can happen of natural or iatrogenic cause (Pukall et al., 2016; Goldstein et al., 2020). The most common natural cause of these changes is menopause, characterized by a generalized decrease in estrogen (Bergeron et al., 2020). Moreover, other natural causes underlying a possible change in the female apparatus might be hypothalamic anovulation and amenorrhea due to biological stressors, such as excessive physical activity and/or dramatic weight loss as in the case of anorexia nervosa (Meczekalski et al., 2008). On the other hand, iatrogenic causes include hysterectomy and combined hormonal contraceptive (CHCs) pills, which decreases estrogen and testosterone production in the ovaries leading to a decrease of serum estradiol and free testosterone (Bergeron et al., 2020; Goldstein et al., 2020). To this regard, Bohm-Starke et al. (2004) conducted a study testing mechanical and heat pain thresholds and detection thresholds of warmth and cold in the anterior and posterior part of the vestibular mucosa of 39 women, half of whom were using CHCs. The authors found that women using oral CHCs had significantly lower mechanical pain threshold, confirming the hypothesis that lower levels of estradiol would make vestibular areas more sensitive to pain and touch (Bohm-Starke et al., 2004). This result was further supported by a study by Wesselmann et al. (2006), who investigated the influence of the ovarian cycle on mechanical hyperalgesia in women with vulvodynia,

and found that tampon-induced vaginal pain significantly changed along the menstrual cycle. As estradiol levels peaked just before ovulation, women experienced reduced pain, whereas during the premenstrual phase, characterized by low estrogen levels, pain reached its highest intensity (Wesselmann et al., 2006). Furthermore, CHCs has been demonstrated to induce morphological changes in the vestibular mucosa, increasing its vulnerability to mechanical strain (Johannesson et al., 2007). Concerning this aspect, Battaglia et al. (2014) conducted a study to evaluate the genital vascular effects and sexual behavior of 40 women treated with CHCs and found a significant decrease in clitoral size, labial thickness, and introital diameter, together with decreased orgasm, decreased sexual frequency, decreased lubrication, and increased dyspareunia.

In an attempt to define a causal relationship between hormonal contraceptive use and vulvodynia, Bazin et al (1994) showed that the relative risk of vulvodynia in women who had used oral contraceptives before age 17 reached 11.0 (95% confidence interval) as compared to those who had never used OCs. Starting from a large body of evidence which causally connected CHC use and the rising of vulvodynia symptoms, Goldstein et al. (2014) identified a polymorphism in the androgen receptor gene that significantly increased the risk of developing CHC-induced vulvodynia. This was done by testing DNA from 30 women who developed provoked vestibulodynia while under CHCs and 17 control women, identifying the number of CAG (citosine-adenine-guanine) trinucleotide repeats in the androgen receptor gene, located in the X chromosome (Goldstein et al., 2014). In this sample, the mean number of CAG repeats in the study group was significantly greater than the control group (22.05±2.98 vs. 20.61±2.19, respectively; P=0.025) (Goldstein et al., 2014). The authors therefore speculated that the risk of developing CHC-induced vestibulodynia may be due to lowered free testosterone

combined with an inefficient androgen receptor that predisposes women to vestibular pain (Goldstein et al., 2014).

In contrast to these findings, research conducted by Arnold et al. (2006) and Reed et al. (2013) revealed no link between symptoms of vulvodynia and hormonal contraceptives. However, a separate study by Foster and Woodruff (1995) indicated a reduction in the risk of vestibulodynia among women using CHCs. These contradictory findings may stem from methodological limitations, such as reliance on self-reported measures of vulvodynia symptoms in the former studies and differences in the dosage of ethinyl estradiol and androgenic progestins in the latter, which exceeded levels reported in subsequent research. In light of such contradictory findings, additional research is needed to elucidate the relationship between sex steroid levels and the onset and persistence of vulvodynia symptoms.

Pelvic floor muscle dysfunction. Like in many other pathologies often coexisting with vulvodynia, pelvic floor muscles play a crucial role in sustaining vulvodynia symptoms (Bergeron et al., 2020). As it happens in other muscle groups of the body, dysfunction of the pelvic floor can arise both from a hypertonicity and a hypotonicity of this group of muscles (Morin et al., 2017). It is not rare to find a hypertonicity of pelvic floor muscles due to spasm contractions in women with vulvovaginal pain, but whether this can be an etiological factor or a consequence of pain (for example, an involuntary contraction of muscles during a painful attempt of penetration) remains unclear, most of all due to the cross-sectional nature of designs of these studies (Pukall, 2016; Wesselmann, 2014). Moreover, as stated in Baker (1993), changes in the physiology of the pelvis can arise from the most different factors, such as vaginal or urinary infection, trauma, vaginal

childbirth, abdominal or pelvic surgery, prolonged sitting, poor posture, muscle bracing in reaction to fear, pain, altered gait patterns, which can cause lasting imbalances in pelvic floor neural tissue and change its functionality. Furthermore, it has been postulated that when these factors coexist with an inflammatory condition, viscerosomatic reflexes activate nociceptive and visceral afferent neurons, contributing to somatic dysfunction and neuropathic upregulation (Prendergast and Weiss, 2003; Hilton and Vandyken, 2011). Within the context of the role of pelvic floor muscle dysfunction in vulvodynia it is of high importance to cite its close relationship with fibromyalgia: the recognition of the overlapping nature of vulvodynia and fibromyalgia has brought researches to highlight the possible role of central sensitization as an overarching mechanism in these chronic conditions (Veasley, 2015). In fact, in cases of prolonged symptoms (i.e., chronic pathologies), changes in neurodynamics and neural tension can lead to tissue oxygen deprivation, causing sensations such as itching, burning, tingling, coldness, or sharp, shooting pain, as referred in PVD (Hilton and Vandyken, 2011).

Neuroinflammatory factors. As discussed earlier, it has been theorized that in vulvodynia and other chronic pain disorders long-lasting central sensitization allows pain to persist beyond the resolution of acute inflammation (Sandkühler, 2009; Rubal et al., 2023). This first inflammatory pathogenesis takes its origin from histological studies, in which an increased number of mast cells were found in vestibular tissue of women with vulvodynia than healthy controls (Chalmers et al., 2016). Moreover, Masterson et al. (1996) found a reduced systemic number of natural killer cells in women with vulvodynia compared with controls, which was hypothesized to be correlated with the high number of recurrent yeast infections reported by women with vulvodynia, most of which refer to Candida albicans.

As previously mentioned in the Genetic section, a genetic susceptibility to Candida infection associated with less capacity to end the resulting inflammation could be a biomarker for vulvodynia, although causal links cannot be drawn (Harlow, 2017). A systematic review operated by Chalmers, Madden and Hutchinson in 2016 highlighted the limited and contradictory nature of evidence of inflammatory factors in vulvodynia, including cytokine levels, prostaglandin E2, T cells, B cells, mast cells, natural killer cells and macrophages.

1.5.2 Social factors

While relational and contextual factors are significant in vulvodynia, research on the social aspects linked to genital pain is relatively new in scientific literature (Bergeron et al., 2020). Indeed, besides the personal experience of the condition, various cultural, environmental, and contextual influences pose obstacles for those with genital pain, which, despite not being tied to a specific symptom, are integral to the disease experience (Shallcross et al., 2019). In the pages that follow, these factors will be discussed, starting from close relationships like partner and family as well as more extensive community and peers.

Partner. Understanding the complexity of vulvodynia necessitates acknowledging the bidirectional impact of the relationship dynamics on the experience of pain. Research underscores the reciprocal influence between the couple's relationship and the manifestation of vulvodynia symptoms, highlighting the need to further explore this interplay (Bergeron et al., 2020; Pâquet et al., 2018). The bidirectionality of effects between the couple's relationship and vulvodynia encompasses how the quality of the

relationship can both influence and be influenced by the woman's pain experience: partners' responses to vulvodynia symptoms may shape the woman's coping mechanisms and overall well-being, while the presence of vulvodynia can strain the dynamics of the relationship, potentially affecting intimacy and communication (Pâquet et al., 2018). In essence, recognizing the bidirectional nature of the relationship-pain dynamic sheds light on the intricate interplay between vulvodynia and the couple's dynamics, emphasizing the importance of addressing both aspects in the management and support of affected individuals and their partners (Dewitte et al., 2018; Pâquet et al., 2018).

In addition to that, partners may respond to pain with solicitous, negative, or facilitative responses (Rosen et al., 2010; 2014). The first two types of response have been found to be significantly associated with worse pain, sexual function, and depressive symptoms, and lower sexual and relationship satisfaction (Rosen et al., 2010). Such behavioral responses have also been associated with the presence of catastrophic thoughts and a partner's negative attributional style, which in turn influences the woman's pain and depressive symptoms (Dewitte et al., 2018). In contrast, facilitative responses, in which the partner supports the partner's efforts and encourages her approach to sexual situations, are the most adaptive, as they are associated with reduced pain and greater sexual and relational satisfaction (Bergeron et al., 2014) Such an attitude can therefore be promoted and encouraged in targeted couple intervention, thus helping to increase intimacy and closeness between partners (Corsini-Munt et al., 2014).

Another element that has been investigated in relation to the couple is relational and sexual intimacy, (i.e., the ability to confront each other, share oneself openly and be empathetic), which according to a study by Bois and colleagues (2013) promotes higher levels of sexual satisfaction, sexual functioning and self-efficacy than pain. Results of the

studies mentioned in this section, while not assigning a specific role to the interpersonal sphere in the development of the disease, underscore its importance and potential: the couple relationship can worsen the way the disease is experienced in daily life or it can act as a protective factor and alleviate the perception of pain-related symptoms (Corsini-Munt et al., 2014; Bois et al., 2013).

Peers and community. As the relational circle of people does not end at the couple, it becomes important to examine the role of the whole community towards women's vulvar pain and its management (Nguyen et al., 2012). A study conducted by Nguyen and colleagues (2012) examined the ease of pain communication across various relational contexts. Their findings indicated that 67% of participants felt comfortable discussing vulvar pain with their partners, whereas only 39% were at ease discussing it with family members, and a mere 26% were able to share their pain with female friends (Nguyen et al., 2012). These statistics highlight the challenges faced by individuals dealing with vulvodynia when it comes to expressing their pain in intimate settings (Nguyen et al., 2012). Moreover, these difficulties extend to the public management of chronic pain affecting sexual functioning, where such conditions are often inadequately addressed (Nguyen et al., 2012).

One of the most important factors when talking about the impact of peers and community on women's pelvic pain and vulvodynia is the invisibilization of several diseases impacting women's sexual and reproductive system, which results in poor social and medical support (Bergeron et al., 2020; Shallcross, et al., 2018). Vulvodynia, but also endometriosis, are pathologies still very little known in the medical world to date, which results in an estimated 40% of women with vulvodynia remaining undiagnosed even after

consulting more than three health professionals (Xie et al., 2012). Precisely because of the lack of training of health professionals who fail to properly explain women's pain and discomfort, only around 2% of women who seek help obtain a diagnosis, making pain of women with vulvodynia an often underestimated condition (Shallcross et al., 2019). Moreover, in Italy, the problem persists not only at the medical level, but also at the institutional level: vulvodynia has not yet been recognized by the National Health System, leaving patients with little public support and large sums of money to spend on private specialists for treatment (Ferritti, 2023).

The unpreparedness of specialists in the country is a reality that adversely impacts women not only in terms of diagnostic delay, but also in terms of treatment: if the professional does not recognize the condition, also, it is possible that he/she will prescribe inadequate treatments that will only exacerbate the women's pain condition, which will then be more difficult to treat later (Metts, 1999; Ferritti, 2023). In addition, as Pukall et al. (2016) point out, the fact that pain is located in the female genital organ and has to do with the sexual sphere is considered a taboo not only among women, who avoid seeking treatment due to a sense of embarrassment, but also among health professionals, which makes a thorough and detailed medical examination impossible. In this regard, education is needed in talking about sexuality both at the lay people level and in medical studies (Wittenberg and Gerber, 2009). Furthermore, in addition to health professionals, listening and comfort from family and friendships are also very important, and these elements, if they are lacking, generate further despondency and loneliness in women (Pukall et al., 2016).

1.5.3 Psychological factors

Starting out from the biopsychosocial model of chronic pain, more specifically chronic pelvic pain, a large body of research has focused on the psychological factors in terms of cognitive and motivational factors, emotional states and personality traits (Chisari et al., 2021; Niedenfuehr et al., 2023). Moreover, as opposed to research investigating biological markers of vulvodynia, studies in this field are more focused on understanding how pain exacerbates and becomes chronic, disabling the patient and turning into a disease itself. Psychological variables explored in the scientific literature, such as depression, anxiety, pain catastrophizing, fear and hypervigilance toward painful symptoms, perceived self-efficacy and pain acceptance, may precede pain, acting as protective or risk factors, or they may develop later, as a consequence of or reaction to the disease (Chisari et al., 2021). Each of these aspects can contribute differently to genital pain, so closer examination on this front is necessary to provide comprehensive support to the patient with vulvodynia.

Anxiety and depression. Among the different psychological factors playing a role in vulvodynia, a large body of literature has focused on anxiety and depression, given that they have been shown to play a particular role in the etiology of vulvodynia (Khandker et al., 2011; Paquêt et al., 2018). For example, the work by Khandker and colleagues (2011) found that women with a history of mood disorders or anxiety were four times more likely to develop vulvodynia compared to those without such a history. Additionally, the rate of new depressive and anxious symptoms was higher among women with vulvodynia, suggesting a two-way relationship where anxiety and depression can be both causes and effects of the condition (Khandker et al., 2011).

Together with the previously mentioned cross-sectional study by Khandker et al. (2011), other research, such as studies by Pâquet et al. (2018), showed that daily levels of anxiety and depression were linked to the intensity of pain during sexual intercourse. On days when participants reported above-average levels of anxiety and depression, they also experienced more pain and reduced sexual function (Pâquet et al., 2018). This effect extended to the partners of those with vulvodynia, indicating that sexual distress affects both partners and is influenced by their emotional states (Pâquet et al., 2018). Although the complex interplay between anxiety, depression, vulvar pain symptoms and a potentially associated sexual discomfort will be the key object of analysis of the second chapter within the present thesis, their role in the etiology of vulvodynia will be briefly exposed here.

At the theoretical level, the fear-avoidance model, as described by Thomtén and Karlsson (2014), can offer deeper insights into the role of anxiety in vulvodynia. According to this model, the anticipation of pain during sexual activity can lead to a reaction that increases the intensity of the pain, creating a vicious cycle (Thomtén and Karlsson, 2014). Three key components arise from this theory: fear of pain, which leads to avoidance behaviors; anxiety about pain, which leads to hypervigilance; and catastrophizing, which includes ruminating and exaggerating the pain (Alappattu and Bishop, 2011; Thomten and Linton, 2013). In summary, the connection between anxiety, depression, and vulvodynia is complex and bidirectional: these mood disorders can both precede and result from vulvodynia, influencing the intensity of pain and the overall quality of life for those affected. Therefore, a therapeutic approach that addresses both the physical and psychological symptoms is crucial for effective treatment and to improve the overall well-being of those with vulvodynia.

Catastrophizing, hypervigilance and self-efficiency. A body of research has focused on the contribution of a range of negative evaluations and beliefs in the maintenance and exacerbation of pain. Among these factors, pain catastrophizing, hypervigilance to pain and self-efficiency have been found to play a crucial role (Lemieux et al., 2013). Pain catastrophizing has been defined by Bergeron et al. (2020) as a "tendency to hold exaggerated negative thoughts and feelings about the pain, that is, rumination, helplessness and magnification". More generally speaking, catastrophizing is believed to be the most robust psychological predictor of persistent pain and is associated with increased pain, increased illness behavior, and physical and psychological dysfunction in several clinical populations (Lemieux et al., 2013). In women with vulvodynia, a significant association has been found between greater catastrophizing - both of the patient herself and her partner - and higher levels of pain intensity (Goldstein et al., 2020; Bergeron et al., 2020). Related to catastrophic thinking is hypervigilance, which plays a role in the development and maintenance of chronic pain and can be defined as an attentional bias toward painful stimuli, which presumably contributes to misinterpretation and worsening of the pain itself (Payne et al., 2005). Some studies of women with vulvodynia suggest that hypervigilance to pain contributes to increasing the salience and intensity of perceived pain, chronicizing it and consequently impairing sexual functioning and quality of life (Payne et al., 2005; Desrochers et al., 2009).

Finally, several studies have identified self-efficacy as another crucial variable. Relative to chronic pain, self-efficacy is the degree to which people believe they can effectively manage pain effectively and is associated with lower pain intensity, greater pain tolerance, and better psychological adjustment (Bergeron et al., 2020; Lemieux et al., 2013). Again, in women with vulvodynia, higher levels of self-efficacy have been

found to be associated with decreased pain, better sexual functioning, and less perceived disability (Desrochers et al., 2009; Lemieux et al., 2013). Dewitte (2017) highlighted that people with higher self-efficacy tend to experience lower pain intensity and less sexual dysfunction. This suggests that psychological treatment for vulvodynia should focus not only on reducing anxiety and depression but also on boosting self-efficacy to break the cycle of fear and pain.

Childhood maltreatment. Generally speaking, it is largely accepted that childhood abuse, defined by Bergeron et al. (2020) as "physical, emotional or sexual abuse, or physical or emotional neglect that occurs during childhood", is likely to be linked with subsequent health problems, both at the psychological and physical level (Gilbert, 2009). In a systematic review examining factors predisposing women to chronic pelvic pain, Latthe et al. (2006) suggested that women with dyspareunia were 2.67 times more likely to report having experienced sexual abuse compared with women without dyspareunia. When comparing sexual abuse and physical abuse, Harlow et al. (2005) showed that in comparison to no-pain controls, women with complaints of vulvovaginal pain were 4.1 times more likely to report severe physical abuse, and 6.5 times more likely to report severe sexual abuse.

Furthermore, results from recent studies underscore how the impact of abuse during childhood on vulvodynia symptoms might have to do with subsequent stress: Khander, Brady, Stewart and Harlow (2014) conducted a survey to 215 case-control pairs of women with and without vulvodynia to examine associations between affect-based chronic stressors (i.e., living in fear of abuse, perceived abuse, and antecedent mood disorders) with vulvodynia. They found that among women with a history of severe

childhood abuse, those with vulvodynia had three times the odds of living in fear of any abuse compared to women without vulvodynia, suggesting that that affect-based chronic stressors may be important to the psychobiological mechanisms of vulvodynia (Khander et al., 2014). Nevertheless, it is important to note that childhood maltreatment, although it might also complicate women and partners' adjustment to vulvodynia, is a common pathway to many chronic illnesses, and, is therefore, not specific for vulvodynia (Bergeron et al., 2020). The documented correlations between childhood abuse and the increased likelihood of experiencing vulvovaginal pain, dyspareunia, and other forms of chronic pelvic pain underscore the imperative for healthcare providers to recognize and address the potential trauma history of patients with vulvodynia, enabling tailored interventions to mitigate its impact on both physical and psychological health outcomes.

Attachment style. The literature also explores the role of attachment patterns in relation to genito-pelvic pain, as attachment orientation affects adult romantic relationships and may shed light on how couple dynamics influence genital pain and associated sexual issues (Leclerc et al., 2015). Studies on sexual pain have found that an insecure-avoidant attachment style is linked to a higher likelihood of experiencing pain consistent with dyspareunia symptoms (Granot et al., 2011). According to Leclerc et al. (2015), although attachment style does not predict pain intensity, both avoidant and anxious attachment styles are associated with lower sexual satisfaction in women with provoked vestibulodynia. Moreover, lower sexual functioning is predicted only by an avoidant attachment style. In particular, avoidant women would have difficulty communicating their pain and seeking support from their partners, while women with anxious attachment might fear being abandoned because of their pain, consequently experiencing greater

catastrophizing (Goldstein et al., 2020). In summary, attachment patterns in relation to genito-pelvic pain reveal insights into how couple dynamics influence the experience of pain and associated sexual issues, emphasizing the importance of addressing attachment orientations in therapeutic approaches.

1.6 Diagnosis

Given and considering the various etiological factors and the complexity of vulvodynia, making a diagnosis of this syndrome is a delicate process (Goldstein et al., 2016; Bergeron et al., 2020). To date, there are still few health professionals who know and are able to diagnose vulvodynia (Graziottin et al., 2020). As stated before, vulvodynia affects different aspects of a woman's life, and it is often not recognized at the first diagnostic intent (Graziottin et al., 2020). The struggle that women report in finding a prepared practitioner makes it of critical importance that the health professional uses reassuring and empathic communication modes in order to build a doctor-patient relationship based on trust and mutual respect (Goldstein et al., 2016). Indeed, it is crucial that patients feel believed and listened to, that their pain is validated in order for them to find in the physician an ally, not an obstacle.

In addition, as pointed out in Rubal et al. (2023), due to mechanisms of central sensitization, which comprehend an amplification of pain signaling in the CNS leading to heightened pain perception and response to stimuli, most of the times pain in women with vulvodynia changes over time: the same woman may initially feel pain in the vaginal opening during intercourse with attempted penetration ("it only hurts when I have intercourse"), then begin to have monthly episodes of discomfort in the vestibular area for other reasons ("it feels like I get a yeast infection every month before my period"), up

to daily episodes of vulvar pain ("I feel burning all over the vulva all the time") (Rubal et al., 2023). Due to such dynamic nature of vulvodynia, a woman may receive different diagnoses (such as provoked vestibulodynia or generalized vulvodynia) depending on the stage of syndrome development at the time of examination. Since vulvodynia shares symptoms with several other conditions of an infectious or inflammatory nature with which it could easily be confused, this syndrome involves a diagnosis by exclusion (Goldstein et al., 2020).

While a universal diagnostic algorithm is lacking, various researchers agree on a set of guidelines to follow (Bergeron et al., 2020; Goldstein et al., 2020; Sadownik, 2014). According to these common guidelines, the first and fundamental step is an initial interview. Such interview aims at gathering information which is not strictly relevant to the diagnosis itself, but it is essential for making the patient feel comfortable and for viewing the pain she experiences from different perspectives (Graziottin et al., 2020). During this interview, a gynecologist/urologist with knowledge of the condition should collect useful information about the patient's pain and her medical, pharmacological, psychological, and sexual history (Bergeron et al., 2020; Goldstein et al., 2020). It is important to ask questions about the characteristics of the pain, how it impacts the patient's daily and sexual life, and what thoughts, behaviors, emotions, and couple interactions precede and accompany it (Sadownik, 2014; Bergeron et al., 2020). At this stage the specialist can be helped by the administration of a questionnaire, for example the Vulvar Pain Assessment Questionnaire (VPAQ), a comprehensive questionnaire that encompasses aspects such as pain severity, emotional response, cognitive response, interference with life, sexual function and self-stimulation or penetration, plus

supplementary scales of pain quality characteristics, coping skills and the effect on romantic relationships (Dargie et al., 2016; Bergeron et al., 2020).

Next, an objective examination by gynecological examination is necessary. As pointed out in the literature and easily derived from patient's reports, women often present to the gynecological examination with high levels of anxiety in response to an examination of the external and internal genitalia, so it is helpful to approach this stage gently (Sadownik, 2014; Goldstein et al., 2016). To this end, Sadownik (2014) suggests using a mirror that allows the patient to observe the steps of the examination step by step and learn more about her anatomy. The gynecologist should begin by reviewing the anatomy of the vulva and perianal area, in order to rule out the histologic diagnosis of an inflammatory skin condition (Sadownik, 2014; Goldstein et al., 2016). Next, the patient should be asked to describe the location of her pain and quantify the pain prior to palpation of the vulva, usually with a 1-10 numerical rating scale (Sadowick, 2014). The tool normally used in this phase is the cotton swab, which is used to inspect the vestibule, labia and hymenal remnants with a gentle pressure in a clockwise manner (cotton swab test) (Sadownik, 2014; Bergeron et al., 2020). Following this, a pelvic floor assessment becomes necessary, typically involving the insertion of a single finger into the vaginal opening and applying gentle to moderate pressure on the pelvic floor muscles towards the back and sides of the vaginal entrance (to evaluate the superficial transverse perineal muscles), on both sides of the opening (to assess the bulbospongiosus muscles towards the center and the ischiocavernosus muscles towards the sides), and deeper into the pelvis (to evaluate the levator ani muscle) (Bergeron et al., 2020). Moreover, as women with vulvodynia often report a difficulty in controlling this function, the gynecologist can ask the patient to contract pelvic floor muscles (Sadownik, 2014; Bergeron et al., 2020).

Finally, is it necessary to examine the vaginal wall and any present vaginal secretion through an insertion of a speculum, with the use of topical lidocaine if the pain is not tolerated by the patient. If necessary, a sample of discharge or moisture from the vaginal wall can be used for laboratory assessment (Bergeron et al., 2020).

In conclusion, despite the available information in numerous scientific reports, routine gynecological practice often lacks the time, resources, and awareness necessary for proper diagnosis and management of vulvodynia (Graziottin et al., 2020). Few professionals are familiar with the condition, and the absence of clinically observable findings for the pain often leads to delayed diagnosis, patient frustration, and a phenomenon that Trutnovsky et al. (2018) called "doctor shopping", where women undergo numerous visits before obtaining a diagnosis. The diagnostic delay for vulvodynia and other conditions associated with genitopelvic pain is extremely high, ranging from 4.7 years for vestibulodynia to 9-11 years for endometriosis sufferers (Graziottin et al., 2015). Additionally, it's crucial to recognize that vulvodynia manifests in various and extremely different ways, making it nearly impossible to find two individuals with identical symptoms in terms of onset, duration, and intensity (Goldstein et al., 2020). All of these factors result in that vulvodynia assessment starts with listening to the patient's symptoms and validating her pain, providing her and her potential partner with supportive tools throughout the diagnostic and therapeutic path.

CHAPTER 2. PSYCHOLOGICAL DISTRESS AND SEXUAL FUNCTION IN WOMEN WITH VULVOVAGINAL PAIN

So far we have analyzed the etiological factors of vulvodynia following a biopsychosocial perspective: we have seen how vulvodynia can be impacted by biological, social, and psychological factors. Indeed, although psychological factors playing a role in the genesis and maintenance of sexual pain have long been overshadowed, more and more evidence is found in the literature in favor of their importance (Bergeron et al., 2020; Bodenmann, Ledermann, 2008). As previously stated, this thesis aims to focus its analysis on the impact of psychological factors such as anxiety and depression on sexual function of women with vulvodynia. By both reviewing the literature and listening to the clinical experiences of patients, it becomes evident that the relationship between negative mood, pain and sexual function is controversial in nature, since all three factors influence each other (Bergeron et al., 2016; Bergeron et al., 2020). Consequently, it seems necessary to further investigate chronic vulvar pain and its psychological and sexological correlates in order to disentangle such an intricate relationship and get to a more straightforward understanding of vulvodynia.

Therefore, in this second chapter, I will first discuss how anxiety and depression can play a role in the genesis and maintenance of chronic vulvar pain. Then, I will analyze the impact of such pain on women's sexual function, more specifically on their sexual desire and arousal. Nevertheless, as previous research shows, negative mood factors can also impact women's sexual function (Bodenmann, Ledermann, 2008). For that reason, I will then present a third section investigating the effect of anxiety and depression on arousal and desire in women. To conclude, I will see how previous research has been fallacious at investigating these variables when leaving behind daily variations data and

individual differences. Finally, I will present the current study as a potential resolution of such variations.

2.1 Anxiety, depression and chronic vulvar pain

Previous research has shown that mood can have an important impact on perceived chronic pain (Gaskin et al., 1992). In particular, two relevant factors are anxiety and depression, given that it has been commonly accepted how they can exacerbate perceived chronic pain (Lerman et al., 2015; Penedo et al., 2020; Gaskin et al., 1992). For example, in the study by Lerman et al. (2015), 428 individuals with chronic pain were asked to complete a questionnaire about their pain, anxiety and depression at four time points, with an average of 5 months between measurements. In every time point, more than half of the sample reported significant symptoms of both depression and anxiety, and a latent depression/anxiety variable longitudinally predicted pain and pain-related disability (Lerman et al., 2015). Vulvodynia, which refers to chronic pain at the vulva, is no exception. In fact, several studies demonstrated how women with vulvodynia are also likely to suffer from depression and anxiety or experience depression or anxiety symptoms (Tribó et al., 2020). Nevertheless, the relationship between depression, anxiety and vulvodynia is still controversial as the direction of the relationship hasn't been clarified yet (Khandker et al., 2011).

To this regard, a cross-sectional study was recently conducted by Tribó et al. (2020) in order to analyze pain, anxiety, and depression and the effects of these factors on quality of life of women with vulvodynia. Their sample comprised 110 patients, 37.3% of whom had psychiatric comorbidities. When comparing anxiety and depression, the authors found that depression was actually more prevalent than anxiety: 61.7% of patients

scored as “abnormal” in the anxiety scale used (for the HADS-A scale, “abnormal” refers to scores ≥8), while for depression this happened in 24.7% of the sample, with HADS-D scores ≥8. Moreover, Tribó et al. (2020) found a correlation of r = 0.8 between pain measured with the SV-MPQ and anxiety measured with the HAM-A questionnaire, and a correlation of r = 0.6 between anxiety and impairment in quality of life. The authors state that the same high correlation wasn’t found for depression, although this is not numerically presented in the article. These findings suggest that women with chronic vulvar pain are more likely to have anxiety than depression. Nevertheless, when investigating these factors it’s important to remember that anxiety and depression are mood symptoms that can be influenced by several other variables and not only vulvodynia, among which demographic variables such as age and income. The fact that all participants from this study were more than 40 years old and the lack of a control group does limit the generalizability of results. In spite of these several limitations, results from this study are in line with the ones of Govind et al. (2020), in whose research of a total of 79 women with confirmed provoked vestibulodynia/pelvic floor dysfunction, 22% met criteria for pain-related anxiety alone, 4% for depression alone, and 27% for both pain-related anxiety and depression. In summary, anxiety appears to be more prevalent than depression among women with vulvodynia. Despite their limitations, findings underscore the complex interplay of pain, mood symptoms, and quality of life.

Although Tribó et al. and Govind et al. found relatively higher percentages of anxiety as compared with depression in their sample, other studies focused on the relevance of depression on vulvar pain. For example, Iglesias-Rios et al. (2015) conducted a multiethnic population-based study, and, using baseline data from 1795 women, found that women who screened positive for depression had a 53% higher prevalence of having

vulvodynia than women who screened negative. Although a large body of research already showed that depression and anxiety are closely related (Khalin, 2020), when looking at research in the context of vulvar pain it becomes important to analyze these constructs in their context-related forms. For example, Govind et al. (2020) found that 49% of women with provoked vestibulodynia/pelvic floor dysfunction experienced pain-related anxiety, the specific form of anxiety related to chronic pain, with or without depression. In conclusion, while studies demonstrate varying degrees of association between depression, anxiety, and vulvar pain, further exploration is needed to understand the nuanced interplay of these constructs within the context of chronic pain disorders like vulvodynia and provoked vestibulodynia.

We have now analyzed the prevalence of anxiety and depression in patients with vulvodynia. Nevertheless, the question of whether anxiety and depression are antecedents or consequences of chronic vulvar pain still remains open. In an attempt to answer such question, epidemiologic research has shed light on the bidirectional relationship between anxiety, depression, and vulvovaginal pain. In a large-scale population-based study, Khandker et al. (2011) revealed that depression and anxiety are both precursors and consequences of vulvodynia. Khandker et al. (2011) indeed started from evidence showing that women with vulvodynia are more psychologically distressed than women without vulvodynia (Stewart et al., 1994; Nylanderlundqvist and Bergdahl, 2003; Masheb et al. 2005), but leaving the wonder of whether anxiety and depression morbidity serves as a precursor risk factor remains uncertain. In order to shed light on the temporal relationship between these variables, the authors recruited 240 case-control pairs of women with and without vulvodynia, and assessed their psychiatric history through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997).

During the interview, the age of initial diagnosis for mood and anxiety disorders was established to determine if symptoms of vulvodynia preceded or followed the onset of these disorders. After adjusting for several other variables, Khander et al. (2011) found that women with a history of mood or anxiety disorders prior to vulvodynia were four times more prone to develop the condition compared to those without such history. Moreover, vulvodynia showed an association with the emergence or recurrence of mood or anxiety disorders with a moderate Hazard Ratio (HR) of 1.7. Finally, the correlation observed between vulvodynia and the emergence or recurrence of depression or anxiety, suggesting the potential existence of bidirectional links between anxiety, depression, and vulvodynia, or a shared underlying risk factor for both chronic pain and psychological disorders (Khander et al., 2011; Bergeron et al., 2020).

The research conducted by Khandker et al. (2011) illustrates the complex interplay between anxiety, depression, and vulvodynia, revealing both precursor and consequential relationships among these variables. Their findings suggest a bidirectional association, shedding light on the temporal dynamics of these conditions. However, the interpretation of depressive and anxiety symptoms among vulvodynia patients remains multifaceted. In recent times, many researchers have tried to interpret them in terms of shared neural substrates. Next, a brief summary will be provided of some of the most recent findings regarding the potential biological basis of the connection between depression and pain, as well as between anxiety and pain.

2.1.1 Neurobiological correlates of depression in chronic pain.

The interpretation of pain and physical symptoms of depression has evolved over time. In the 1950s, physical pain was often viewed as a “masked depression”, meaning it was

considered a symptom of depression (Graziottin, 2006). Alternatively, some believed that physical symptoms, including pain, served depression by garnering increased attention from family and medical professionals, together with believing that it was muscular tension associated with depressive-anxious states that caused widespread pain (Graziottin, 2006). In the 1990s, attention shifted towards understanding how fluctuations in anxiety levels and mood, in general, heightened the perception and expression of pain (Graziottin, 2006). Finally, with the development of neuroimaging and neuromodulation techniques, contemporary research has linked pain and depression through shared neurochemical and anatomical pathways, suggesting a potential coexistence rather than a straightforward causal relationship (Graziottin, 2006; Goldstein et al., 2020; Arnold et al., 2006). Consequently, it remains unclear whether depression in vulvodynia patients acts as a causal factor or evolves as a progressive response to the chronic pain condition.

In light of new neuroanatomical findings, Sheng et al. (2017) reviewed the link between depression and chronic pain in terms of neural mechanisms, and found five potential key factors contributing to the coexistence of chronic pain and depression. To start with, research has identified common brain regions involved in mood regulation and pain processing, including the insular cortex, prefrontal cortex, anterior cingulate, thalamus, hippocampus, and amygdala, which underlie the coexistence of depression and chronic pain (Li and Hu, 2016). These shared neural substrates play a significant role in the manifestation and progression of both depression and chronic pain (Sheng et al., 2017). In conditions like vulvodynia, where vulvar pain is persistent, alterations in these brain regions due to chronic pain and depression may contribute to the amplification of pain perception and emotional distress.

Moreover, changes in the brain have been shown to happen not only at the anatomical level, but also at the functional one, such as in the case of neuroplasticity. There are significant overlaps between neuroplasticity changes induced by pain and depression, alongside shifts in neurobiological mechanisms (Sheng et al., 2017). These shared changes are crucial in facilitating the occurrence and progression of chronic pain-induced depression (Sheng et al., 2017). Chronic pain and depression may stem from common neuroplasticity mechanism changes, which play a vital role in the initiation and exacerbation of both conditions.

Furthermore, at the neurochemical level, decreased availability of serotonin (5-HT), dopamine (DA), and norepinephrine (NE) in the central nervous system is associated with depression, while their role in pain modulation has also been studied (Cohen and Mao, 2014; Sheng et al., 2017). Finally, neuropathic pain treatment focuses on blocking brain-derived neurotrophic factor (BDNF) transmission, a crucial signal molecule between microglia and neurons, together with a potential target for chronic pain-induced depression treatment (Sheng et al., 2017). Taken together, these factors collectively highlight the intricate interplay between chronic pain and depression, suggesting a shared underlying mechanism that contributes to their coexistence, such as in conditions like vulvodynia (Sheng et al., 2017).

2.1.2 Neurobiological correlates of anxiety in chronic pain.

Chronic pain often results in emotional changes such as anxiety and fear and, as previously seen in the case of depression, anxiety or fear can also enhance the suffering of pain (Wiech and Tracey, 2009; Zhuo, 2016). Until recently, few research directly investigated the interaction between pain and anxiety at network and synaptic levels

(Zhuo, 2016). Recent studies investigating the topic with neuroimaging techniques showed that three main brain areas are involved in both conditions: the anterior cingulate cortex (ACC), insular cortex (IC), and the amygdala (LeDoux, 2000). Nevertheless, while different forms of anxiety may share certain brain structures such as amygdala and ACC, it is possible that they are processed and encoded by different mechanisms at both neuronal network and molecular signaling levels (Zhuo, 2016).

To this regard, Zhuo in a 2016 review puts forward what I believe is an interesting proposal. The author posits that chronic anxiety triggered by injury or chronic pain would be mediated by presynaptic long-term potentiation (LTP) in the anterior cingulate cortex (ACC), a key cortical region for pain perception (Zhuo, 2016). Conversely, NMDA receptor-dependent postsynaptic LTP would play a more important role in behavioral sensitization in chronic pain (Zhuo, 2016). Highlighting postsynaptic and presynaptic LTP in ACC neurons as key cellular mechanisms for causing chronic pain and its associated anxiety, the author proposes shifting focus from current medications targeting glutamate modulation, which often lead to side effects with chronic use, towards inhibiting presynaptic LTP for potentially safer and more effective treatment (Zhuo, 2016).

In summary, when we talk about neuroplasticity, we are referring to the brain's remarkable ability to adapt its structure, which in turn reflects the intricate and ever-changing nature of our psychological experiences (Graziottin, 2006). Vulvar pain, especially when chronic, is no exception. Nevertheless, at the same time every psychological event has a biological impact. Thus, it is possible to understand the complexity of chronic vulvar pain by recognizing this reciprocal relationship between biology and psychology (Graziottin, 2006). Despite the prevalence of anxiety and

depression symptoms among vulvodynia patients, this understanding often fails to translate into clinical practice (Metts, 1999; Arnold et al., 2006; Xie et al., 2012). The challenge for modern medicine and psychology would therefore be bridging the gap that emerged long ago between a "soulless medicine", increasingly specialized and technological but less person-centered, and a "body-less psychology", inadequately prepared to grasp the neurobiological foundations of every psychological process (Graziottin, 2006).

2.2 Impact of chronic vulvar pain on female sexual function

Given the nature of genital pain, most women with vulvodynia also show significant impairments in the experience of sexuality (Bergeron et al., 2020; Goldstein et al., 2020). In fact, because pain often occurs with touch or penetration in the genital area, rates of sexual dysfunction are very high in this population (Goldstein et al., 2016; Pukall et al., 2016). Sometimes the impact of pain on sexuality becomes so adverse that women might develop a so-called "erotophobia", defined as a "persistent fear toward sexuality in general", which can be considered a full sexual dysfunction from a clinical perspective (Desrochers, et al., 2009). As sexual satisfaction plays a key role as an indicator of quality of life (Davidson et al., 2009), it becomes crucial to investigate the role of pain in women's sexual life and factors that can contribute to this relationship, such as the partner. As this thesis mainly focuses on sexual arousal and desire within the female sexual function, we will now examine the impact of chronic vulvar pain on these variables.

2.2.1 Impact of chronic vulvar pain on female sexual arousal

Previous research has shown that chronic pain, especially chronic vulvar pain, does have an impact on female sexual arousal (Meana and Binik, 1994; Segraves and Segraves, 1991). In particular, this becomes particularly relevant in the context of dyspareunia (Bergeron et al., 2020). To this regard, several theoretical models have been suggested to explain such pain. Initially proposed by Spano and Lamont (1975), a circular model of dyspareunia suggests that both pain during intercourse and the fear of experiencing pain, which can become conditioned over time, may contribute to diminished sexual arousal during sexual activity. This diminished arousal can in turn lead to vaginal dryness and increased pelvic floor muscle tension, potentially resulting in friction upon the vulvar skin, exacerbating pain and possibly causing tissue damage. Contrarily, Kaplan (1974) attributed vulvar pain primarily to insufficient vasocongestion, implicating a lack of sexual arousal as the primary cause of pain. In summary, the connection between vulvodynia and sexual arousal issues emphasizes how difficulties with arousal play a key role in causing and sustaining superficial dyspareunia.

Women's sexual arousal is a multifaceted construct, involving both physiological changes in the genitals, such as increased blood flow and vaginal lubrication, and non-genital cues like elevated heart rate, sweating, dilated pupils, and nipple erection, triggered by sexual stimuli (Meston and Stanton, 2019). These responses are in turn influenced by psychological factors such as relationship status and past sexual experiences, which contribute to the subjective feeling of arousal (Meston and Stanton, 2019). Thanks to new advances in research, it is now commonly accepted that women sexual arousal comprises two main components: genital arousal, involving physiological changes such as genital vasocongestion, and subjective arousal, which refers to the mental

engagement and positive focus in response to sexual stimuli (Meston and Stanton, 2019). Many scholars assume that physiological and subjective sexual arousal are interdependent aspects of the same underlying latent construct of sexual arousal (Bollen and Lennox, 1991). Nevertheless, both clinical observations and laboratory studies have often pointed to a desynchrony in subjective and physiological sexual arousal in women (Laan and Everaerd, 1995). Although such discrepancy between women's genital and subjective sexual arousal has been largely studied in healthy women (for a review, see Meston and Stanton, 2019), the same attention hasn't been paid to women with vulvovaginal pain.

I will now present a series of results regarding the impact of chronic vulvar pain on women's sexual arousal obtained with different measures. In my opinion, focusing extensively on the measures used in studies investigating the impact of vulvar pain on sexual arousal is crucial for three reasons. First, the choice of measurement tools directly influences the interpretation and comparability of study findings across different research studies. Secondly, understanding the strengths and limitations of various measurement techniques helps researchers select the most appropriate methods for their specific study objectives, ensuring the validity and reliability of their results. Finally, by scrutinizing the methodologies employed in past research, researchers can identify gaps in knowledge and methodological advancements needed to further our understanding of the complex relationship between vulvar pain and sexual arousal.

In research practice, sexual arousal is typically induced with participants being exposed to films with erotic content. In this context, subjective sexual arousal is normally assessed with self-questionnaires reporting their degree of sexual arousal in response to such erotic stimulus, while genital sexual arousal is operationalized by increase in blood flow to the vagina and vulva, together with vaginal lubrication. Among studies measuring

genital arousal in women, the majority of them used a device called vaginal photoplethysmograph (VPP), which is about the size of a menstrual tampon, inserted into the vagina (Meston and Stanton, 2019). This device contains a light source that emits orange-red light and a sensor that detects the light reflected by the vaginal wall and the blood flowing within it (Meston and Stanton, 2019). By connecting the signal from the sensor to an amplifier, the vaginal pulse amplitude (VPA) is measured (Meston and Stanton, 2019). VPA reflects the rhythmic changes in vaginal blood flow associated with each heartbeat, with larger amplitudes indicating greater levels of vaginal engorgement or arousal (Laan and Everaerd, 1995; Meston and Stanton, 2019).

Although the vaginal photoplethysmograph represents a validated measure of genital sexual arousal, results from studies using this device with women affected by vulvovaginal pain are contradictory. Wouda et al. (1998) utilized the vaginal photoplethysmograph to assess genital arousal in women with and without dyspareunia while watching film segments depicting sexual acts. While there were no notable differences in genital arousal during oral sex, the dyspareunia group experienced decreased arousal during intercourse compared to an increase in arousal observed in the control group (Wouda et al., 1998). Notably, subjective arousal ratings did not differ between the groups following the intercourse segment (Wouda et al., 1998). Similarly, Brauer et al. (2006) utilized the VPP to compare arousal in women with and without dyspareunia during film segments depicting sexual acts. In contrast to previous findings, no significant differences in genital arousal were observed between the groups. Interestingly, there was a trend suggesting higher genital arousal in the dyspareunia group during intercourse, whereas lower levels of arousal were observed during the oral sex segment compared to the control group. Women with dyspareunia reported significantly

less positive sexual affect compared to the control group across both segments. In summary, results from studies using the VVP end up as contradictory, which may be partially explained by methodological and procedural differences (Meston, 2000).

In light of this discrepancy among findings using the VVP, other authors have used the labial thermistor clip, an external tool for assessing vulvar temperature, indirectly reflecting blood flow to the genitals, in which higher temperatures are assumed to correlate with increased blood flow. Research supports the utility of external measures, showing a stronger association between female genital and subjective arousal compared to vaginal photoplethysmography (Payne, 2007). In a study implying this measure, Payne et al. (2007) found no significant differences in genital or subjective arousal between women with PVD and non-affected women. Genital temperature change was measured using a labial thermistor clip while participants viewed erotic and neutral films and there was a trend towards lower subjective arousal in the PVD group, although not statistically significant. Additionally, women with PVD reported less desire to engage in intercourse after watching the erotic film compared to the control group. This suggests that while women with PVD experienced similar levels of genital arousal as controls, they were less inclined to act on their arousal. Although this study provides interesting insights on the discrepancy between genital and subjective arousal, further results are needed using the labial thermistor clip in order to capture a more comprehensive understanding of the relationship between genital and subjective arousal in women with chronic vulvar pain.

In order to address genital and subjective arousal differences between women with and without PVD with a different methodological approach, Boyer et al. (2013) decided to use laser Doppler imaging (LDI), a non-invasive, direct and external measure of blood flow over the entire vulvar region, to determine whether women with or without PVD

differ in genital and subjective arousal in response to an erotic visual stimulus. Contrary to expectations, no significant differences were found in subjective arousal or anxiety levels between the two groups. However, women with PVD exhibited lower genital arousal in response to erotic stimuli, particularly when baseline blood flow levels were higher. This discrepancy was attributed to variations in vulvar anatomy, potentially affecting blood flow measurements. Furthermore, while baseline blood flow significantly predicted arousal levels in both groups, the variance explained was notably lower in the PVD group, suggesting additional factors influencing arousal. Overall, the study by Boyer et al. (2013) supports the association between subjective arousal difficulties, lubrication issues, and pain in women with PVD, highlighting the potential role of decreased arousal in both the development and perpetuation of the condition.

In summary, the findings of studies examining the impact of chronic vulvar pain on sexual arousal reveal notable obstacles encountered by individuals with conditions like vulvodynia, such as diminished sexual arousal during intercourse due to pain and fear of pain, as well as potential physiological changes such as vaginal dryness and increased pelvic floor muscle tension. While some studies suggest a discrepancy between subjective and physiological arousal in women with vulvovaginal pain, others highlight lower levels of genital arousal in response to erotic stimuli. These results underscore the multifaceted nature of sexual arousal and its complex relationship with chronic vulvar pain, emphasizing the need for further research to better understand and address sexual dysfunction in affected individuals.

2.2.2 Impact of chronic vulvar pain on female sexual desire

As previously mentioned, previous research has shown that chronic pain has an impact on sexual function (Ambler et al., 2001; Kwan et al., 2005). As for arousal, this is also true for sexual desire, since many studies demonstrated how chronic pain can worsen women's sexual desire (Laursen et al., 2006). Interestingly, a study by Laursen et al. (2006) compared a sample of 40 female patients suffering from four different chronic pain syndromes and 41 healthy controls: when asked for their ability to experience sexual desire at all, 58% of the clinical sample answered "no ability to feel sexual desire at all". To this regard, chronic pain due to vulvodynia is no exception. To explore the epidemiology of vulvar pain and its correlates, Graziottin et al. (2020) conducted a study with a large sample of 1183 cases, among which 22.1 % reported comorbid sexual desire disorder, leaving us to believe that this is a common issue among women. In fact, several studies indicated that women with vulvodynia report significantly less sexual desire than controls (Meana et al., 1997; Desroches et al., 2009). Nevertheless, the relationship between vulvar pain and sexual desire is still intricate due to a significant gap in research and contradictory findings, and needs further in-depth analysis.

The link between chronic pain and lower sexual desire has long been known. There are several possible ways in which sexual desire can be impacted by chronic vulvar pain. At the physical level, when pain is very intense, a rather common consequence is avoidance of sexual intercourse, which in turn contributes to reduced sexual desire and lubrication and increased tension of the pelvic musculature (Dewitte et al., 2011; Gordon et al., 2003). In a study by Bachmann et al. (2019) aimed at exploring the impact of gabapentin on vulvar pain and female sexual function, the authors investigated the effect of gabapentin versus placebo on sexual function in 89 women with provoked

vestibulodynia, as measured with the FSFI. Gabapentin is a medication which has been shown to reduce pain in fibromyalgia patients, and was found to be relatively effective for vulvodynia too: measuring patients' sexual function with the FSFI, the highest increases were seen for arousal (mean difference = 0.3) and desire (mean difference = 0.2), especially in women with highest pain. The authors interpreted these results according to the hypothesis that gabapentin would improve sexual functioning secondary to a beneficial effect on pain, and found that gabapentin intervention had a better overall response in women with a higher median baseline algometer pain score (>5/10).

Another layer of connection between chronic vulvar pain and decreased sexual desire is given by medications. Vulvodynia is one of the most severe forms of neuropathic pain, for which tricyclic antidepressants (TCAs) represent first-line treatment (Holbech, 2017). The most commonly prescribed medical treatment is amitriptyline, which has been associated with favorable outcomes regarding pain in retrospective and non-controlled trials (Van Beekhuizen et al., 2018; Reed et al., 2006). Although antidepressants might have a positive effect on pain, previous studies have highlighted their detrimental impact on sexual function, in particular sexual desire (Kennedy and Rizvi, 2009). Even though randomized controlled trials in order to explore the effects of antidepressants for sexual desire in vulvodynia patients haven't been performed yet, from the results obtained in previous studies it could be inferred that medical treatment can be a factor causing a decrease in sexual desire (Kennedy and Rizvi, 2009).

In conclusion, chronic vulvar pain, notably in conditions like vulvodynia, consistently correlates with reduced sexual desire in women. Of note, in the realm of chronic pain's impact on sexual desire, there is a notable lack of data. To our knowledge, studies on the impact of chronic vulvar pain on sexual desire in women with vulvodynia

are scarce because most studies utilize the total score of the Female Sexual Function Index (FSFI; Rosen et al., 2000). Although the total score of the FSFI is an important and statistically recognized measure, it is important to focus on individual domains (arousal, desire, orgasm, etc.) to gain a more comprehensive understanding of the impact of vulvar pain on sexual function in women with vulvodynia.

2.2.3 Role of the partner

In the context of genital pain, interpersonal factors are particularly important as partners serve as primary witnesses to a woman's pain and can also be the very cause of pain during sexual activity (Rosen et al., 2013; 2014). Numerous studies in the literature have investigated the role of the partner in relation to various outcomes of pain, sexual functioning, and satisfaction. Overall, it has been observed that the support and response of the partner to pain deeply impacts the relational satisfaction and intimacy of the couple, with direct effects on both the pain itself and the woman's psychosocial adaptation (Rosen et al., 2014). Indeed, partners can directly influence a woman's experience of pain and the associated disability (Rosen et al., 2013). However, findings are only partially consistent with each other, suggesting that couple interactions in this context still require further study and clarification. Of note, while this thesis primarily focuses on sexual function in terms of desire and arousal, the distinction is not always explicitly made in studies investigating the role of the partner. Therefore, we will discuss sexual function in general in the context of partner-related research.

The role of a partner's response to a woman's pain has been extensively explored in the literature, revealing its potential to either ameliorate or exacerbate the experience of illness. As anticipated in the first chapter, Rosen et al. (2014) identified three main

patterns in which partners respond to women's pain during or after intercourse: a solicitous way (providing attention and sympathy), a negative way (expressing hostility and frustration), and a facilitative way (expressing affection and encouraging adaptive coping). Within this context, past research showed that greater partner solicitous and negative responses, as well as lower facilitative responses, are associated with poorer relationship satisfaction in chronic pain patients (Raichle et al., 2011), and poorer sexual and relationship satisfaction in women with PVD (Rosen et al., 2012; Rosen et al., 2013).

Even so, earlier investigations always used cross-sectional designs, an experimental design that leaves behind the daily intrapersonal variability, which leads to data simplification. To address this issue, Rosen et al. (2015) conducted a dyadic daily experience study of women with PVD and their male partners, in order to investigate within-person associations between male partner responses to painful intercourse and the sexual relationship satisfaction of affected couples. This was done with a sample of 69 heterosexual couples who completed online-based questionnaires each day for 8-weeks, each partner independently from the other. The analyses revealed that when women experienced more facilitative partner behaviors (e.g., expressions of affection and pleasure) on days of sexual activity, they expressed greater satisfaction in both their sexual experiences and relationships, and the opposite happened with more negative partner responses, as measured with the Other Response Scale through items such as "expresses frustration at me" (Sharp and Nicholas, 2000). This could be because facilitative responses may help both partners to involve in more adaptive, approach-oriented strategies to engage in non-painful sexual activities, fostering intimacy feelings and positively reinforcing sexual experience. On the other hand, negative responses focus

the couple's attention towards pain, as they communicate a lack of empathy and disrupt adaptive emotion regulation.

Likewise, when men reported increased facilitative responses on such days, their female partners indicated slightly higher relationship satisfaction. Results were different on days in which men recorded more solicitous responses, where both men and women reported lower sexual satisfaction. This is particularly important in clinical settings, as men might engage in solicitous responses (offering comfort or stopping the sexual activity) in order to demonstrate support and concern, unconscious of the harmful outcomes of these actions (Rosen et al., 2015). Men's solicitousness may in fact encourage greater avoidance and reinforce negative cognitive affective appraisals of pain such as catastrophizing and anxiety, elements that are known to be associated with higher distress in partners and greater pain in women with PVD (Rosen et al., 2015; Desrochers et al., 2009).

Taken together, these findings are in line with operant learning models and intimacy models, according to which partner responses may play a role in maintaining or reinforcing relationship and sexual satisfaction in pain-affected areas and affect the emotional regulation of the couple (Rosen et al., 2015). According to the authors of the present study, positive and supportive partner responses during penile-vaginal intercourse seem to enhance the sexual satisfaction of couples dealing with PVD, while negative or overly concerned responses may have detrimental effects on their well-being (Rosen et al., 2015). Therefore, such findings illustrate the potential benefits of including the couple's dimension within clinical therapy, as healthcare professionals could advise couples to examine and recognize their own encounters with partner reactions to pain (Rosen et al., 2015). Understanding these experiences may shed light on their influence

on behavioral avoidance, cognitive and emotional assessments of pain, and overall intimacy within the couple (Rosen et al., 2015).

To conclude, in the present section we analyzed the impact of chronic vulvar pain on sexual function, in particular desire and arousal, and its associated factors. Although results from the presented studies illustrate the detrimental effects of vulvar pain on sexual desire and arousal, it is important to emphasize that vulvodynia does not necessarily preclude the ability to enjoy one's sexuality. Many studies indeed highlight that the majority of women with ongoing genital pain continue to engage in sexual intercourse regularly, aiming to maintain intimacy with their partner or to avoid relational conflict (Chisari et al., 2021). In this regard, the development of better sexual communication, more positive attitudes towards sex, and approach-oriented goals rather than avoidance can assist the couple in maintaining and nurturing mutual intimacy, exploring alternative ways to penetrative sex.

2.3 Impact of anxiety and depression on female sexual function

There are many psychosocial factors that have been found to influence sexual desire and arousal in women. Among these factors, particular emphasis has been placed on psychological factors such as anxiety and depression, given that the majority of studies conducted have highlighted the deleterious impact of negative mood on female sexual function (Graham et al., 2004; Brotto et al., 2016; Bodenmann and Ledermann, 2008). Although an extensive body of research has been conducted on healthy women, the same attention hasn't been paid to women with vulvovaginal pain. In this section, I will therefore explore the impact of anxiety and depression on sexual function in women, with a particular focus on women with vulvovaginal pain. Since the present thesis aims at

focusing on desire and arousal within the female sexual response, we will first present the impact of anxiety on desire and arousal, followed by the impact of depression on the same variables.

2.3.1 Impact of anxiety on female sexual function

Previous research on healthy women has found that anxiety can have an impact on sexual desire and arousal (Lykins et al., 2006). Despite the general perception that anxiety negatively impacts individuals' sexual functioning, several results have brought to light a contradictory association. For example, Barlow (1986) proposed a theory focused on sexually functional vs dysfunctional men indicating that anxiety could have both positive and negative effects on sexual functioning. Although Barlow's results were focusing on men and obtained with laboratory manipulations of threat and anxiety, qualitative research in women has led to similar conclusions. In particular, Graham et al. (2004) conducted a study using focus groups in order to investigate factors influencing sexual desire and arousal in women. Participants discussed various factors that were identified as exerting either positive or negative effects on sexual arousal, among which anxiety played an intriguing role: some women reported experiencing a heightened sexual response when anxious, while other women reported the opposite. Two years later, a similar paradoxical effect was found by Lykins et al. (2006), as 34% of women in their sample noted a reduction in sexual desire when they were extremely anxious, whereas 23% mentioned an increase. As for sexual arousal, 23% of women participants reported a negative effect of anxiety symptoms, but 21% reported an increase of their sexual arousal when feeling anxious. Given the previous literature has demonstrated the high prevalence of anxiety among women suffering from vulvovaginal pain (Khandker et al.,

2011), it becomes important to investigate its impact on patients' sexual functioning, particularly on sexual desire and arousal.

As previously stated, research investigating the impact of anxiety on women with vulvovaginal pain is notably lacking and has brought to different results. Corsini-Munt et al., (2017) conducted a dyadic perspective study on 49 heterosexual couples struggling with provoked vestibulodynia, and found a significant correlation of r = -0.30 between women's anxiety and their general sexual function. Nevertheless, it is important to note that Corsini-Munt et al. (2017) used a general measure both for anxiety and for sexual function index. Apart from using the total score of the FSFI without distinguishing among its 7 subcomponents (namely: desire, arousal, lubrication, orgasm, satisfaction, and pain), the authors also used a total score for "anxiety" without further deepening between its subcomponents. However, previous literature investigating anxiety among women with vulvar pain has found several different facets of such construct, which in turn have been found to differently impact women's sexual desire and arousal (Brauer et al., 2006; 2007).

In addition to what previously said, anxiety is a multifaceted construct. Among the specific ways in which it can manifest and influence individuals' psychological and physical well-being, the ones that have been studied the most in the context of vulvovaginal pain are state anxiety (i.e., a temporary condition of heightened anxiety in response to a specific situation or event; Desrochers et al., 2009), pain-related anxiety (i.e., anxiety activated by the prospect of painful intercourse; Spano and Lamont, 1975), body exposure anxiety (i.e., self-consciousness, anxious focus, and exposure avoidance of one's body while engaging in sexual activities; Cash et al., 2004), and hypervigilance (i.e., a heightened awareness and sensitivity to pain or discomfort often stemming from

or leading to increased anxiety; Desroches et al., 2009). Each subcategory does not exist in isolation but rather they interact and overlap with each other, and each one plays a different role within women's sexual functioning. These different anxiety manifestations do not only exist within a theoretical distinction, but also the experimental level: in a 2009 study with 75 women affected by PVD, Desrochers et al. investigated the relationship between female sexual function and several measures such as state anxiety, pain-related anxiety and hypervigilance, each one measured with a different questionnaire. Results showed a significant negative correlation of female sexual function with state anxiety ($r = -0.26$) and pain-related anxiety ($r = -0.28$) but not with hypervigilance ($r = -0.12$). In another study specifically addressing sexual arousal, Brauer et al. (2007) found that pain-related anxiety reduced sexual arousal in women with and without dyspareunia. Overall, this result highlights the importance of further examining the various forms of anxiety and their unique impacts on sexual function in women with vulvovaginal pain, as they can provide valuable insights for developing more effective treatment and support strategies.

A particular manifestation of anxiety which has been particularly linked to vulvovaginal pain is body exposure anxiety, which in turn is strongly linked to body image (BI). Body image is a multidimensional construct defined as individuals' experience of their body, including affective, perceptual, and evaluative components (Maillé et al., 2015). This construct has been studied in relation to vulvovaginal pain, as around 63% of all women with provoked vestibulodynia report a negative change in their body image after symptoms onset (Maillé, et al., 2015). Starting from the fact that women with PVD have been reported to have a poorer BI, Maillé et al. (2015) conducted a study on 39 women with PVD and 18 controls to examine associations between body image

and sexual function in women with vulvovaginal pain. Among the different measures of body image, the authors used the Body Exposure during Sexual Activity Questionnaires. After the analysis, Maillé et al. (2015) found that higher levels of body exposure anxiety during sexual activities were significantly associated with lower sexual function in women with vulvodynia ($r = -0.50$). Overall, results from empirical studies corroborate the importance of examining all different facets of anxiety in women with vulvar pain to better understand how they impact sexual function and psychological well-being. Focusing on these nuances can help develop more targeted treatment strategies and provide more effective support, recognizing that different forms of anxiety can have distinct effects on pain perception, sexual functioning, and the overall experience of the condition.

2.3.2 Impact of depression on female sexual function

As previously examined for anxiety, researchers have also explored how depressive symptoms influence women's sexual function. Earlier studies have indicated that individuals with major depressive disorder often experience reduced sexual desire, which can result either from the depression itself or from the adverse effects of antidepressant medications (Montejo-González et al., 1997). However, the widely accepted notion that depression negatively affects sexual desire has recently been questioned, since several results suggest that depression can lead to higher levels of sexuality. For example, Mathew and Weinman (1982) conducted a study on 51 male and female drug-free depressed patients comparing them to matched controls, and found significant results both for "loss of libido" and for "excessive libido". In a 2006 study by Lykins et al. conducted on 663 female college students and specifically addressing sexual desire and arousal,

results showed a paradoxical effect of depressive symptoms on women's sexual function: while 50.5% reported experiencing a decrease in sexual desire when depressed, 9.5% reported experiencing an increase in sexual desire under the same conditions. Reports of decreased sexual arousal when feeling depressed were less frequent, with about one-third of the women saying that their sexual arousal decreased. Taken together, these data suggest that depressive symptoms can be accompanied by dysregulation in sexual function both in terms of desire and arousal, manifesting as either excessive or diminished sexuality.

Although many studies have been conducted on the effects of depressive symptoms on male's sexual function, less attention has been paid to women, especially women with vulvovaginal pain. Among the few studies investigating this topic in women with vulvar pain, results are still lacking. For example, findings from two cross sectional studies conducted on women with genitopelvic pain would corroborate the hypothesis that depressive symptoms do have a negative impact on sexual function in patients, with correlations of r = -0.29 between depression and sexual function and r=0.49 between depression and sexual distress (Maillé et al., 2015; Pâquet et al., 2016 respectively). Overall, these results suggest that depressive symptoms are significantly associated with a decline in sexual function among women with vulvovaginal pain.

While results from cross-sectional studies are consistent, it is important to acknowledge that such study design does not allow the authors to draw causal conclusions between the analyzed variables. To obviate these problems, other authors addressed a similar research question with prospective daily diary studies, which in turn allow for the assessment of within-person variations over time and the exploration of causal relationships. For example, Pâquet et al. (2018) recruited 127 women diagnosed with

vulvodynia and their partners, and asked them to complete daily measures for eight weeks. The authors examined how daily deviations in anxiety and depressive symptoms from both women and their partners' own mean were associated with pain, sexual function, and sexual distress. With regard to both partners' sexual function, only women's appeared to be shaped by their mood, since it turned out to be more positive on days when women felt less anxious and depressed. As for the couple, neither of them reported being influenced by their partner's affective symptoms on their sexual function. The variable which resulted most influenced by the other member of the couple was sexual distress. While anxiety didn't have an impact on women's distress during sexual activity, depression did, as shown by the fact that on days in which women felt less depressed, they related less sexual distress. On the other hand, the absence of anxiety and depressive symptoms in partners had an impact in lowering both their own and women's sexual distress, while women's ones were not associated with the sexual distress of their partners. Overall, although the lack of anxiety and depression in both partners seemed to reduce overall sexual distress, it were the depressive symptoms in women that had the most significant impact on their own sexual distress, whereas their mood did not appear to affect their partners' sexual distress (Pâquet et al., 2018).

A similar study was conducted by Glowacka et al. (2018), who recruited 125 women who received a diagnosis of PVD from one of the study's gynecologists and their partners. Participants filled out questionnaires about sexual distress, sexual satisfaction, anxiety, depressed mood, and, for women only, pain during intercourse. The study found that on days when women with PVD engaged in sexual activity, greater sexual distress was associated with greater anxiety ($r = .12$) and depressed mood ($r = .21$). Additionally, women reported lower sexual satisfaction and greater pain during intercourse on days

when they experienced higher levels of anxiety and depressed mood. Even though the effect sizes are smaller compared to those in the study by Pâquet et al. (2018), results from this study align with previous findings suggesting that depressed mood, more than anxiety, could negatively impact sexual function in women with PVD.

Crucially, when examining the existing literature on the effects of anxiety and depression on the sexual function of women with vulvovaginal pain, several significant limitations become apparent. First, in the studies discussed earlier, researchers assessed sexual function using the overall score of the FSFI. While this is a practical approach for analyzing data, it doesn't allow for differentiation among the various aspects of female sexual function, such as sexual desire and arousal. This distinction between the 7 subscales of the FSFI is particularly important, given the variations among these factors. However, research that specifically addresses this differentiation remains scarce.

Another important aspect which contributes to limiting previous findings on this topic is the fact that many daily studies, aiming at capturing temporal patterns, reducing recall bias, and providing a more accurate and contextual understanding of participants' experiences and behaviors, often ask them to complete measures of sexual function only on days of sexual activity. For example, in Glowacka et al.'s study, participants completed measures of anxiety and depressed mood every day, but assessments of sexual distress and sexual satisfaction were taken only on the days of sexual activity with their partners. This selective data collection can be problematic because it excludes crucial information on sexual function on days when no sexual activity occurs, potentially leading to a biased understanding of sexual function and its relationship with emotional states like anxiety and depression. By limiting data collection to active sexual days, researchers might miss patterns or factors that contribute to the absence of sexual activity, such as underlying

stress, fatigue, or relationship issues. This approach can skew results, preventing a full picture of how sexual function is influenced by a range of variables over time. Additionally, it can lead to an overemphasis on days of sexual activity, reinforcing heteronormative or activity-based assumptions about sexual health and missing out on the full range of human sexual experiences and behaviors.

An illustration of an effort to address these limitations is a study conducted by Bittoni and Kiesner (2022), which was conducted on a sample of 213 healthy women. Participants completed daily questionnaires for approximately 2 months regarding their negative mood symptoms and their sexual desire, while controlling for the influence of the menstrual cycle. Overall, the authors found an average effect of decrease in sexual desire as negative mood symptoms increased. Nevertheless, results from this study brought to light the importance of monitoring individual differences among participants. Basing their analyses on the associations between negative mood symptoms and sexual desire, the authors identified three distinct clusters: the Negative Linear cluster, comprising the largest group, exhibited a consistent negative linear trend, indicating a decrease in sexual desire as negative mood symptoms increased. The Negative Accelerating cluster, the second largest group, displayed a flat slope with a rapidly accelerating negative trend, suggesting a more pronounced decline in sexual desire with escalating negative mood. Lastly, the Positive Paradoxical cluster, the smallest group, demonstrated a paradoxical effect where both high and low levels of depressed mood were associated with increases in sexual desire, highlighting a unique pattern of response within this subgroup. These clusters provide valuable insights into the diverse ways in which women's sexual desire may be influenced by varying levels of negative mood symptoms, underscoring the importance of considering individual differences in

understanding the complex interplay between mood and sexual desire (Bittoni and Kiesner, 2022).

While Bittoni and Kiesner's (2022) study addresses some previous limitations, its focus on healthy women means it does not consider clinical populations, particularly those with vulvovaginal pain. However, the findings discussed in this chapter emphasize the importance of further investigating how negative mood affects sexual desire and arousal in women with vulvodynia. This thesis seeks to bridge this research gap by addressing the methodological issues found in earlier studies. In the following sections, I will outline the aims and methodology of this thesis, demonstrating how it aims to overcome past challenges and contribute to a deeper understanding of this complex topic.

2.4 Current study

As previously mentioned, the present study aims to replicate findings from Bittoni and Kiesner (2022) in a distinct symptomatic population, expecting similar effects of mood symptoms on sexual desire and arousal compared to healthy women. More specifically, the previous study identified a significant average effect across the entire sample, indicating that depressed mood and anxiety were associated with decreased sexual desire (Bittoni and Kiesner, 2022). However, the authors found substantial individual variability among women, suggesting that average effects did not fully capture the relationship between mood and sexual desire (Bittoni and Kiesner, 2022). Therefore, we anticipated our results in women with vulvovaginal pain to align significantly with those reported in healthy women, reflecting similar patterns of association between mood and sexual desire and arousal.

The present study and Bittoni and Kiesner's (2022) study can be compared because both conducted daily assessments of anxiety, depressed mood, and sexual desire over a period of approximately two months per participant. Both studies explore the relationship between mood fluctuations and changes in sexual desire at the group level (average effects) and for each participant individually (individual differences). An important difference to be stated is that while Bittoni and Kiesner's (2022) study statistically controlled for the effect of the menstrual cycle on participants' data, the same thing wasn't possible for the present data as there weren't enough observations given by participants regarding their menstrual cycle. More specifically, upon examination of the distribution of the variable "menstrual cycle", there appears to be a clear absence of data, rendering it inconclusive and thus excluded from analysis.

Additionally, this study introduces a crucial element in the study of sexual desire, which is "desire to masturbate". In fact, in our questionnaire we specifically asked about participants' desire to masturbate as a distinct aspect of sexual desire. This approach was justified by a theoretical distinction of sexual desire, which will be briefly explained here and respected in the subsequent analyses, conducted separately for each question. Traditionally, probably because of a lack of consensus on its definition, sexual desire has often been measured either with a single dichotomous answer (for example, Laursen et al. 2006) or through the frequency of sexual intercourse (for example, Harvey, 1987). Nevertheless, both these approaches have theoretical limitations. To start with, relying solely on single dichotomous questions overlooks the various nuances inherent within this complex construct. Secondly, relying on the frequency of sexual intercourse as a proxy for sexual desire overlooks the multifaceted nature of women's sexual experiences, as it disregards the possibility that engagement in sexual activity may be influenced by

factors beyond spontaneous desire, such as partner availability, and fails to acknowledge the potential persistence and accumulation of unfulfilled desires over time (Meston and Buss, 2007). Moreover, the inclusion of "desire to masturbate" as a component of sexual desire provides a more direct measure of an individual's inclination for experiencing sexual pleasure, free from interpersonal influences such as intimacy (Basson, 2002). This aspect of desire is distinct from the previously cited one in that it is not contingent upon relationships or emotional connections with others, thus offering a clearer indicator of the desire for sexual gratification.

Overall, the current study seeks to address the limitations observed in previous research by adopting a more nuanced approach to measuring sexual desire and arousal, especially in women with vulvovaginal pain. Previous studies often relied on cross-sectional designs or limited their data collection to days of sexual activity, which can result in biased understandings of sexual function and its relationship with mood. For example, studies such as those by Glowacka et al. (2018) and Pâquet et al. (2018) demonstrated correlations between mood symptoms and sexual function but did not capture the full spectrum of daily variations in sexual desire and arousal. Furthermore, the study by Bittoni and Kiesner (2022) highlighted the need for considering individual differences when examining the impact of mood on sexual desire. Their identification of distinct clusters of women based on their mood and sexual desire relationships underscores the complexity of these interactions. By focusing on a clinical population of women with vulvovaginal pain, the present study aims to extend these findings and explore whether similar individual differences can be observed in this group.

In conclusion, the present study aims to replicate and extend the findings of previous research by adopting a daily diary method to assess the impact of mood

symptoms on sexual desire and arousal in women with vulvovaginal pain. By incorporating the "desire to masturbate" as a distinct measure of sexual desire, this study seeks to provide a more comprehensive understanding of the nuances of sexual desire and its relationship with mood in this population. This approach will help to address the limitations of previous research and contribute to a deeper understanding of the complex interplay between mood and sexual function in women with vulvovaginal pain.

CHAPTER 3. METHOD

The present thesis draws upon findings from the comprehensive research project "Luci e Ombre della Sessualità e Salute Genitale Femminile," conducted by the Padova Sex Lab. The study aimed at looking into the psychological, social, and medical aspects of female sexual behavior and habits, including pain perception and genital health. More specifically, it was designed to look at the characteristics and prevalence of female genito-pelvic region problems as well as vulvar/vaginal discomfort. The information collected in this study aims to better understand how biological, psychological factors, sociocultural factors might affect vulvovaginal pain, in order to hopefully find ways to either reduce or manage such pain. The University of Padova Psychological Research Ethics Committee gave its approval for the study, which was held completely online through different surveys. In the following sections, I will discuss the participants, procedure, and measures utilized in this study.

3.1 Participants

Participants for the present study were recruited based on two inclusion criteria: 1) being assigned female at birth and 2) being 18 years of age or older. Recruitment was carried out both in-person and online. Moreover, an invitation to participate in the study was spread through the Instagram page @padovasexlab, created by our research group in order to promote awareness on issues related to sexuality and genital health. More specifically, the first phase of the study comprised a sample of 2901 participants. Out of the initial 2901 participants, 448 (15.44%) appeared to suffer from genitopelvic pain and continued with the study by completing the second questionnaire. Finally, 258

participants chose to download the Vulvae App and proceeded to the third phase of the study, which involved submitting daily reports for 60 days. However, in order to face the problem of insufficient data we decided to exclude participants with fewer than 40 days of observations, resulting in the exclusion of 195 participants and leaving 63 participants. This criterion also reduced the total number of observations from 5831 to 4120. Additionally, 13 of the remaining participants did not provide their birth dates. Thus, the average age of the 50 participants who did provide their birth dates was 29.28 years. Regarding sexual orientation, the majority identified as heterosexual (64%), followed by bisexual and bicurious (each at 12%), then pansexual (6%), fluid (4%), and asexual (2%). We also inquired about the age at which participants first had sex, and the responses indicated that the average age was 18.6 years, with a standard deviation of 2.94 years. Additionally, when asked about the age at which they first masturbated, participants reported an average age of 16.7 years, with a standard deviation of 4.39 years.

3.2 Procedure

The present research was divided into three sections, each one requiring participants to complete one or more online surveys. Before the beginning, a form for informed consent was presented, which details the processing and anonymity of the data and ensures that it will only be used for the intended research with full confidentiality. By providing consent, participants certified they were more than 18 years old, they had agreed to participate in the study willingly, they were aware of the project's goals and that their data will be treated with secrecy. Moreover, once they submitted the questionnaire, they were not able to get their data back.

First questionnaire. By scanning the QR-code, participants had access to the first phase of the study, found on Qualtrics digital platform. Opening a link first led to a video, prepared by the Padova Sex Lab students in order to briefly explain the objectives of the study and to encourage participation. Following the video and the consent, participants could fill out the first questionnaire, which took about 15 minutes. The first questionnaire was divided into 8 main parts: Demographic information and general health (17 questions); Menstrual health and contraceptive use (7 questions); Pain, hygiene and genital health (10 questions); Physical symptoms (15 questions); Depressive symptoms (12 questions); Anxiety (8 questions); Sexual behaviors and attitudes (25 questions); Negative sexual experiences (3 questions). If participants' responses indicated that they are experiencing vulvar/vaginal pain, they were invited to proceed to the next phase of the study, which involved completing a second questionnaire to gather more detailed information about their pain experience. Before accessing the second questionnaire, participants were shown a new video, in which they were thanked for their participation and were given the opportunity to answer additional questions.

Second questionnaire. The second phase of the study again started with a brief explanation of the structure and the topics explored in this section. Before starting the compilation, which took 15 minutes, participants were asked to give their email address, which was used to pair data from different questionnaires. The second questionnaire again was composed of 8 main parts: Body image (3 questions); Sentimental relationship (9 questions); Emotions and thoughts related to pain (24 questions); Concerns and influences on sexuality (26 questions); Influences on daily activities (5 questions); Strategies for coping with pain (21 questions); General emotions (12 questions); Social support (4

questions). At the end of the second questionnaire, participants were given the opportunity to leave a comment or suggestion regarding the study. Afterwards, they were thanked and invited to access the third and final stage of the research. The methods and features of the latter were explained in a new video, made like the previous ones.

Third questionnaire. The final phase of the study was accessible through an app called "Vulvae", created by the French research team Les Observables SAS and dedicated to vulvar health and vulvar pain. Once they downloaded the app, participants were asked to fill out a short daily questionnaire lasting about 3 minutes for two months, in order to collect data useful for monitoring genital pain. Not only was this data useful for the study, but also for participants themselves. If participants said they wanted to proceed, they were sent the link to download the app and a password in order for them to access it for free. To avoid missing data, each day the app sent a notification to remember participants of the completion. The questionnaire is divided into 7 main parts, each question referring to the last 24 hours: Genital pain (8 questions); Menstruation (2 questions); Mood (13 questions); Physical symptoms (12 questions); Sexual response (16 questions); Daily habits/hygiene (10 questions); Genital pain treatment and care (6 questions). At the end of two months, participation in the study is completed.

3.3 Measures

Measures presented below are those relevant to the purposes of this thesis.

Depressive symptoms. Depressive symptoms were measured with two questions, namely "how much have you felt depressed?" and "how much have you felt sad?". Both questions

referred to the previous 24 hours. Each question was measured through a 5-points scale from 0 to 4. With regards to the first question, results showed a mean answer of M= 0.73, with a standard deviation of SD = 1. A similar result was found for the second question, which in turn displayed a mean answer of M = 1.06 with a standard deviation of SD = 1.10. These two questions were combined together to create the reference variable "depressive symptoms", whose mean in our sample was M = 0.89, SD = 1.01.

Anxiety symptoms. Anxiety symptoms were measured with two questions, namely "how much have you felt nervous?" and "how much have you felt tense, on edge?". Both questions referred to the previous 24 hours. Each question was measured through a 5-points scale from 0 to 4. With regards to the first question, results showed a mean answer of M = 1.24, with a standard deviation of SD = 1.16. However, mean answers for "tense, on edge" were M = 1.47, with a standard deviation of SD = 1.18. These two questions were combined together to create the reference variable "anxiety symptoms", whose mean in our sample is M = 1.36, SD = 1.05.

Sexual desire. Sexual desire was measured with two questions, each referring to the previous 24 hours. Participants were asked to rate their "desire to have sex" and "desire to masturbate" on a scale from 0 = "No desire" to 4 = "Very high desire". "Desire to have sex" was coded in the variable "sexual desire, libido", whose mean in our sample resulted to be of M = 0.78, with a standard deviation of SD = 1.06. On the other hand, the mean value for "desire to masturbate" was M = 0.44, with a standard deviation of SD = 0.88.

Sexual arousal. As stated in Chapter 2, sexual arousal is a complex construct that encompasses two key components: subjective arousal and genital arousal. In the present study, we measured both constructs only on days in which participants reported an engagement in sexual activity, being it alone (masturbation) or with a partner (sexual intercourse). Genital arousal was addressed with the question "level of genital arousal (lubrication, wetness) during sexual activity", while subjective arousal was addressed with the question "level of mental arousal (feeling turned on) during sexual activity". For each question participants rated their arousal levels on a scale ranging from 0 = "Absent" to 4 = "Very high". In our sample, the mean value for mental arousal was M = 2.08, with a standard deviation of SD = 1.26.

CHAPTER 4. RESULTS

4.1 Data analysis

The aims of the following analyses are 1) to investigate the influence of daily variations of depressive and anxiety symptoms on participants' sexual desire and arousal, and 2) to compare the present results with those of Bittoni and Kiesner (2022)'s study, which was conducted on healthy women. In the present analyses, we utilized JMP Pro 15 software (SAS Institute, 2019) to perform mixed models analysis. We examined both the linear and quadratic effects of mood (specifically, depressed mood and anxiety). These effects were treated as both fixed effects (representing average effects across the entire sample) and random effects (estimated independently for each participant, allowing for the assessment of individual differences across participants). Regarding the effects of depressed mood and anxiety on sexual desire and arousal, we examined both the linear and quadratic (curvilinear) associations to understand whether these mood states are associated with changes in sexual desire and arousal, and if so, whether those associations are linear or nonlinear. These associations may take various forms, including linear slopes, U-shaped or inverted U-shaped slopes, representing the relationship between mood symptoms and sexual desire and arousal.

4.2 Results

Results will be exposed as follows: first, I will present results from the correlations among analyzed variables of the present study in a table, namely Table 3. Then, I will present results obtained with regards to sexual desire, desire to masturbate and finally those regarding sexual arousal.

Table 3. Correlations among variables of the present study.

	Depressed	Sad	Nervous	Tense, on edge	Sexual desire	Desire to masturbate	Mental arousal
Depressed	-						
Sad	.701	-					
Nervous	.377	.407	-				
Tense, on edge	.428	.426	.610	-			
Sexual desire	-.102	.073	.059	-.087	-		
Desire to masturbate	-.034	.004	.094	-.024	.617	-	
Mental arousal	.079	.137	.038	-.237	.737	.390	-

4.2.1 Sexual desire (libido)

Results from the mixed model analysis are presented in Table 1, Table 1.1 and Table 2. Each table is constructed in a similar manner: in the top half of the table are presented results obtained using depressive symptoms as a predictive variable, while results obtained when using anxiety symptoms as the predictive variable are shown in the bottom half. Additionally, the table is further subdivided into fixed and random effects, shown in the top half and bottom half of each set of analyses respectively. Results from each table will be extensively explained in the following paragraphs, starting with Table 1, where results from the analyses conducted treating sexual desire as the dependent variable are illustrated.

Findings concerning depressed mood reveal significant results for both fixed and random effects. The linear coefficient is significant (-0.18), indicating that an increase in depressed mood is associated with a decrease in libido across the entire sample. However, the quadratic effect is not significant, suggesting the absence of a curvilinear association between the variables. Thus, on average, an increase in depressed mood is associated with a decrease in libido in the studied sample, but there is no evidence of a curvilinear

association between the two variables. Nevertheless, tests for random effects unveil another important consideration. The intercept exhibits significant variation (0.47), indicating substantial variability between subjects. Moreover, there is significant variation in the linear effect between subjects (0.12), but not in the quadratic effect. Such significant variation is graphically presented here in Figure 1, where each color represents a single participants' result. In summary, random effects demonstrate significant variations in the intercept and linear effects among subjects, implying that the impact of depressed mood on libido may vary from person to person.

With regard to anxiety, results show a similar pattern. Within fixed effects, a significant coefficient was found in the linear but not quadratic effect. Hence, on average, across the entire sample, there exists a notable negative correlation of -.19 between anxiety and sexual desire. However, random effects differ from those of depressive mood in that both linear and quadratic associations are significant. This suggests that there are significant variations among individuals regarding both the linear and quadratic impacts of anxiety on sexual desire, and average effects alone cannot sufficiently capture these associations across individual participants. Quadratic associations between anxiety and sexual desire for each participant are here represented in Figure 2.

Table 1. Coefficients and test statistics for mixed model for sexual desire (libido), with fixed and random effects.

Predictor	Coefficient	Variance Component	t	95% CI Wald p
Depressed Mood				
Fixed Effects				
Intercept	0.92		9.90***	
Depressed Mood	-.18		-2.87*	
Depressed Mood ^{2}	.025		1.50	
Random Effects				
Intercept		.47		.29 - .66***
Depressed Mood		.12		.02 - .21*
Depressed Mood ^{2}		.005		-.001 - .011
Residual		.71		.68 – .75
Anxiety				
Fixed Effects				
Intercept	1.05		10.01***	
Anxiety	-.19		-3.10*	
Anxiety ^{2}	.01		0.61	
Random Effects				
Intercept		.57		.32 - .84***
Anxiety		.08		.001 - .17*
Anxiety ^{2}		.005		.000 - .011*
Residual		.707		.67 – .74

* p < .05; **p < .001; ***p < .0001.

Fixed Effects dfs for Depressed Mood: Intercept df = 60.2; Depressed Mood df = 46.0; Depressed Mood^2 df = 36.7.

Fixed Effects dfs for Anxiety: Intercept df = 50.1; Anxiety df = 45.1; Anxiety^2 df =57.1.

Fig. 1. Individual variability across linear associations between depressive mood and sexual desire (libido) in the analyzed sample, whereby each line represents a single participants' score.

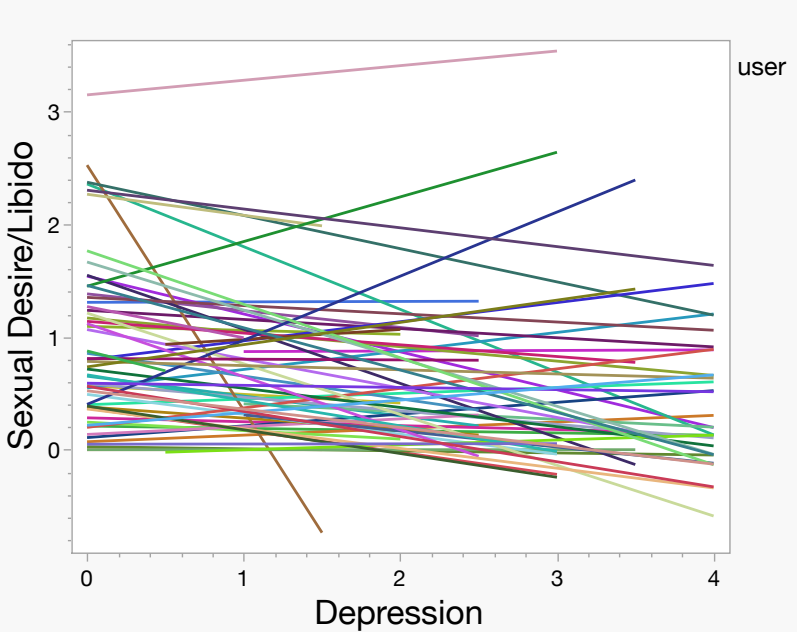
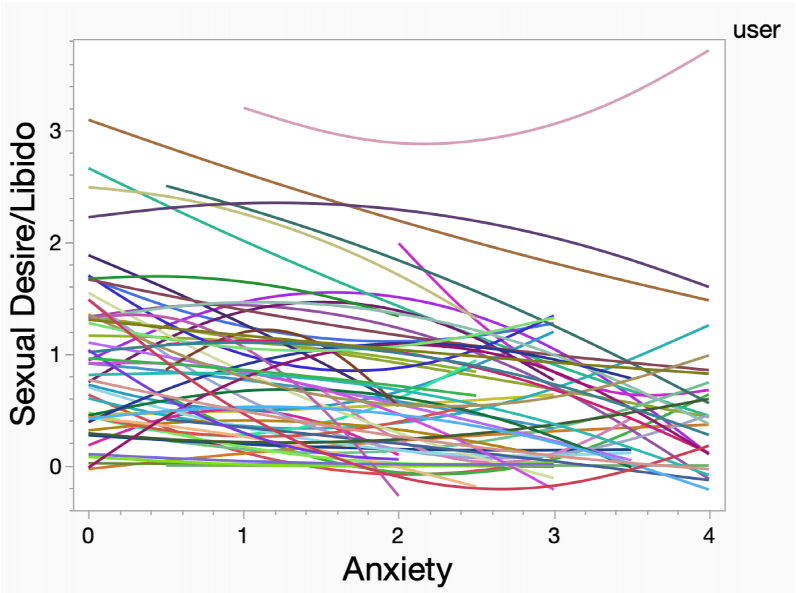


Fig. 2. Individual variability across quadratic associations anxiety depressive mood and sexual desire (libido) in the analyzed sample, whereby each line represents a single participants' score.



4.2.2 Desire to masturbate

Results obtained using desire to masturbate as the predictive variable are shown in Table 1.1, whose structure has already been explained in the previous paragraph. When comparing the results for the desire to masturbate with those for sexual desire, distinct patterns emerge regarding both depressive mood and anxiety. Beginning with the fixed effects of depressive mood, neither the linear nor the quadratic effects are significant. The lack of significance in the linear coefficient suggests no evidence for a linear relationship between depressive mood and the desire to masturbate. Similarly, the non-significance of the quadratic effect indicates no significant change in slope for the quadratic relationship. However, the linear association is significant in terms of random effects, indicating variability among subjects in how their mood influences their desire to masturbate. Conversely, the lack of significance for the random effect of the quadratic association suggests no significant variation among subjects in the curvature of this relationship. To sum up, while individuals vary in how their mood directly influences their desire, there is no significant variation in the curvature of this relationship across subjects.

Results for anxiety follow a comparable, though not identical, trend. In terms of fixed effects, the pattern mirrors that of depressive mood: the linear coefficient lacks significance, suggesting no evidence of a linear relationship between anxiety and the desire to masturbate. Additionally, the quadratic effect is also non-significant, indicating the absence of a significant quadratic relationship. In essence, these results imply that anxiety does not show a linear or quadratic association with the desire to masturbate. Nevertheless, when looking at random effects, we found a significant value for both linear and quadratic effects of anxiety, meaning that the average effect fails to sufficiently capture these connections among individual participants.

Table 1.1 Coefficients and test statistics for mixed model for desire to masturbate, with fixed and random effects.

Predictor	Coefficient	Variance Component	t	95% CI Wald p
Depressed Mood				
Fixed Effects				
Intercept	0.46		6.35***	
Depressed Mood	.01		0.19	
Depressed Mood ^{2}	-.01		-0.68	
Random Effects				
Intercept		.28		.17 - .39***
Depressed Mood		.099		.029 - .168*
Depressed Mood ^{2}		.005		-.000 - .011
Residual		.5		.47 – .52
Anxiety				
Fixed Effects				
Intercept	.52		6.80***	
Anxiety	-.08		-1.96	
Anxiety ^{2}	.009		0.75	
Random Effects				
Intercept		.30		.17 - .43***
Anxiety		.006		-.03 - .04
Anxiety ^{2}		.001		-.001 - .005
Residual		.505		.48 – .53

* p < .05; **p < .001; ***p < .0001.

Fixed Effects dfs for Depressed Mood: Intercept df = 60.9; Depressed Mood df = 53.7; Depressed Mood^2 df = 39.6.

Fixed Effects dfs for Anxiety: Intercept df = 57.2; Anxiety df = 34.0; Anxiety^2 df =40.1.

4.2.3 Sexual arousal

As outlined in the methodology section, the present study addressed arousal through both genital (lubrication) and subjective (mental) arousal. Nevertheless, we asked about both types of arousal only on days of sexual activity, which led to a significant reduction in analyzable data. When entering genital arousal within the mixed model, the model did not converge, leaving only mental arousal to be analyzed. Moreover, the same thing happened when trying to analyze the relationship between mental arousal and depressive mood: the statistical model was evaluated and it did not converge.

Therefore, the only analyses feasible in our sample were the ones investigating the relationship between mental arousal and anxiety, and are here represented in Table 2. In examining fixed effects, neither the linear nor the quadratic coefficients for anxiety reached statistical significance, indicating that, on average, anxiety levels did not predict significant changes in mental arousal difference scores in this sample of women with vulvovaginal pain. However, upon examining the random effects, a different picture emerged. Despite the lack of significance in the fixed effects, both the linear and quadratic coefficients for anxiety were found to be statistically significant at the random effects level. This suggests that while there may not be a consistent overall relationship between anxiety and mental arousal difference scores across the entire sample, there is significant variability among individuals in both the linear and quadratic relationship between anxiety and mental arousal difference scores.

Table 2. Coefficients and test statistics for mixed model for mental arousal, with fixed and random effects.

Predictor	Coefficient	Variance Component	t	95% CI Wald p
Anxiety				
Fixed Effects				
Intercept	2.45		18.68***	
Anxiety	.13		.87	
Anxiety ^{2}	-.08		-1.49	
Random Effects				
Intercept		.60		.52 - .68***
Anxiety		-.01		-.01 - .01***
Anxiety ^{2}		.008		.007 - .009***
Residual		.585		.51 – .67

* p < .05; **p < .001; ***p < .0001.

Fixed Effects dfs for Anxiety: Anxiety df = 419; Anxiety^2 df = 419.

CHAPTER 5. DISCUSSION

In this section, I will now discuss results from the present study, which were detailed in the previous chapter. The present investigation focused on the impact of negative mood on sexual desire and arousal among women suffering from vulvovaginal pain. Key findings include a significant negative association between depressive symptoms and sexual desire, as well as considerable variability in this relationship across individuals. Similarly, anxiety symptoms showed a significant negative linear association with sexual desire, with notable individual differences. Interestingly, depressive and anxiety symptoms did not show a significant linear effect on the desire to masturbate, highlighting the complex interplay between mood and solitary sexual activities. Additionally, no significant fixed effects of daily anxiety on mental sexual arousal were found, suggesting unique interactions in this population. Therefore, in the paragraphs that follow, I will first elaborate on the impact of negative mood on sexual desire (libido), including depressive and anxiety symptoms, and their variability across individuals. Next, I will explore the relationship between negative mood and the desire to masturbate, followed by a discussion on the impact of negative mood on sexual arousal. In conclusion, I will emphasize the importance of these findings in understanding sexual health in women with vulvovaginal pain and suggest directions for future research.

5.1 Impact of negative mood on sexual desire (libido)

When looking at the impact of negative mood on sexual desire in our sample of women suffering from vulvovaginal pain, results largely replicate those obtained with healthy women (Bittoni and Kiesner, 2022; Pâquet et al., 2018). As shown in the upper

top of Table 1, depressive symptoms exhibited a significant negative linear association with sexual desire. Therefore, generally speaking, sexual desire decreases as women become more depressed in our sample. This not only is in line with previous results from Bittoni and Kiesner (2022), but also with past research showing an association between mood disorders and decreased sexual desire in healthy women (Angst, 1998; Beck, 1967; Figueira et al., 2001). For example, a study by Angst (1998) involving a sample of both non-depressed and depressed participants found that sexual problems concerning libido were present in 45% of non-treated depressed patients and 63% of treated depressed patients, compared to a lower prevalence of 26% in non-depressed subjects. This negative link between depressive symptoms and a diminished libido is of no surprise as depression is often associated with diminished interpersonal behavior (Davidson et al., 1989), anhedonia and fatigue (Pizzagalli, 2014) and social withdrawal (Girard et al., 2014), all of which are relatively important components of interpersonal sexual action.

In light of such previous studies, finding a similar negative correlation in a sample of women with vulvovaginal pain is of no surprise, taking into consideration the additional burden that such pain brings into their lives. To this regard, Pâquet et al. (2018) conducted a daily study on couples coping with vestibulodynia, and found similar results: on days of sexual activity, when women with vulvodynia reported higher depressive symptoms compared to their average, they experienced lower sexual function. Although the study by Pâquet et al. (2018) primarily focused on sexual function as measured by the FSFI general score, rather than specifically addressing sexual desire, it is important to recognize that sexual desire is a crucial component of overall sexual function: while the two variables are distinct, they are often highly correlated.

Of note, as already stated in the first and second chapters of the present thesis, women with vulvovaginal pain are more likely to experience depressive symptoms than are healthy women (Khandker et al., 2011; Iglesias-Rios et al., 2015). In fact, such pain conditions expose them to chronic stressors beyond pain itself, which in turn contribute to depressive symptoms: difficulties in having satisfying sexual relationships, fear of disappointing their partner, and lack of validation of their pain by healthcare professionals are just three examples of the daily challenges that can increase the risk of depression in women with vulvovaginal pain (Chisari et al., 2021; Bergeron et al., 2020). The significant negative association between depressive symptoms and sexual desire in women with vulvovaginal pain sheds light on the pervasive impact of mood disorders on sexual functioning. Replication of results found in healthy women within this specific group emphasizes the robustness of the relationship between mood and sexual desire also in chronic pain population, underscoring the importance of considering psychological factors in research on sexual health, and suggesting that future studies should continue to explore these connections to better understand the comprehensive impact of depression on sexual functioning.

Another important result concerns the significant variability across women in the previously explained negative correlation between depression and sexual desire. Similary to what already found in healthy women (Bittoni and Kiesner, 2022), random effects analyses revealed a significant degree of variability between women in the linear relationship between depressive symptoms and sexual desire. In fact, the significant coefficient of the linear regression highlighted how the fixed effect of negative correlation between depressive symptoms and sexual desire does not adequately capture the variability across women with vulvovaginal pain. When hypothesizing what might be the

cause of such variability, two key points should be pointed out, namely the causes of depressive symptoms and the coping strategies to address them.

Starting with the causes of depressive symptoms, previous literature already highlighted how vulvovaginal pain can itself be a cause of negative mood symptoms (Tribó et al., 2020). Therefore, when the experience of pain becomes prolonged and/or chronic as in our sample, it might exacerbate depressive symptoms, leading to greater variability in sexual desire. In addition to that, since the pain itself may be a cause of depression in many women with vulvovaginal pain, I hypothesize the variability found in its correlation with sexual desire might depend less on the cause of the pain and more on personal motivations and coping strategies employed by women and their partners. Corsini-Munt et al. (2020) investigated sexual goals and coping strategies of women with PVD and their partners. The authors found a significant association between self-focused sexual goals (i.e., personal reasons or motivations for engaging in sexual activities that are centered on the individual's own desires, feelings, or needs rather than solely focusing on the partner or the relationship) and depressive symptoms for both women and their partners. Specifically, women with higher self-focused avoidance sexual goals and men with higher self-focused approach goals experienced higher depressive symptoms. This indicates that the personal motivations for sexual activity can impact depressive symptoms differently among partners dealing with vulvovaginal pain. Moreover, the study by Corsini-Munt et al. (2020) takes into consideration coping strategies in understanding the impact of depression on couples' sexual desire: effective coping strategies, such as communication, emotional support, and mutual understanding between partners, can mitigate depressive symptoms and their impact on sexual desire. Therefore, although in the present analyses we did not control for personal motivation or coping

strategies, a possible data interpretation based on previous literature underscores the role of individual and relational factors in shaping this variability: the interplay between personal motivations, coping strategies, and partner interactions can significantly influence how depressive symptoms affect sexual desire, explaining why some women may experience this relationship differently than others.

Results concerning the impact of anxiety on sexual desire show a similar pattern. Fixed effects analyses displayed a significant negative linear association between anxiety and sexual desire in our sample, meaning that as anxiety increased, sexual desire decreased. As already discussed for depressive symptoms, in order to better understand the possible reasons behind this negative association it is important to reflect upon the different causes of anxiety and its distribution in our sample. Not only did previous research already show a significant prevalence of anxiety symptoms in women with vulvovaginal pain, but it also demonstrated how such anxiety is oftentimes linked to pain or pain-derived sexual dysfunction (Tribó et al., 2020; Mautz et al., 2022). Therefore, the negative association between anxiety and sexual desire can possibly be attributed to the fact that while healthy individuals might experience anxiety unrelated to physical pain, which might not significantly interfere with their sexual desire, women with vulvovaginal pain often suffer from anxiety that is directly linked to their pain. In fact, previous literature has focused on pain-related anxiety, which includes forms such as pain catastrophizing, where individuals magnify the threat and feel helpless about their pain (Burri et al., 2020). This type of anxiety discourages engagement in sexual activities and reduces sexual desire and libido (Burri et al., 2020). The chronic nature of vulvar pain can lead to persistent worry and fear about experiencing pain during sexual intercourse, creating a cycle where anxiety and pain perpetuate each other, further diminishing sexual

desire. Moreover, anxiety experienced by these women is likely to be directly connected to their sexual dysfunction, thus explaining the negative association with sexual desire observed in our sample.

In Chapter 2, I emphasized the importance of distinguishing between different types of anxiety, as each type is more likely to be experienced within specific contexts. In particular, I explored the concept of "body exposure anxiety", which is closely related to body image (Maillé et al., 2014). As we move into the discussion and interpretation of the data, I believe it is important to revisit this concept, as it serves as a clear example of how contextualized anxiety may significantly contribute to the reduction of sexual desire in women experiencing vulvovaginal pain. In fact, although body exposure anxiety and, more generally, body image anxiety is common among healthy women, women with vulvovaginal pain are more frequently and intensely affected by these types of anxiety (Maillé et al., 2014). In a definition given by Maillé et al. (2014), body exposure anxiety involves worry and distress related to one's body perception and exposing one's body to others, especially during sexually-exposed moments. Although in our daily study we did not measure this specific construct, it is plausible that body image anxiety might be closely linked to the experience of pain, anxiety, and consequently, the reduction in sexual desire in our sample. Women with vulvovaginal pain might feel particularly self-conscious and anxious about their bodies, which can exacerbate their pain experience and further diminish their libido and sexual engagement. This hypothesis underscores the complexity of factors contributing to the relationship between anxiety and sexual desire, suggesting that future research should consider body image issues when examining the psychological aspects of sexual dysfunction in women with vulvovaginal pain.

In addition to significant fixed effects, we observed significant random effects for both anxiety and the quadratic term of anxiety in our sample. Significant results for random effects for anxiety imply that the relationship between anxiety and sexual desire varies across individuals: although there exists a general trend of decreasing sexual desire with increasing anxiety, the strength of this association is not uniform across all women. Some women may experience a stronger negative impact of anxiety on sexual desire, while for others, the impact might be less pronounced. As for depression, I believe this result brings to light how each person might differ in terms of causes and management of anxiety, regardless of vulvovaginal pain. In fact, such high variability has been echoed in studies involving women without vulvovaginal pain, indicating that the variability in how anxiety impacts sexual desire is not unique to this population (Bittoni and Kiesner, 2022). Therefore, it underscores the importance of recognizing and addressing individual differences when considering the relationship between anxiety and sexual desire in both clinical and research settings.

While the random effect for the quadratic term in depression was not significant, the situation differs significantly for anxiety, further emphasizing the individual differences in the relationship between anxiety and sexual desire. This significant quadratic term suggests that the rate of change in sexual desire relative to changes in anxiety also varies among individuals: for some women, moderate levels of anxiety might have a different impact on sexual desire compared to very high or very low levels of anxiety. This phenomenon, visually depicted in Figure 2 of the previous chapter, echoes findings reported by Bittoni and Kiesner (2022) in their study with healthy women. The inadequacy of a single average slope to fully capture not just the linear correlation between anxiety and sexual desire in each participant, but also the quadratic term, within

our cohort of women with vulvovaginal pain, underscores the persistence of individual variability even in the context of pain. Such variability highlights significant distinctions among women in terms of their response to anxiety regarding sexual desire, emphasizing the risk of overlooking individual differences when addressing pain through clinical protocols without considering the nuanced individual experiences that lie behind it. To conclude, this observation fully supports the hypothesis posited in this study, emphasizing how these women can traverse the entire spectrum of sexual desire across their negative mood. Moreover, it underscores the necessity for a nuanced understanding of individual responses to anxiety, which is imperative to avoid generalized treatments that may overlook the diverse needs and experiences of these women.

5.2 Impact of negative mood on desire to masturbate

While previous research has provided valuable insights into the relationship between mood and sexual desire in healthy women (Bittoni and Kiesner, 2022), in the present study we aimed to explore several dimensions of such relationship, particularly focusing on the distinction between desire for partnered sexual activity and solitary sexual activity. To do so, I will first start with discussing the impact of depression on desire to masturbate and then focus on the impact of anxiety and the desire to masturbate.

One of the key findings of the present study which was discussed before was that depression had a significant negative effect on overall sexual desire. However, interestingly, this significant negative effect was not observed when specifically considering desire for masturbation. This absence of a significant effect for masturbation suggests that the relationship between mood and sexual desire may differ depending on the target of sexual desire, whether it be dyadic (partnered) or solitary sexual activity.

This is in line with existing literature, which has highlighted the importance of distinguishing between solitary and dyadic sexual desire (Dosh et al., 2016a; Peixoto, Lopes, 2023). For example, Frohlich and Meston (2002) have shown that depressed women, as compared to non-depressed women, report higher levels of desire for solitary sexual activity, but not for partnered sexual activity. These insights underscore the complexity of how mood influences sexual desire and emphasizes the need to consider the specific context in which sexual desire manifests.

When discussing findings related to solitary sexual activity, two variables which must be taken into consideration are the presence/absence of interpersonal relationships and pain. In the context of vulvovaginal pain, the presence of a partner as opposed to solitary masturbation can have a strong influence on sexual desire, both in a positive and negative way: partners who are empathetic and communicative about the pain experience can help alleviate anxiety and distress, fostering an environment conducive to sexual intimacy, while partners who lack understanding or pressure for sexual activity may exacerbate feelings of anxiety and discomfort, leading to decreased sexual desire (Corsini Munt et al., 2020; Rosen et al., 2014; Rosen et al., 2015).

Furthermore, the nature of vulvovaginal pain itself can impact the dynamics of sexual desire within the context of partnered versus solitary activities. To this regard, one key aspect can be the sense of control and autonomy that solitary sexual activities afford: in a solitary sexual situation, individuals have complete control over their own bodies and the pace and intensity of sexual stimulation. Moreover, I hypothesize such control can be empowering, especially for women experiencing vulvovaginal pain, as it allows them to engage in sexual pleasure on their terms, without the pressure or expectations often associated with partnered intercourse. In addition to that, solitary sexual activities provide

a private and intimate space for self-exploration and self-pleasure: for women with vulvovaginal pain, who may experience heightened sensitivity or discomfort during sexual intercourse, it is possible that engaging in masturbation can offer a way to explore their own bodies and sexual responses in a safe and comfortable environment, fostering a positive relationship with one's own sexuality and body image in a situation of chronic pain or discomfort.

Additionally, the emotional and psychological aspects of solitary sexual activities may differ from those of partnered intercourse. Masturbation can serve as a form of self-care and stress relief, offering a coping strategy to release tension and promote relaxation. This can be particularly valuable for women with vulvovaginal pain who may experience emotional distress or anxiety related to their condition. Engaging in solitary sexual activities might allow them to focus solely on their own pleasure and well-being, free from the potential performance pressure or emotional complexities that may arise in interpersonal sexual situations. Nevertheless, it is important to note that the random linear effect was significant, indicating that there is high variability with respect to the relationship between solitary sexual desire and depressive symptoms. This means that while masturbation can be an effective coping strategy towards depressive symptoms for some women, providing relief and promoting well-being, it may not be as beneficial for others. As shown in the Results section, such variability is reflected by a significant linear random effect. Taken together, these hypotheses provide a plausible explanation for why we did not observe a significant negative effect of depression on the desire for masturbation, suggesting that the control, autonomy, and personal comfort afforded by solitary sexual activities may mitigate the impact of depressive symptoms on sexual desire.

Within the context of desire to masturbate, results of anxiety symptoms highly resemble those of depression. In particular, neither the linear nor the quadratic fixed effect were significant, meaning that there is no consistent, predictable relationship between anxiety symptoms and the desire to masturbate in our sample. This lack of significance can be partly attributed to the inconsistency of data, but it also suggests that individual differences play a major role, and the impact of anxiety on the desire to engage in solitary sexual activities may vary greatly from person to person. The interpretation of such data turns out to be similar to that of depressive symptoms for two main reasons, which in turn are interconnected with each other: the similarity of results and the high correlation between depressive and anxiety symptoms, which is the present study is of $r = 0.5$ without controlling for nested data. As previously said, one hypothesis for why these results make sense in the context of vulvovaginal pain is that women experiencing this condition may have highly individualized coping mechanisms and sexual responses. For some, masturbation may serve as a therapeutic activity that helps alleviate anxiety by providing a sense of control and a safe space to explore pleasure without the pressure of partnered intercourse. This could lead to an increased desire to masturbate when anxiety levels are high. Conversely, for other women, anxiety associated with vulvovaginal pain might exacerbate feelings of distress and discomfort, making any sexual activity, including masturbation, less appealing. The pain and anxiety could create a negative feedback loop where the anticipation of pain reduces sexual desire, including the desire to masturbate.

An additional point that is important to highlight in this context is that such variability in coping strategies can also depend significantly on individual and cultural attitudes towards masturbation in general. Cultural norms and societal messages about sexuality can shape personal beliefs and comfort levels that women have with

masturbation, with or without genitopelvic pain. In cultures or communities where masturbation is more stigmatized or considered as a taboo, women might feel guilt or shame about engaging in it, which could further exacerbate anxiety and reduce the likelihood of using masturbation as a coping mechanism. Conversely, in more sex-positive cultures where masturbation is viewed as a natural and healthy part of sexual expression, women may be more likely to embrace it as a form of self-care and anxiety relief. These cultural attitudes, combined with personal experiences and psychological factors, create a complex and highly individualized landscape for how women with vulvovaginal pain navigate their sexual health and well-being.

In summary, our study reveals an intricate link between mood and sexual desire among women with vulvovaginal pain. The divergent outcomes observed between sexual desire (libido) and desire to masturbate underscore the necessity for a finer dissection of this construct both at the theoretical and data analysis levels. While we found no significant linear effect of depressive or anxiety symptoms on the desire to masturbate, the presence of significant random effects suggests a notable variability among individuals. This underscores the importance of considering individual differences and the potential influence of unobserved factors on the relationship between mood and solitary sexual activities.

5.3 Impact of negative mood on sexual arousal

We will now discuss results obtained when entering mental arousal within the statistical mixed model. As explained in the Results section, due to statistical constraints we were only able to calculate the impact of anxiety symptoms on mental arousal, as the model with mental arousal and depressive symptoms did not converge. Once acknowledged that

our data may lack consistency, analyses found no significant fixed effects of daily anxiety on mental sexual arousal. This result is in contrast with several studies conducted on healthy women or those with sexual dysfunctions, which have suggested complex interactions between anxiety and sexual arousal (Barlow et al., 1983; Bradford, Meston, 2006). Nevertheless, as already discussed in Chapter 2, it is of crucial importance to distinguish between subjective and genital arousal, both at the theoretical level and in their relationship with anxiety. With regards to genital arousal, at the experimental level anxiety preexposure increased genital arousal in both sexually functional and dysfunctional women, although subjective arousal decreased, indicating desynchronous patterns between physiological and subjective sexual responses (Palace and Gorzalka, 1990). Similarly, Meston & Gorzalka (1995) demonstrated that sympathetic activation from exercise increased genital arousal, highlighting that physiological arousal can occur independently from subjective anxiety.

These studies collectively suggest that anxiety might facilitate sexual arousal by lowering the threshold for sexual cues (Bittoni & Kiesner, 2022). However, this facilitation is experimentally evident in genital arousal rather than mental arousal, which could explain the discrepancy with our findings. In this context, Barlow (1986) noted that individuals with healthy sexual functioning respond differently to moderate-to-high levels of anxiety compared to those with sexual dysfunctions. This insight is particularly relevant when interpreting our results, as it underscores how anxiety can differentially impact individuals based on their sexual health status. Of note, our analyses are different to those of previously cited studies in that we examined only mental arousal and not genital arousal, and we used daily measures rather than controlled experimental conditions. Such difference is crucial because mental arousal is a subjective cognitive

state that may not align with physiological measures of genital arousal. Therefore, one hypothesis can be that the lack of a significant fixed effect in our study could be due to the unique nature of vulvovaginal pain, which might disrupt the typical anxiety-arousal relationship observed in other populations. Women with vulvovaginal pain may experience anxiety differently and particularly in relation to sexual activity, where anxiety might be more closely tied to pain anticipation and avoidance rather than excitation transfer. This unique context could override the general sympathetic arousal mechanisms described in previous studies on healthy or sexually dysfunctional women (Palace and Gorzalka, 1990; Meston and Gorzalka, 1995). Furthermore, daily measures used in our study capture fluctuations in anxiety and arousal in a real-world setting, providing a more nuanced understanding of these dynamics. Random effects were significant, indicating substantial individual variability and thus suggesting that the relationship between anxiety and mental arousal is highly individualized. Such variability could be influenced by personal factors such as the severity and chronicity of pain, coping mechanisms, and the psychological impact of living with vulvovaginal pain.

Given our sample of women with vulvovaginal pain, there could be two different explanations for the lack of significant fixed effects. The first explanation, already exposed in the previous paragraph, has its focus on the complex interactions between pain and anxiety: in women with vulvovaginal pain, the relationship between anxiety and mental sexual arousal may be influenced by the complex interactions between pain, anxiety, and sexual arousal. Pain itself can be a source of anxiety, and this anxiety might not translate into mental arousal because it is directly linked to a negative experience, which could disrupt the potential for anxiety to lower the threshold for sexual arousal as seen in other studies. Nevertheless, a second possible hypothesis has its focus on

individual variability in pain perception and coping mechanisms: the significant random effects in our study suggest that there is considerable individual variability in how anxiety and mental sexual arousal interact in women with vulvovaginal pain. Some women might have developed coping mechanisms that allow them to separate anxiety from their sexual experiences, while others might experience heightened anxiety that overshadows any potential arousal. Such individual variability might mask any overall fixed effect of anxiety on mental arousal.

With regards to the second hypothesis, an important theoretical reference is given by Engman et al. (2018), who theorized the Fear-Avoidance-Endurance Model (FAEM) and specifically applied it to vulvodynia. According to this model, fear and catastrophizing of pain lead to avoidance of activities that could trigger the pain (Engman et al., 2018). This avoidance, while initially aimed at preventing pain, results in several negative consequences, such as decreased sexual functioning, lower levels of sexual arousal, reduced lubrication, and increased sensitization of nociceptors (the sensory receptors for painful stimuli), which in turn further exacerbate the pain (Engman et al., 2018). Additionally, this cycle of fear and avoidance can worsen the chronic nature of vulvovaginal pain, creating a persistent loop of pain and dysfunction (Engman et al., 2018). In order to illustrate the application of the Fear-Avoidance-Endurance Model (FAEM) in the variability we observed, we can consider two women with vulvodynia, who will be here called “Woman A” and “Woman B”: Woman A experiences anxiety related to her vulvovaginal pain, particularly around sexual activity. According to Engman’s model, Woman A has developed a fear-avoidance pattern: she catastrophizes her pain, which leads her to avoid sexual activity in order to prevent pain episodes. Such avoidance lowers her overall sexual functioning, causing lower levels of sexual arousal

and increased sensitization of nociceptors towards pain. As a result, her anxiety does not translate into mental sexual arousal, but rather into heightened avoidance and decreased arousal. In turn, Woman B also experiences anxiety due to her vulvovaginal pain, but she has adopted a different coping mechanism. In an approach which aligns with the endurance aspect of Engman's model, Woman B uses relaxation techniques and engages in open communication with her partner to manage her anxiety. Thus, her ability to manage her anxiety helps maintain her mental sexual arousal despite her pain. Therefore, daily fluctuations in anxiety have less impact on her mental arousal, showing a more stable sexual functioning compared to Woman A. This example demonstrates how individual differences, influenced by coping mechanisms and the nature of anxiety related to vulvovaginal pain, can lead to different outcomes in mental sexual arousal.

In summary, our study revealed no significant fixed effects of daily anxiety on mental sexual arousal among women with vulvovaginal pain, diverging from findings in healthy or sexually dysfunctional women. This suggests a distinct relationship in this population, potentially influenced by the intricate interplay between pain and anxiety, alongside individual differences in coping strategies. Nevertheless, it is important to underscore that the data for arousal analyses are less extensive than those for desire, as arousal data were only collected on days when sexual activity occurred. Therefore, caution must be exercised in interpreting these results. Once acknowledged such limitations, results from the present study emphasize the need for further investigation into the nuanced mechanisms underlying the association between anxiety and mental sexual arousal in women with vulvovaginal pain, contributing to a more comprehensive understanding of sexual health in this context.

5.4 Limitations and future directions

The present study has several strengths, first of which is the use of daily reports, which allows to capture detailed information and avoid recall bias. Moreover, we also gathered a large amount of data, with 5831 observations from 258 participants, to provide a thorough look at mood symptoms and sexual arousal in our sample. However, there are some limitations to consider, both at the methodological and non-methodological level. First, our sample is nonclinical, meaning participants self-reported their genital pain instead of being medically diagnosed. This allowed us to reach a higher number of women suffering from chronic pelvic pain, but it might limit the generalizability of our findings to clinical settings. Also, all of our questionnaires were in Italian. Therefore, women who couldn't read Italian well were excluded, reducing the ethnic and cultural diversity of our sample. The online format of the study when filling out questionnaires and with the daily Vulvae App required participants to have electronic devices, which might have excluded older women who are less likely to own such devices. Moreover, the length and daily completion of the questionnaire could lead to participant fatigue and missing data, affecting the consistency of the responses we received. Of note, we almost always used predefined response options, meaning participants couldn't fully express their experiences, and leading to a possible oversimplification of their feelings. The initial focus of the study is also important: the present study was indeed designed to give an overall view of genital health, pain, and related psychological and social factors, rather than focusing specifically on the relationship between mood symptoms and sexual arousal. As a result, some variables might have been measured less precisely. Furthermore, there is some information regarding our sample that we did not examine during data analyses and which could have affected our results, such as coping strategies,

personality traits, or differences in autonomic nervous system responses, nor did we control for antidepressant use or hormonal contraception.

All these limitations acknowledged, the present study lays an important groundwork for future directions regarding research on women with vulvovaginal pain. Firstly, the high variability across women highlighted the importance of focusing on individual differences, both in healthy women and in the clinical population. This is mainly possible through the use of daily longitudinal measures as compared to cross-sectional ones, which in turn erase the nuances of individual difference over time. Moreover, the inclusion of a clinical sample of women with vulvovaginal pain extends previous findings in this often-overlooked population, highlighting the necessity for ongoing investigation. Future research should focus on women with pelvic pain to elucidate the underlying causes and broader consequences of vulvovaginal and genitopelvic chronic pain. This approach will contribute to a more comprehensive understanding of these conditions, ultimately aiding in the development of targeted treatments and interventions to improve patient outcomes.

CONCLUSIONS

At the end of this thesis, it is possible to draw some conclusive reflections based on what has been discussed so far, addressing the topic from both a macroscopic and microscopic perspective. Starting with the study conducted with the Padova Sex Lab, its purpose was to investigate how daily variations in psychological factors such as anxiety and depression influence the sexual function of women with vulvovaginal pain, with specific reference to sexual desire and arousal. Most of the findings of the present study are consistent with previous literature on healthy women, such as the negative correlation between negative mood symptoms and sexual desire and arousal, as well as the high individual variability observed among participants. Specifically, I believe it is important to highlight this second result, brought to light by the use of daily measures of symptoms. The significant individual variability observed in our sample not only reflects the importance of including the complex differences among participants as much as possible in scientific studies but also, and especially, within the clinical context of vulvovaginal pain, since each woman may have different symptoms for different reasons and cope with them using different strategies.

Building on this understanding of individual variability, in the present study, we included innovative variables compared to previous literature, such as the "desire to masturbate". Although this construct has been present in previous scientific studies, it has received little attention in vulvovaginal pain research. Nevertheless, results like those obtained in this study highlight not only the importance of analyzing this variable but also of separating it from the more general "sexual desire", especially in light of the substantial interpersonal differences, which become crucial in the context of vulvovaginal pain.

In addition to the aforementioned points, this study was also conducted with a second, though not less important, objective: to shed light on vulvovaginal pain conditions, which have long been rendered invisible. To this regard, a large portion of the first chapter is dedicated to the actual need for studies that closely address these conditions, both from a research and clinical perspective. Therefore, the value of the present thesis lies in its role as a denunciation of issues regarding female sexuality and invisible conditions. In conclusion, the aspiration at the end of this thesis is to contribute to greater awareness and better understanding, ultimately leading to improved care and support for women affected by vulvovaginal pain.

REFERENCES

Alappattu, M. J., & Bishop, M. D. (2011). Psychological factors in chronic pelvic pain in women: relevance and application of the fear-avoidance model of pain. *Physical therapy*, *91*(10), 1542-1550.

Amalraj, P., Kelly, S., & Bachmann, G. A. (2009). Historical perspective of vulvodynia. *Female sexual pain disorders*, 1-3.

Ambler, N., de C Williams, A. C., Hill, P., Gunary, R., & Cratchley, G. (2001). Sexual difficulties of chronic pain patients. *The Clinical journal of pain*, *17*(2), 138-145.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)

Angst, J. (1998). Sexual problems in healthy and depressed persons. *International Clinical Psychopharmacology*, 13(4), S1–S4.

Arnold, L. D., Bachmann, G. A., Rosen, R., Kelly, S., & Rhoads, G. G. (2006). Vulvodynia: characteristics and associations with comorbidities and quality of life. *Obstetrics & Gynecology*, *107*(3), 617-624.

Bachmann, G. A., Brown, C. S., Phillips, N. A., Rawlinson, L. A., Yu, X., Wood, R., ... & Wesselmann, U. (2019). Effect of gabapentin on sexual function in vulvodynia: a randomized, placebo-controlled trial. *American journal of obstetrics and gynecology*, *220*(1), 89-e1.

Baker, P. K. (1993). Musculoskeletal origins of chronic pelvic pain: diagnosis and treatment. *Obstetrics and gynecology clinics of North America*, *20*(4), 719-742.

Barlow, D. H. (1986). Causes of sexual dysfunction: The role of anxiety and cognitive interference. *Journal of Consulting and Clinical Psychology*, 54(2), 140–148.

Barnes, R. (1878). *A clinical history of the medical and surgical diseases of women*. Henry C. Lea.

Basson, R. (2002). Women's sexual desire--disordered or misunderstood?. *Journal of Sex & Marital Therapy*, *28*, 17-28.

Basson, R., Althof, S., Davis, S., Fugl-Meyer, K., Goldstein, I., Leiblum, S., ... & Wagner, G. (2004). Summary of the recommendations on sexual dysfunctions in women. *The journal of sexual medicine*, *1*(1), 24-34.

Battaglia, C., Morotti, E., Persico, N., Battaglia, B., Busacchi, P., Casadio, P., ... & Venturoli, S. (2014). Clitoral vascularization and sexual behavior in young patients treated with drospirenone–ethinyl estradiol or contraceptive vaginal ring: a prospective, randomized, pilot study. *The journal of sexual medicine*, *11*(2), 471-480.

Bazin, S., Bouchard, C., Brisson, J., MOWN, C., Meisels, A., & Fortier, M. (1994). Vulvar vestibulitis syndrome: an exploratory case-control study. *Obstetrics & Gynecology*, *83*(1), 47-50.

Beck, A. T. (1967). *Depression: Clinical, experimental and theoretical aspects*. London: Staples Press.

Bergeron, S., Reed, B. D., Wesselmann, U., & Bohm-Starke, N. (2020). Vulvodynia. *Nature reviews disease primers*, *6*(1), 36.

Binik, Y. M., Meana, M., Berkley, K., & Kalifé, S. (1999). The sexual pain disorders: Is the pain sexual or is the sex painful?. *Annual Review of Sex Research*, *10*(1), 210-235.

Bittoni, C., & Kiesner, J. (2022). Sexual desire in women: paradoxical and nonlinear associations with anxiety and depressed mood. *Archives of Sexual Behavior*, *51*(8), 3807-3822.

Boardman, L. A., & Stockdale, C. K. (2009). Sexual pain. *Clinical obstetrics and gynecology*, *52*(4), 682-690.

Bodenmann, G., & Ledermann, T. (2008). Depressed mood and sexual functioning. *International Journal of Sexual Health*, *19*(4), 63-73.

Bohm-Starke, N., Brodda-Jansen, G., Linder, J., & Danielsson, I. (2007). The result of treatment on vestibular and general pain thresholds in women with provoked vestibulodynia. *The Clinical Journal of Pain*, *23*(7), 598-604.

Bois, K., Bergeron, S., Rosen, N. O., McDuff, P., & Grégoire, C. (2013). Sexual and relationship intimacy among women with provoked vestibulodynia and their partners: associations with sexual satisfaction, sexual function, and pain self-efficacy. *The journal of sexual medicine*, *10*(8), 2024–2035.

Bollen, K., & Lennox, R. (1991). Conventional wisdom on measurement: A structural equation perspective. *Psychological bulletin*, *110*(2), 305.

Bornstein, J., Goldstein, A. T., Stockdale, C. K., Bergeron, S., Pukall, C., Zolnoun, D., ... & International Society for the Study of Vulvovaginal Disease (ISSVD). (2016). 2015 ISSVD, ISSWSH, and IPPS consensus terminology and classification of persistent vulvar pain and vulvodynia. *The journal of sexual medicine*, *13*(4), 607-612.

Boyer, S. C., Pukall, C. F., & Chamberlain, S. M. (2013). Sexual arousal in women with provoked vestibulodynia: The application of laser Doppler imaging to sexual pain. *The Journal of Sexual Medicine*, *10*(4), 1052-1064.

Bradford, A., & Meston, C. M. (2006). The impact of anxiety on sexual arousal in women. *Behaviour research and therapy*, *44*(8), 1067-1077.

Brauer, M., Laan, E., & ter Kuile, M. M. (2006). Sexual arousal in women with superficial dyspareunia. *Archives of Sexual Behavior*, *35*, 187-196.

Brauer, M., ter Kuile, M. M., Janssen, S. A., & Laan, E. (2007). The effect of pain-related fear on sexual arousal in women with superficial dyspareunia. *European Journal of Pain*, *11*(7), 788-798.

Brotto, L., Atallah, S., Johnson-Agbakwu, C., Rosenbaum, T., Abdo, C., Byers, E. S., ... & Wylie, K. (2016). Psychological and interpersonal dimensions of sexual function and dysfunction. *The journal of sexual medicine*, *13*(4), 538-571.

Burri, A., Hilpert, P., & Williams, F. (2020). Pain catastrophizing, fear of pain, and depression and their association with female sexual pain. *The journal of sexual medicine*, *17*(2), 279-288.

Cantarella, E. (2022). *Gli inganni di Pandora*. Feltrinelli Editore.

Cash, T. F., Maikkula, C. L., & Yamamiya, Y. (2004). Baring the body in the bedroom": Body image, sexual self-schemas, and sexual functioning among college women and men. *Electronic Journal of Human Sexuality*, *7*, 1-9.

Chalmers, K. J., Madden, V. J., Hutchinson, M. R., & Moseley, G. L. (2016). Local and systemic inflammation in localized, provoked vestibulodynia: a systematic review. *Obstetrics & Gynecology*, *128*(2), 337-347.

Chisari, C., Monajemi, M. B., Scott, W., Moss-Morris, R., & McCracken, L. M. (2021). Psychosocial factors associated with pain and sexual function in women with Vulvodynia: A systematic review. *European Journal of Pain*, *25*(1), 39-50.

Cohen, S. P., & Mao, J. (2014). Neuropathic pain: mechanisms and their clinical implications. *Bmj*, *348*.

Corsini-Munt Serena, Bergeron Sophie, Rosen Natalie O., Mayrand Marie-Hélène, e Delisle Isabelle. Feasibility and Preliminary Effectiveness of a Novel Cognitive–Behavioral Couple Therapy for Provoked Vestibulodynia: A Pilot Study. *International Society for Sexual Medicine*, 2014.

Corsini-Munt, S., Bergeron, S., Rosen, N. O., Beaulieu, N., & Steben, M. (2017). A dyadic perspective on childhood maltreatment for women with provoked vestibulodynia and their

partners: Associations with pain and sexual and psychosocial functioning. *The Journal of Sex Research*, *54*(3), 308-318.

Crowley, T., Goldmeier, D., & Hiller, J. (2009). Diagnosing and managing vaginismus. *Bmj*, *338*.

Dargie, E. E. (2016). *Constructing the Vulvar Pain Assessment Questionnaire Inventory* (Doctoral dissertation).

Davidson, J., Zisook, S., Giller, E., & Helms, M. (1989). Symptoms of interpersonal sensitivity in depression. *Comprehensive Psychiatry*, *30*(5), 357-368.

Davison, S. L., Bell, R. J., LaChina, M., Holden, S. L., & Davis, S. R. (2009). The relationship between self-reported sexual satisfaction and general well-being in women. *The journal of sexual medicine*, *6*(10), 2690-2697.

Desrochers, G., Bergeron, S., Khalifé, S., Dupuis, M. J., & Jodoin, M. (2009). Fear avoidance and self-efficacy in relation to pain and sexual impairment in women with provoked vestibulodynia. *The Clinical journal of pain*, *25*(6), 520-527.

Dewitte, M., Borg, C., & Lowenstein, L. (2018). A psychosocial approach to female genital pain. *Nature Reviews Urology*, *15*(1), 25-41.

Dewitte, M., De Schryver, M., Heider, N., & De Houwer, J. (2017). The actual and ideal sexual self concept in the context of genital pain using implicit and explicit measures. *The Journal of Sexual Medicine*, *14*(5), 702-714.

Dewitte, M., Van Lankveld, J., & Crombez, G. (2011). Understanding sexual pain: a cognitive-motivational account. *Pain*, *152*(2), 251-253.

Dodson, M. G., & Friedrich, E. G. (1978). Psychosomatic vulvovaginitis. *Obstetrics & Gynecology*, *51*(1), 26s.

Dosch, A., Ghisletta, P., & Linden, M. V. der. (2016a). Body Image in Dyadic and Solitary Sexual Desire: The Role of Encoding Style and Distracting Thoughts. *The Journal of Sex Research* 53(9), 1-14.

Engel George L. The Application of the Biopsychosocial Model. *The American Journal of Psychiatry,* 1980.

Engman, L., Flink, I. K., Ekdahl, J., Boersma, K., & Linton, S. J. (2018). Avoiding or enduring painful sex? A prospective study of coping and psychosexual function in vulvovaginal pain. *European Journal of Pain*, *22*(8), 1388-1398.

Farmer, M. A., Taylor, A. M., Bailey, A. L., Tuttle, A. H., MacIntyre, L. C., Milagrosa, Z. E., ... & Mogil, J. S. (2011). Repeated vulvovaginal fungal infections cause persistent pain in a mouse model of vulvodynia. *Science translational medicine*, *3*(101), 101ra91-101ra91.

Ferritti, V. (2023). Vulvodinia tra invisibilità e invisibilizzazione.: La tortuosa strada per il riconoscimento. *AG About Gender-International Journal of Gender Studies*, *12*(23).

Figueira, I., Possidente, E., Marques, C., & Hayes, K. (2001). Sexual dysfunction: A neglected complication of panic disorder and social phobia. *Archives of Sexual Behavior*, *30*, 369-377.

First, M. B., Spitzer, R. L., Gibbon Miriam, W., & Janet, B. W. (1997). Structured clinical interview for DSM-IV axis I disorders: SCID-I: clinical version.

Fitzpatrick, C. C., DeLancey, J. O., Elkins, T. E., & McGuire, E. J. (1993). Vulvar vestibulitis and interstitial cystitis: A disorder of urogenital sinusderived epithelium?. *Obstetrics & Gynecology*, *81*(5), 860-861.

Foster, D. C., & Woodruff, J. D. (1995). Case-control study of vulvar vestibulitis syndrome. *Journal of Women's Health*, *4*(6), 677-680.

Foster, D. C., Dworkin, R. H., & Wood, R. W. (2005). Effects of intradermal foot and forearm capsaicin injections in normal and vulvodynia-afflicted women. *Pain*, *117*(1-2), 128-136.

Frohlich, P., & Meston, C. (2002). Sexual functioning and self-reported depressive symptoms among college women. *Journal of Sex Research*, 39(4), 321–325.

Galizia Giorgio. Vulvodinia. *Dossier scientifico – Vulvodinia E Neuropatia Del Pudendo: Un Dolore Senza Voce*, 2022.

Gaskin, M. E., Greene, A. F., Robinson, M. E., & Geisser, M. E. (1992). Negative affect and the experience of chronic pain. *Journal of psychosomatic research*, *36*(8), 707-713.

Giesecke, J., Reed, B. D., Haefner, H. K., Giesecke, T., Clauw, D. J., & Gracely, R. H. (2004). Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. *Obstetrics & Gynecology*, *104*(1), 126-133.

Gilbert, R., Widom, C. S., Browne, K., Fergusson, D., Webb, E., & Janson, S. (2009). Burden and consequences of child maltreatment in high-income countries. *The lancet*, *373*(9657), 68-81.

Girard, J. M., Cohn, J. F., Mahoor, M. H., Mavadati, S. M., Hammal, Z., & Rosenwald, D. P. (2014). Nonverbal social withdrawal in depression: Evidence from manual and automatic analyses. *Image and vision computing*, *32*(10), 641-647.

Glowacka, M., Bergeron, S., Delisle, I., & Rosen, N. O. (2019). Sexual distress mediates the associations between sexual contingent self-worth and well-being in women with genitopelvic pain: A dyadic daily experience study. *The Journal of Sex Research*, *56*(3), 314-326.

Goldstein, A. T. et al. Polymorphisms of the androgen receptor gene and hormonal contraceptive induced provoked vestibulodynia. *J. Sex. Med.* 11 , 2764–2771 (2014).

Goldstein, A. T., Pukall, C. F., & Goldstein, I. (Eds.). (2020). *Female sexual pain disorders: Evaluation and management*. John Wiley & Sons.

Gómez, I., Coronado, P. J., Martín, C. M., Alonso, R., & Guisasola-Campa, F. J. (2019). Study on the prevalence and factors associated to vulvodynia in Spain. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *240*, 121-124.

Gordon, A. S., Panahian-Jand, M., McComb, F., Melegari, C., & Sharp, S. (2003). Characteristics of women with vulvar pain disorders: responses to a Web-based survey. *Journal of sex & marital therapy*, *29*(sup1), 45-58.

Govind, V., Krapf, J. M., Mitchell, L., Barela, K., Tolson, H., Casey, J., & Goldstein, A. T. (2020). Exploring pain-related anxiety and depression in female patients with provoked vulvodynia with associated overactive pelvic floor muscle dysfunction. *Sexual medicine*, *8*(3), 517-524.

Graham, C. A., Sanders, S. A., Milhausen, R. R., & McBride, K. R. (2004). Turning on and turning off: A focus group study of the factors that affect women's sexual arousal. *Archives of sexual behavior*, *33*, 527-538.

Graziottin, A. (2006). *Il dolore segreto: le cause e le terapie del dolore femminile durante i rapporti sessuali*. Oscar Mondadori.

Graziottin, A., & Rovei, V. (2007). Sexuality after breast cancer. *Sexologies*, *16*(4), 292-298.

Graziottin, A., Gambini, D., & Bertolasi, L. (2015). Genital and sexual pain in women. *Handbook of clinical neurology*, *130*, 395-412.

Graziottin, A., Murina, F., Gambini, D., Taraborrelli, S., Gardella, B., Campo, M., & VuNet Study Group. (2020). Vulvar pain: The revealing scenario of leading comorbidities in 1183 cases. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *252*, 50-55.

Harlow, B. L. et al. Recurrent yeast infections and vulvodynia: can we believe associations based on self-reported data? J. Womens Health 26, 1069–1076 (2017).

Harlow, B. L., & Stewart, E. G. (2005). Adult-onset vulvodynia in relation to childhood violence victimization. *American journal of epidemiology*, *161*(9), 871-880.

Harlow, B. L., Kunitz, C. G., Nguyen, R. H., Rydell, S. A., Turner, R. M., & MacLehose, R. F. (2014). Prevalence of symptoms consistent with a diagnosis of vulvodynia: population-based

estimates from 2 geographic regions. *American journal of obstetrics and gynecology*, *210*(1), 40-e1.

Harvey, S. M. (1987). Female sexual behavior: Fluctuations during the menstrual cycle. *Journal of Psychosomatic Research*, *31*(1), 101-110.

Hilton, S., & Vandyken, C. (2011). The puzzle of pelvic pain—a rehabilitation framework for balancing tissue dysfunction and central sensitization, I: pain physiology and evaluation for the physical therapist. *The Journal of Women's & Pelvic Health Physical Therapy*, *35*(3), 103-113.

Holbech, J. V., Jung, A., Jonsson, T., Wanning, M., Bredahl, C., & Bach, F. W. (2017). Combination treatment of neuropathic pain: Danish expert recommendations based on a Delphi process. *Journal of pain research*, 1467-1475.

Iglesias-Rios, L., Harlow, S. D., & Reed, B. D. (2015). Depression and posttraumatic stress disorder among women with vulvodynia: evidence from the population-based woman to woman health study. *Journal of women's health*, *24*(7), 557-562.

Ji, R. R., Nackley, A., Huh, Y., Terrando, N., & Maixner, W. (2018). Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology*, *129*(2), 343-366.

Johannesson, U., de Boussard, C. N., Jansen, G. B., & Bohm-Starke, N. (2007). Evidence of diffuse noxious inhibitory controls (DNIC) elicited by cold noxious stimulation in patients with provoked vestibulodynia. *Pain*, *130*(1-2), 31-39.

Kalfon, L., Azran, A., Farajun, Y., Golan-Hamu, O., Toben, A., Abramov, L., ... & Bornstein, J. (2019). Localized provoked vulvodynia: association with nerve growth factor and transient receptor potential vanilloid type 1 genes polymorphisms. *Journal of Lower Genital Tract Disease*, *23*(1), 58-64.

Kalin, N. H. (2020). The critical relationship between anxiety and depression. *American Journal of Psychiatry*, *177*(5), 365-367.

Kaplan, H. S. (1974). The classification of the female sexual dysfunctions. *Journal of sex & marital therapy*, *1*(2), 124-138.

Kennedy, S. H., & Rizvi, S. (2009). Sexual dysfunction, depression, and the impact of antidepressants. *Journal of clinical psychopharmacology*, *29*(2), 157-164.

Khandker, M., Brady, S. S., Vitonis, A. F., MacLehose, R. F., Stewart, E. G., & Harlow, B. L. (2011). The influence of depression and anxiety on risk of adult onset vulvodynia. *Journal of women's health*, *20*(10), 1445-1451.

Kwan, K. S., Roberts, L. J., & Swalm, D. M. (2005). Sexual dysfunction and chronic pain: the role of psychological variables and impact on quality of life. *European Journal of Pain*, *9*(6), 643-652.

Laan, E., & Everaerd, W. (1995). Determinants of female sexual arousal: Psychophysiological theory and data. *Annual Review of Sex Research*, *6*(1), 32-76.

Lahaie, M. A., Amsel, R., Khalifé, S., Boyer, S., Faaborg-Andersen, M., & Binik, Y. M. (2015). Can fear, pain, and muscle tension discriminate vaginismus from dyspareunia/provoked vestibulodynia? Implications for the new DSM-5 diagnosis of genito-pelvic pain/penetration disorder. *Archives of sexual behavior*, *44*, 1537-1550.

Latthe, P., Mignini, L., Gray, R., Hills, R., & Khan, K. (2006). Factors predisposing women to chronic pelvic pain: systematic review. *Bmj*, *332*(7544), 749-755.

Lauria, G., & Lombardi, R. (2007). Skin biopsy: a new tool for diagnosing peripheral neuropathy. *Bmj*, *334*(7604), 1159-1162.

Laursen, B. S., Overvad, K., Olesen, A. S., Delmar, C., & Arendt-Nielsen, L. (2006). Ongoing pain, sexual desire, and frequency of sexual intercourses in females with different chronic pain syndromes. *Sexuality and Disability*, *24*, 27-37.

Leclerc, B., Bergeron, S., Brassard, A., Bélanger, C., Steben, M., & Lambert, B. (2015). Attachment, sexual assertiveness, and sexual outcomes in women with provoked vestibulodynia and their partners: A mediation model. *Archives of sexual behavior*, *44*, 1561-1572.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual review of neuroscience*, *23*(1), 155-184.

Lemieux, A. J., Bergeron, S., Steben, M., & Lambert, B. (2013). Do romantic partners' responses to entry dyspareunia affect women's experience of pain? The roles of catastrophizing and self-efficacy. *The Journal of Sexual Medicine*, *10*(9), 2274-2284.

Lerman, S. F., Rudich, Z., Brill, S., Shalev, H., & Shahar, G. (2015). Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. *Psychosomatic medicine*, *77*(3), 333-341.

Lewis, R. W., Fugl-Meyer, K. S., Bosch, R., Fugl-Meyer, A. R., Laumann, E. O., Lizza, E., & Martin-Morales, A. (2004). Epidemiology/risk factors of sexual dysfunction. *The journal of sexual medicine*, *1*(1), 35-39.

Li, X., & Hu, L. (2016). The role of stress regulation on neural plasticity in pain chronification. *Neural plasticity*, *2016*(1), 6402942.

Lykins, A. D., Janssen, E., & Graham, C. A. (2006). The relationship between negative mood and sexuality in heterosexual college women and men. *Journal of Sex Research*, *43*(2), 136-143.

Maillé, D. L., Bergeron, S., & Lambert, B. (2015). Body image in women with primary and secondary provoked vestibulodynia: a controlled study. *The journal of sexual medicine*, *12*(2), 505-515.

Masheb, R. M., Wang, E., Lozano, C., & Kerns, R. D. (2005). Prevalence and correlates of depression in treatment-seeking women with vulvodynia. *Journal of obstetrics and gynaecology*, *25*(8), 786-791.

Masterson, B. J., Galask, R. P. & Ballas, Z. K. Natural killer cell function in women with vestibulitis. *J. Reprod. Med.* 41, 562–568 (1996).

Mathew, R. J., & Weinman, M. L. (1982). Sexual dysfunctions in depression. *Archives of sexual behavior*, *11*, 323-328.

Mautz, T. T., Mulroy, M. E., Krapf, J. M., Goldstein, A. T., & Pukall, C. F. (2023). Pleasure despite pain: Associations between experiences of vulvar pleasure, vulvar pain, and sexual function in patients with chronic vulvar pain conditions. *Sexual Medicine*, *11*(4), qfad047.

McEvoy, M., McElvaney, R., & Glover, R. (2021). Understanding vaginismus: a biopsychosocial perspective. *Sexual and Relationship Therapy*, 1-22.

Meana, M., Binik, Y. M., Khalifé, S., & Cohen, D. R. (1997). Biopsychosocial profile of women with dyspareunia. *Obstetrics & Gynecology*, *90*(4), 583-589.

Meczekalski, B., Podfigurna-Stopa, A., Warenik-Szymankiewicz, A., & Genazzani, A. R. (2008). Functional hypothalamic amenorrhea: current view on neuroendocrine aberrations. *Gynecological endocrinology*, *24*(1), 4-11.

Meston, C. M. (2000). Sympathetic nervous system activity and female sexual arousal. *The American journal of cardiology*, *86*(2), 30-34.

Meston, C. M., & Buss, D. M. (2007). Why humans have sex. *Archives of sexual behavior*, *36*, 477-507.

Meston, C. M., & Gorzalka, B. B. (1995). The effects of sympathetic activation on physiological and subjective sexual arousal in women. *Behaviour Research and Therapy*, *33*(6), 651-664.

Meston, C. M., & Stanton, A. M. (2019). Understanding sexual arousal and subjective–genital arousal desynchrony in women. *Nature Reviews Urology*, *16*(2), 107-120.

Metts, J. F. (1999). Vulvodynia and vulvar vestibulitis: challenges in diagnosis and management. *American Family Physician*, *59*(6), 1547-1556.

Montejo-Gonzalez, A. L., Llorca, G., Izquierdo, J. A., Ledesma, A., Bouso o, M., Calcedo, A., ... & De la Gandara, J. (1997). SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *Journal of Sex and Marital Therapy*, *23*, 176-194.

Morgan, T. K., Allen-Brady, K. L., Monson, M. A., Leclair, C. M., Sharp, H. T., & Cannon-Albright, L. A. (2016). Familiality analysis of provoked vestibulodynia treated by vestibulectomy supports genetic predisposition. *American journal of obstetrics and gynecology*, *214*(5), 609-e1.

Morin, M., Binik, Y. M., Bourbonnais, D., Khalifé, S., Ouellet, S., & Bergeron, S. (2017). Heightened pelvic floor muscle tone and altered contractility in women with provoked vestibulodynia. *The Journal of Sexual Medicine*, *14*(4), 592-600.

Nguyen, R. H., Ecklund, A. M., MacLehose, R. F., Veasley, C., & Harlow, B. L. (2012). Co-morbid pain conditions and feelings of invalidation and isolation among women with vulvodynia. *Psychology, health & medicine*, *17*(5), 589-598.

Niedenfuehr, J., Edwards, M., & King, L. M. (2023). A scoping review: the psychosocial barriers that exist for people with vulvodynia. *The Journal of Sexual Medicine*, *20*(6), 833-858.

Nylanderlundqvist, E., & Bergdahl, J. (2003). Vulvar vestibulitis: Evidence of depression and state anxiety in patients and partners. *Acta dermato-venereologica*, *83*(5), 369-373.

Pacik, P. T. (2014). Understanding and treating vaginismus: a multimodal approach. *International urogynecology journal*, *25*, 1613-1620.

Palace, E. M., & Gorzalka, B. B. (1990). The enhancing effects of anxiety on arousal in sexually dysfunctional and functional women. *Journal of abnormal Psychology*, *99*(4), 403.

Pâquet, M., Rosen, N. O., Steben, M., Mayrand, M. H., Santerre-Baillargeon, M., & Bergeron, S. (2018). Daily anxiety and depressive symptoms in couples coping with vulvodynia: Associations

with women's pain, women's sexual function, and both partners' sexual distress. *The Journal of Pain*, *19*(5), 552-561.

Pathak, D., Agrawal, S., & Dhali, T. K. (2011). Prevalences of and risk factors for vulvar diseases in Nepal: a hospital-based study.

Payne, K. A., Binik, Y. M., Amsel, R., & Khalifé, S. (2005). When sex hurts, anxiety and fear orient attention towards pain. *European journal of pain*, *9*(4), 427-436.

Payne, K. A., Binik, Y. M., Pukall, C. F., Thaler, L., Amsel, R., & Khalifé, S. (2007). Effects of sexual arousal on genital and non-genital sensation: A comparison of women with vulvar vestibulitis syndrome and healthy controls. *Archives of sexual behavior*, *36*, 289-300.

Peixoto, M. M., & Lopes, J. (2023). Solitary and dyadic sexual desire and sexual satisfaction in women with and without sexual concerns. *Journal of Sex & Marital Therapy*, *49*(1), 77-87.

Penedo, J. M. G., Rubel, J. A., Blättler, L., Schmidt, S. J., Stewart, J., Egloff, N., & grosse Holtforth, M. (2020). The complex interplay of pain, depression, and anxiety symptoms in patients with chronic pain: a network approach. *The Clinical Journal of Pain*, *36*(4), 249-259.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual review of clinical psychology*, *10*, 393-423.

Prendergast, S. A., & Weiss, J. M. (2003). Screening for musculoskeletal causes of pelvic pain. *Clinical obstetrics and gynecology*, *46*(4), 773-782.

Pukall, C. F., Goldstein, A. T., Bergeron, S., Foster, D., Stein, A., Kellogg-Spadt, S., & Bachmann, G. (2016). Vulvodynia: definition, prevalence, impact, and pathophysiological factors. *The journal of sexual medicine*, *13*(3), 291-304.

Raichle, K. A., Romano, J. M., & Jensen, M. P. (2011). Partner responses to patient pain and well behaviors and their relationship to patient pain behavior, functioning, and depression. *PAIN®*, *152*(1), 82-88.

Reed, B. D., Caron, A. M., Gorenflo, D. W., & Haefner, H. K. (2006). Treatment of vulvodynia with tricyclic antidepressants: efficacy and associated factors. *Journal of lower genital tract disease*, *10*(4), 245-251.

Reed, B. D., Harlow, S. D., Legocki, L. J., Helmuth, M. E., Haefner, H. K., Gillespie, B. W., & Sen, A. (2013). Oral contraceptive use and risk of vulvodynia: a population-based longitudinal study. *BJOG: An International Journal of Obstetrics & Gynaecology*, *120*(13), 1678-1684.

Reed, B. D., Harlow, S. D., Sen, A., Legocki, L. J., Edwards, R. M., Arato, N., & Haefner, H. K. (2012). Prevalence and demographic characteristics of vulvodynia in a population-based sample. *American journal of obstetrics and gynecology*, *206*(2), 170-e1.

Rosen, N. O., Bergeron, S., Glowacka, M., Delisle, I., & Baxter, M. L. (2012). Harmful or helpful: Perceived solicitous and facilitative partner responses are differentially associated with pain and sexual satisfaction in women with provoked vestibulodynia. *The journal of sexual medicine*, *9*(9), 2351-2360.

Rosen, N. O., Bergeron, S., Lambert, B., & Steben, M. (2013). Provoked vestibulodynia: Mediators of the associations between partner responses, pain, and sexual satisfaction. *Archives of Sexual Behavior*, *42*, 129-141.

Rosen, N. O., Bergeron, S., Leclerc, B., Lambert, B., & Steben, M. (2010). Woman and partner-perceived partner responses predict pain and sexual satisfaction in provoked vestibulodynia (PVD) couples. *The journal of sexual medicine*, *7*(11), 3715-3724.

Rosen, N. O., Bergeron, S., Sadikaj, G., & Delisle, I. (2015). Daily associations among male partner responses, pain during intercourse, and anxiety in women with vulvodynia and their partners. *The Journal of Pain*, *16*(12), 1312-1320.

Rosen, N. O., Bergeron, S., Sadikaj, G., Glowacka, M., Baxter, M. L., & Delisle, I. (2014). Relationship satisfaction moderates the associations between male partner responses and

depression in women with vulvodynia: a dyadic daily experience study. *PAIN®*, *155*(7), 1374-1383.

Rosen, N. O., Bergeron, S., Sadikaj, G., Glowacka, M., Delisle, I., & Baxter, M. L. (2014). Impact of male partner responses on sexual function in women with vulvodynia and their partners: a dyadic daily experience study. *Health Psychology*, *33*(8), 823.

Rosen, C. Brown, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D. Ferguson, R. D'Agostino, R. (2000). The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *Journal of sex & marital therapy*, *26*(2), 191-208.

Rowen, T. S., & Goldstein, A. T. (2020). Nosology of Pelvic Pain and Vulvodynia. *Female Sexual Pain Disorders: Evaluation and Management*, 1-8.

Rubal, C., Pereira, A., Sastre, L. C., Pérez-Cejuela, B. A., Gámiz, S. H., Chaves, P., & Medina, T. P. (2023). Managing vulvodynia with central sensitization: challenges and strategies. *Journal of Clinical Medicine*, *12*(11), 3851.

Sadownik, L. A. (2014). Etiology, diagnosis, and clinical management of vulvodynia. *International journal of women's health*, 437-449.

Sandkuhler, J. (2009). Models and mechanisms of hyperalgesia and allodynia. *Physiological reviews*, *89*(2), 707-758.

Seehusen, D. A., Baird, D. C., & Bode, D. V. (2014). Dyspareunia in women. *American family physician*, *90*(7), 465-470.

Segraves, RT & Segraves, K. B. (1991). Sexual function: solutions to evaluation and treatment dilemmas in primary care. *Modern Medicine*, *16*(6), 99-112. Sex Research, 53(9), 1–14.

Shallcross, R., Dickson, J. M., Nunns, D., Taylor, K., & Kiemle, G. (2019). Women's experiences of vulvodynia: An interpretative phenomenological analysis of the journey toward diagnosis. *Archives of sexual behavior*, *48*, 961-974.

Sharp, T. J., & Nicholas, M. K. (2000). Assessing the significant others of chronic pain patients: the psychometric properties of significant other questionnaires. *Pain*, *88*(2), 135-144.

Sheng, J., Liu, S., Wang, Y., Cui, R., & Zhang, X. (2017). The link between depression and chronic pain: neural mechanisms in the brain. *Neural plasticity*, *2017*(1), 9724371.

Sims, J. M. (1862). Cases of Vagismus, with the Method of Treatment. *Chicago Medical Examiner*, *3*(6), 355.

Spano, L., & Lamont, J. A. (1975). Dyspareunia: a symptom of female sexual dysfunction. *The Canadian Nurse*, *71*(8), 22-25.

Stewart, D. E., Reicher, A. E., Gerulath, A. H., & Boydell, K. M. (1994). Vulvodynia and psychological distress. *Obstetrics & Gynecology*, *84*(4 Part 1), 587-590.

Sutton, K., Pukall, C., Wild, C., Johnsrude, I., & Chamberlain, S. (2015). Cognitive, psychophysical, and neural correlates of vulvar pain in primary and secondary provoked vestibulodynia: a pilot study. *The journal of sexual medicine*, *12*(5), 1283-1297.

T Jones, G. (2016). Psychosocial vulnerability and early life adversity as risk factors for central sensitivity syndromes. *Current rheumatology reviews*, *12*(2), 140-153.

Tarr, G., Selo-Ojeme, D. O., & Onwude, J. L. (2003). Coexistence of vulvar vestibulitis and interstitial cystitis. *Acta Obstetricia et Gynecologica Scandinavica*, *82*(10), 969-969.

Thomtén, J., & Karlsson, A. (2014). Psychological factors in genital pain: the role of fear-avoidance, pain catastrophizing and anxiety sensitivity among women living in Sweden. *Scandinavian journal of pain*, *5*(3), 193-199.

Thomtén, J., & Linton, S. J. (2013). A psychological view of sexual pain among women: applying the fear-avoidance model. *Women's Health*, *9*(3), 251-263.

Tribó, M. J., Canal, C., Baños, J. E., & Robleda, G. (2020). Pain, anxiety, depression, and quality of life in patients with vulvodynia. *Dermatology*, *236*(3), 255-261.

Trutnovsky, G., Plieseis, C., Bjelic-Radisic, V., BertholinyGalvez, M. C., Tamussino, K., & Ulrich, D. (2019). Vulvodynia and chronic pelvic pain in a gynecologic outpatient clinic. *Journal of Psychosomatic Obstetrics & Gynecology*, *40*(3), 243-247.

Tympanidis, P., Terenghi, G., & Dowd, P. (2003). Increased innervation of the vulval vestibule in patients with vulvodynia. *British Journal of Dermatology*, *148*(5), 1021-1027.

van Beekhuizen, H. J., Oost, J., & van der Meijden, W. I. (2018). Generalized unprovoked vulvodynia; A retrospective study on the efficacy of treatment with amitriptyline, gabapentin or pregabalin. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *220*, 118-121.

Veasley, C. et al. Impact of chronic overlapping pain conditions on public health and the urgent need for safe and effective treatment: 2015 analysis and policy recommendations. Chronic Pain Research Alliance http://www.chronicpainresearch.org/Resources (2015).

Vieira-Baptista, P., Lima-Silva, J., Cavaco-Gomes, J., & Beires, J. (2014). Prevalence of vulvodynia and risk factors for the condition in Portugal. *International Journal of Gynecology & Obstetrics*, *127*(3), 283-287.

Viola, A. (2022). *Il sesso è (quasi) tutto: evoluzione, diversità e medicina di genere*. Feltrinelli Editore.

Walitt, B., Ceko, M., L Gracely, J., & H Gracely, R. (2016). Neuroimaging of central sensitivity syndromes: key insights from the scientific literature. *Current rheumatology reviews*, *12*(1), 55-87.

Wesselmann, U., Bonham, A., & Foster, D. (2014). Vulvodynia: Current state of the biological science. *PAIN®*, *155*(9), 1696-1701.

Wesselmann, U., Garrett-Mayer, E., Kaplan Gilpin, A. M., Zhang, L. & Czakanski, P. P. The influence of the ovarian cycle on mechanical hyperalgesia in vulvar vestibulitis–a neuropathic urogenital pain syndrome. Ann. Neurol. 60 (Suppl. 3), S29 (2006).

Wiech, K., & Tracey, I. (2009). The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage*, *47*(3), 987-994.

Wittenberg, A., & Gerber, J. (2009). Original research—education: Recommendations for improving sexual health curricula in medical schools: Results from a two-arm study collecting data from patients and medical students. *The Journal of Sexual Medicine*, *6*(2), 362-8.

Woolf, C. J. (2007). Central sensitization: uncovering the relation between pain and plasticity. *The Journal of the American Society of Anesthesiologists*, *106*(4), 864-867.

Wouda, J. C., Hartman, P. M., Bakker, R. M., Bakker, J. O., van de Wiel, H. B., & Weijmar Schultz, W. C. (1998). Vaginal plethysmography in women with dyspareunia. *Journal of Sex Research*, *35*(2), 141-147.

Xie, Y., Shi, L., Xiong, X., Wu, E., Veasley, C., & Dade, C. (2012). Economic burden and quality of life of vulvodynia in the United States. *Current medical research and opinion*, *28*(4), 601-608.

Yeung, J., & Pauls, R. N. (2016). Anatomy of the vulva and the female sexual response. *Obstetrics and Gynecology Clinics*, *43*(1), 27-44.

Zhang, Z., Zolnoun, D. A., Francisco, E. M., Holden, J. K., Dennis, R. G., & Tommerdahl, M. (2011). Altered central sensitization in subgroups of women with vulvodynia. *The Clinical journal of pain*, *27*(9), 755-763.

Zhuo, M. (2016). Neural mechanisms underlying anxiety–chronic pain interactions. *Trends in neurosciences*, *39*(3), 136-145.