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Original Research

Psychiatric morbidity across the life course and provoked vulvodynia: is it dependent upon the presence of non–stress-related immune dysfunction?

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Abstract

Background: Vulvodynia impacts up to 8% of women by age 40, and these women may have a more compromised immune system than women with no vulvar pain history.
Aim: Given that psychiatric morbidity is associated with vulvodynia and is known to activate immune inflammatory pathways in the brain and systemically, we sought to determine whether the association between psychiatric morbidity and vulvar pain was independent of or dependent upon the presence of immune-related conditions.
Methods: Women born in Sweden between 1973 and 1996 with localized provoked vulvodynia (N76.3) and/or vaginismus (N94.2 or F52.5) diagnosed between 2001 and 2018 were matched to two women from the same birth year with no vulvar pain. *International Statistical Classification of Diseases and Related Health Problems* (ICD-9 or -10 codes) were used to identify women with a history of depression, anxiety, attempted suicide, neurotic disorders, stress-related disorders, behavioral syndromes, personality disorders, psychotic disorders, or chemical dependencies, as well as a spectrum of immune-related conditions. The Swedish National Prescribed Drug Register was used to identify women with filled prescriptions of antidepressants or anxiolytics.
Outcomes: Vulvodynia, vaginismus, or both were outcomes assessed in relation to psychiatric morbidity.
Results: Women with vulvodynia, vaginismus, or both, relative to those without vulvar pain, had adjusted odds ratios between 1.4 and 2.3, with CIs highly compatible with harmful effects. When we assessed women with and those without a lifetime history of immune-related conditions separately, we also observed elevated odds ratios in both groups for mood, anxiety, and neurotic and stress disorders.
Clinical implications: Documenting psychiatric impairment as a cause or consequence of vulvodynia is critical in clinical practice because psychiatric conditions may impact treatment efficacy.
Strengths and Limitations: Strengths of this study include a data source that represents the entire population of women in Sweden that is known to be highly accurate because Sweden provides universal healthcare. Limitations include difficulty in making an accurate assessment of temporality between psychiatric morbidity and the first onset of vulvar pain. In addition, because Swedish registry data have limited information on lifestyle, behavioral, and anthropomorphic factors such as smoking, diet, physical activity, and obesity, these conditions could not be assessed as confounders of psychiatric morbidity and vulvar pain.
Conclusions: Immune pathways by which women with psychiatric conditions increase their risk of vulvar pain could be independent from other immune pathways.

Keywords: vulvodynia; psychiatric morbidity; stress immune dysfunction; risk factors; inflammation.

Introduction

Vulvodynia is a debilitating and stigmatizing condition shown to impact up to 8% of women by the age of 40 years.[1] Women with vulvodynia may have a more compromised immune system either at birth or at points across the life course than women with no vulvar pain history.[2] In addition, psychiatric morbidities such as mood and anxiety disorders are bidirectionally associated with vulvodynia.[3-6]

Psychiatric morbidity activates immune inflammatory pathways in the brain and systemically.[7-9] However, it remains unclear whether immune-related disorders have confounded the associations we and others have seen with respect to mood and anxiety disorders and vulvodynia. Therefore, in this study we sought to assess whether psychiatric morbidity across the life course is associated with vulvodynia and whether it is confounded by the prevalence of immune-related conditions.

Materials and methods

Data sources, sampling frame, and study design

We used Swedish administrative data for the period 1973-2018 after obtaining the approval of the Swedish Ethical

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Review Authority (reference number: 2018/1475-32/3). All Swedish residents obtain a unique personal identification number at birth, or upon arrival to Sweden, which enables investigators to cross-link data from multiple national administrative registers. These registers document all medical conditions and procedures carried out during inpatient care or specialized outpatient care and are used to guide healthcare policy and utilization and support research. Several studies have assessed the validity of inpatient and outpatient registry data and results have shown strong validity.[10,1112] In the present study we included all women born in Sweden during this time period, excluding those who emigrated as all of their medical history data would not be available. We drew data from various registers that are maintained by the Swedish National Board of Health and Welfare and Statistics Sweden.

Obstetrical data were obtained from the Swedish Medical Birth Register, including detailed information on conditions during pregnancy, delivery, and postpartum. These data also contain detailed information on maternal characteristics, including age, parity, and previous and current health conditions. The Medical Birth Register also includes information on infant growth (birth weight, height, and length), gestational age, health conditions, and medical procedures during delivery.

The Swedish National Board of Health and Welfare maintains the National Patient Register, which includes data for all inpatient visits between 1987 and 2018 and >80% of outpatient visits to specialized healthcare physicians between 2001 and 2018. The National Patient Register contains diagnoses, date of admission and discharge, procedures, and treatments. Deaths were identified via the Causes of Death Register of the Swedish National Board of Health and Welfare. We excluded women who died at 15 years of age or younger or who were not alive in 2001. Information on highest level of education was obtained from the Statistics Sweden Longitudinal Integration Database for Health Insurance and Labor Market Studies. These data include annual information on education for all individuals older than 16 years, between 1990 and 2016.

Study design

We conducted a case–control study using a sampling frame of all women born in Sweden between 1973 and 1996, virtually all of whom are registered in the Medical Birth Register (N = 832 276). We only included women still living and residing in Sweden as of 2018 (N = 745 291). Included as cases were all women diagnosed with localized provoked vulvodynia (n = 4787), vaginismus (n = 2063), or both (n = 867) based on *International Statistical Classification of Diseases and Related Health Problems* (ICD) codes recorded in the National Patient Register between 2001 and 2018 (see below). Each case was matched by the birth year to two randomly selected controls without a diagnosis of either vulvodynia or vaginismus (n = 15 434).

Classification of outcomes—vulvodynia and vaginismus

In Sweden, the ICD-10 code of N76.3 is used for provoked vulvodynia and N94.2 or F52.5 for vaginismus. Vulvodynia is often accompanied with, or misclassified as, varying degrees of vaginismus and we therefore consider both conditions for this analysis.[13,14] By including both conditions, we increased the sensitivity of our outcome and maximized the likelihood of capturing data for most women who met the diagnostic criteria for provoked vulvodynia. Although an ICD code of N90.8 refers to unprovoked or generalized vulvodynia, in consultation with clinical colleagues, the consensus was reached that this code is not valid for the assessment of localized provoked vulvodynia. Therefore, we conservatively chose to exclude women due to the presence of the N90.8 code: 372 women with vulvodynia only, 126 with vaginismus only, and 118 with vulvodynia and vaginismus. Thus, our final sample of cases included 4415 women with vulvodynia only, 1937 with vaginismus only, and 749 with both (N = 7101). We also excluded 102 women with N90.8 codes from our sample of controls, leaving a total of 15 332 for our analyses. A flow chart illustrating how we obtained our final sample of cases and controls can be found elsewhere.[2]

Description of exposures—psychiatric morbidity

As shown in Table 1, we used ICD-9 and ICD-10 codes identified within the National Patient Register to identify women with each psychiatric code associated with the following psychiatric events or morbidity categories: depression, anxiety, suicide attempt, neurotic disorders, stress related disorders, behavioral syndromes, personality disorders, psychotic disorders, chemical dependencies, and other disorders not otherwise specified. In addition, we used the National Prescribed Drug Register, for which data collection began in July 2005, to identify women with filled prescriptions of antidepressants or anxiolytics using codes from the Anatomical Therapeutic Chemical classification system of the World Health Organization.

Description of exposures—events at birth that could impact immune dysfunction.

We used the Medical Birth Register to identify events at birth that could impact immune function later in life. We limited our assessments to mode of delivery, gestational age at birth, and birth weight. Although use of antibiotics, presence of infections, and choice to breastfeed in the mothers of study participants could have had impacts on offspring immune function, we were unable to link these maternal events to the women included in our study. Thus, each woman was classified as having the following birth related events when the corresponding ICD-9 or ICD-10 code was present: cesarean section delivery, small for gestational age delivery, preterm birth defined as <37 weeks, or low birth weight defined as <2500 g.

Description of exposures—events after birth that could impact immune dysfunction.

We used the National Patient Register to identify clinical diagnoses of immune-related conditions from after birth through 2018. We created categories of immune- related conditions across the life course, including the following: (1) disorders involving the immune system (immunodeficiencies), (2) single-organ autoimmune conditions, (3) multiorgan autoimmune conditions, (4) allergy and atopy conditions, and (5) malignancies involving immune cells. The ICD codes aligned with these categories are shown in Supplemental Table S1. We also assessed whether individuals had multiple ICD codes across the 5 different immune categories listed above.

Table 1. Psychiatric disorder ICD codes.

Psychiatric conditions and disorders	ICD-9 codes	ICD-10 codes
Depression	300E, 311	F32 (excludingF32.3), F33 (excluding F33.3), F34-F39
Anxiety	300A, 300C	F40-F41
Antidepressants or anxiolytics[a]		N06A, N05B
Suicide attempt	E950-E959 E980-E988	X60-X84 Y10-Y34
Neurotic disorders (includingobsessive/dissociative/somatoform disorder)[a]	300 (except 300A, 300C, 300E)	F42, F44-F45, F48
Stress-related disorders	308-309	F43
Behavioral syndromes[b] (eating, sleep disorders)	307B, 307F	F50, F52, F54-59, F64-F66, F68
Personality disorder	301	F60-F62, F69
Psychotic disorders	291-292, 295, 296A-296E, 296X, 297-298, 296 W	F10.5-F19.5 (only XX.5 between F10-F19), F20-F25, F28-F29, F30-F31, F32.3, F33.3
Chemical dependencies	303, 304, 305A, 305X	F10-F19 (excl FXX.5),
Other	295-319 but not included in the above	F10-F99 but not included in the above

[a] Available starting in 2005. [b] F52 relating to other sexual disorders omitted.

Statistical analyses

We assessed the distributions of birth year, history of live births, region of residency, and education in those with or without vulvodynia or vaginismus, and then within strata of those with or without any immune-related conditions across the life course. We further assessed the distribution of categories of psychiatric events and conditions among cases and controls stratified by those with and those without vulvodynia or vaginismus, and then within strata of those with or without immune-related conditions across the life course. We found that the distributions between the three vulvar pain categories (vulvodynia, vaginismus, or both) were similar across the participant demographics and therefore we combined all vulvar pain categories in our analyses.[2]

We used multivariable conditional logistic regression to calculate odds ratios (ORs) and 95% CIs that estimated associations with vulvar pain of the various psychiatric events and conditions across the life course. We adjusted for birth year, parity, education, and region of residence at birth in all analyses. We also controlled for all birth-related events when assessing the associations between psychiatric morbidity and vulvar pain because birth-related events have been shown to be associated with vulvar pain[2] and are known to have immune effects which could influence onset of psychiatric morbidity.

We further assessed these associations within the subgroups of women with and those without immune- related disorders across the life course to remove confounding effects. Last, we assessed these associations within the subgroups of women with and without adverse maternal/fetal events (cesarean section, preterm delivery, small for gestational age, and low birth weight).

Results

All of our results compare women with and those without a wide spectrum of psychiatric conditions in relation to vulvodynia, vaginismus, or both; we did this analysis first in all women and then stratified by women with and those without immune-related conditions across the life course.

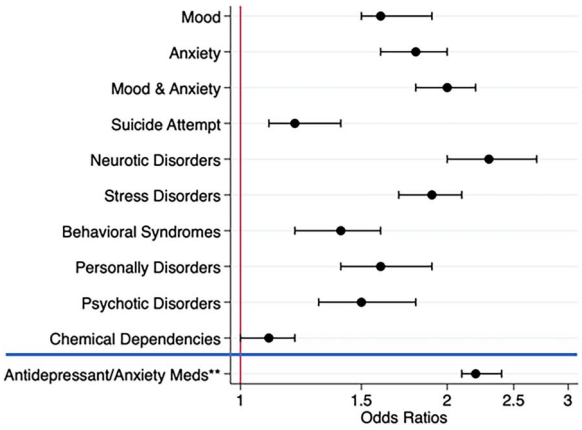


Figure 1. Forest plot of odds ratios∗ and 95% CIs for the association between psychiatric disorders or pharmaceutical prescriptions of antidepressants or anxiolytics and vulvar pain.

Women with vulvodynia, vaginismus, or both had a median age of 23 years at their first vulvar pain code in the registry. Fewer than 10% were entered at age 18 years or younger or 30 years or older. The distributions of women with no vulvar pain, vulvodynia only, vaginismus only, or both were similar by birth year compared to controls (Table 2). Women with vulvodynia, vaginismus, or both were less likely to be multiparous and more highly educated relative to controls. There was no difference between women with vulvar pain and controls by region of residence. These findings did not differ by women with and those without immune-related conditions across the life course.

Women with a wide spectrum of psychiatric morbidity were more likely to experience vulvodynia, vaginismus, or both than women without these conditions (Table 3). These findings were similar among women with and those without a history of immune-related conditions across the life course. As shown in Fig. 1, according to conditional logistic regression odds ratios, all psychiatric conditions other than suicide attempts and chemical dependencies had associations that ranged from 1.4- to 2.5-fold after adjustment for birth year,

Table 2. Distribution of demographic characteristics by women with and without vulvar pain, and then further stratified by those with and without immune related conditions.

Demographic Characteristics	All women		Only women with immune conditions		Women without immune conditions	
	No vulvar pain (N = 15 332)	Vulvodynia, vaginismus, or both (N = 7101)	No vulvar pain (N. = 3941)	Vulvodynia, vaginismus, or both (n = 2558)	No vulvar pain (N = 11 391)	Vulvodynia, vaginismus, or both (N = 4543)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Birth year						
1980-1984	3742 (24.4)	1730 (24.4)	916 (23.2)	635 (24.8)	2826 (24.8)	1095 (24.1)
1985-1989	5571 (36.3)	2557 (36.0)	1455 (36.9)	914 (35.7)	4116 (36.1)	1643 (36.2)
1990-1994	4989 (32.5)	2322 (32.7)	1318 (33.4)	844 (33.0)	3671 (32.2)	1478 (32.5)
1995-1999	1030 (6.7)	492 (6.9)	252 (6.4)	165 (6.5)	778 (6.8)	327 (7.2)
Parity						
0	8770 (57.2)	4477 (63.0)	2247 (57.0)	1653 (64.6)	6523 (57.3)	2824 (62.2)
1	2613 (17.0)	1219 (17.2)	693 (17.6)	419 (16.4)	1920 (16.9)	800 (17.6)
2 or more	3949 (25.8)	1405 (19.8)	1001 (25.4)	486 (19.0)	2948 (25.9)	919 (20.2)
Region of residence at birth						
South	3491 (22.8)	1342 (18.9)	988 (25.1)	501 (19.6)	2503 (22.0)	841 (18.5)
Middle	8694 (56.7)	4117 (58.0)	2211 (56.1)	1497 (58.5)	6483 (56.9)	2620 (57.7)
North	3146 (20.5)	1642 (23.1)	742 (18.8)	560 (21.9)	2404 (21.1)	1082 (23.8)
Missing	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Highest education						
<High school (<9 y)	1119 (7.3)	288 (4.1)	310 (7.9)	118 (4.6)	809 (7.1)	170 (3.7)
High School (9 y)	6436 (42.0)	2430 (34.2)	1700 (43.1)	889 (34.8)	4736 (41.6)	1541 (33.9)
> High School (>9 y)	7775 (50.7)	4383 (61.7)	1931 (49.0)	1551 (60.6)	5844 (51.3)	2832 (62.3)
Missing	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)

parity, education, birth region of residency, cesarean section delivery, preterm birth, small for gestational age, or low birth weight, with CIs all mostly compatible with harmful effects. When stratified by women with and those without immune conditions across the life course, the associations remained largely unchanged (Fig. 2).

We further assessed associations among women with and those without events at birth such as cesarean section delivery, preterm birth, or low birth weight (Fig. 3). Mood and anxiety disorders and neurotic and stress disorders were significantly associated with vulvodynia, vaginismus, or both regardless of the presence or absence of these maternal fetal events.

Discussion

We found that women with localized provoked vulvodynia, vaginismus, or both were more likely to experience a wide spectrum of psychiatric morbidities compared with women who had never been diagnosed with a vulvar pain syndrome. These associations were present regardless of whether or not women had experienced other immune-related conditions across the life course. Even in the presence or absence of events at birth known to impact vulvar pain onset later in life (cesarean section, low birth weight, preterm birth)[14] we observed strong associations for mood and/or anxiety disorders and neurotic and stress disorders.

Several investigators have shown an association between psychiatric morbidity and vulvar pain. However, most of this research has focused on how vulvodynia can lead to the onset of psychiatric morbidity.[15,16] However, other investigators have shown that depression and anxiety may also have impacts on the onset of vulvodynia.[3] This finding is particularly relevant in women who have experienced childhood victimization.[5,17] Although our findings showed strong associations between psychiatric conditions and vulvar pain even among women with no immune-related disorders, there is evidence that chronic stress may have a profound and direct impact on the immune system.[18] Proinflammatory cytokines are elevated in patients with anxiety, depression, and posttraumatic stress disorder.[8,18] In addition, Medina-Rodriguez and colleagues found that stress-induced inflammatory processes in female mice differed from those of male mice, with less effective antidepressant measures observed among females.[19] Thus, it is possible that in the pathogenesis of vulvar pain stress-induced disorders operate similarly to the observations in our earlier research showing strong associations with immune-related disease.[2]

A strength of our study is the use of data that represent the entire population of women in Sweden. The Swedish registers are known to be highly accurate, and because of universal healthcare, most outpatient and inpatient diagnoses are captured and not self-reported.[12] However, we recognize that our study is not without limitations. Although we have increased our sensitivity for true vulvodynia by including vaginismus, vulvodynia, or both together, we also recognize that this increased sensitivity comes at a cost of specificity (including true vaginismus as vulvodynia). However, these conditions are highly correlated and may have similar etiologies. Thus, we were less concerned about this misclassification issue.

Because the first onset of vulvar pain cannot be accurately documented by the date of entry into the Swedish register, we chose not to carry out a prospective analysis with time to event data. Rather, we chose a case–control study approach that allowed us to assess associations of psychiatric morbidity across the life course in those patients with the outcomes of vulvodynia, vaginismus, or both at some point in their lifetime in comparison to those with no such vulvar pain history. Although this approach does not allow us to do a comparison of incidence, it does allow us to assess the odds of

Table 3. Distribution of psychiatric disorders and pharmaceutical prescriptions of antidepressants or anxiolytics by women with and without vulvar pain in those with and without immune related conditions.

Disorders at any time	All women		Only women with immune conditions		Women without immune conditions	
	No vulvar pain (N = 15 332) No. (%)	Vulvodynia, vaginismus, or both (N = 7101) No. (%)	No vulvar pain (N = 3941) No. (%)	Vulvodynia, vaginismus, or both (N = 2558) No. (%)	No vulvar pain (N = 11 391) No. (%)	Vulvodynia, vaginismus, or both (N = 4543) No. (%)
Mood disorders with no anxiety	704 (4.6)	508 (7.2)	229 (5.8)	197 (7.7)	475 (4.2)	311 (6.8)
Anxiety disorders with no depression	873 (5.7)	656 (9.2)	278 (7.1)	287 (11.2)	595 (5.2)	369 (8.1)
Both mood and anxiety disorders	1010 (6.6)	820 (11.5)	354 (9.0)	377 (14.7)	656 (5.8)	443 (9.8)
Suicide attempt	652 (4.3)	328 (4.6)	225 (5.7)	136 (5.3)	427 (3.7)	192 (4.2)
Neurotic disorders	413 (2.7)	409 (5.8)	174 (4.4)	192 (7.5)	239 (2.1)	217 (4.8)
Stress-related disorders	964 (6.3)	727 (10.2)	377 (9.6)	330 (12.9)	587 (5.2)	397 (8.7)
Behavioral syndromes	587 (3.8)	369 (5.2)	198 (5.0)	152 (5.9)	389 (3.4)	217 (4.8)
Personality syndromes	385 (2.5)	252 (3.5)	154 (3.9)	123 (4.8)	231 (2.0)	129 (2.8)
Psychotic disorders	409 (2.7)	258 (3.6)	129 (3.3)	117 (4.6)	280 (2.5)	141 (3.1)
Chemical dependencies	890 (5.8)	390 (5.5)	290 (7.4)	167 (6.5)	600 (5.3)	223 (4.9)
Antidepressants/anxiety medications	4837 (31.5)	3433 (48.3)	1596 (40.5)	1426 (55.7)	3241 (28.5)	2007 (44.2)

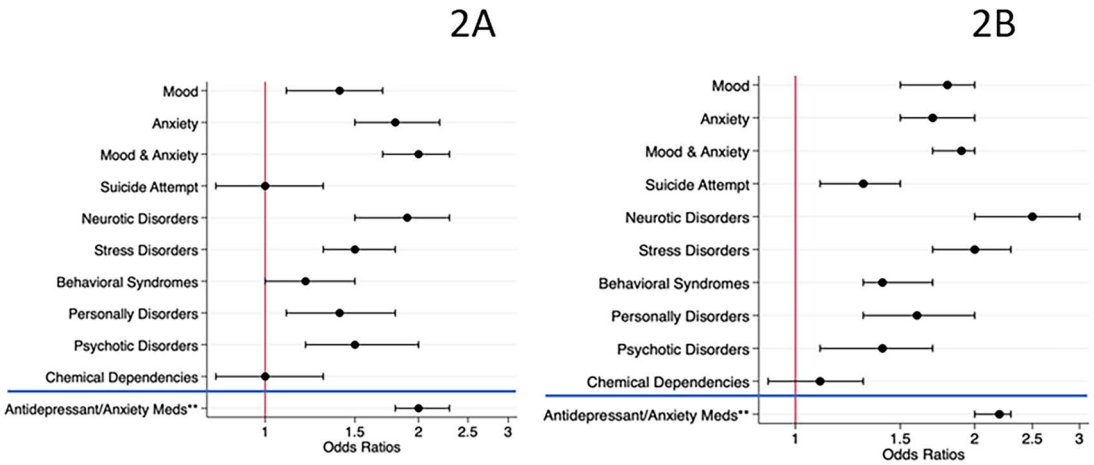
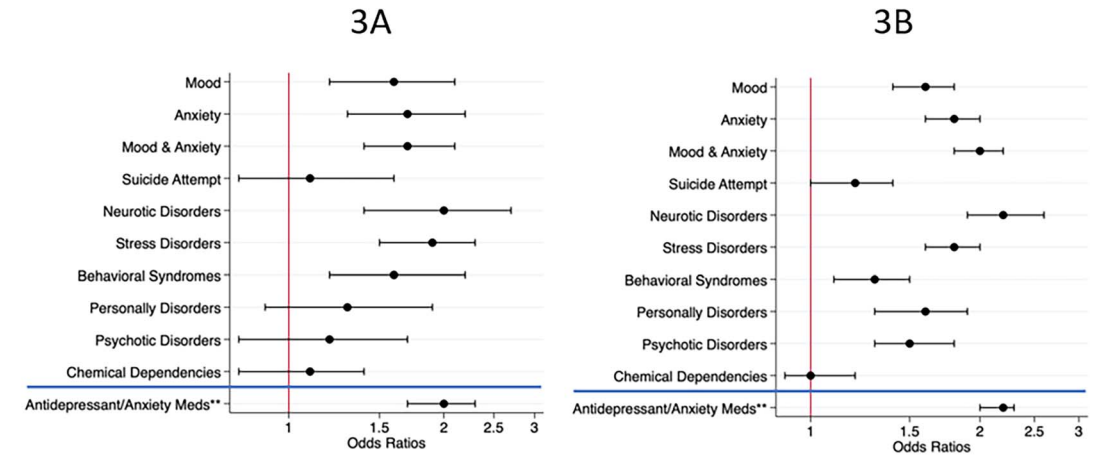


Figure 2. A and 2B. Forest plot of odds ratios* and 95% CIs for the association between psychiatric disorders or pharmaceutical prescriptions of antidepressants or anxiolytics and vulvar pain among those with (2A) and those without (2B) a history of immune related conditions.



* Adjusted for Birth Year, Parity, Education, Birth region of Residency, and presence of immune related conditions.

**Includes codes beginning in 2005

Figure 3. A and 3B. Forest plot of odds ratios* and 95% CIs for the association between psychiatric disorders or use of antidepressant or anxiety medications and vulvar pain among those that did (3A) and did not (3B) experience certain maternal fetal events.

vulvar pain in relation to the various psychiatric conditions. Thus, we cannot be sure of the temporal assessments of when psychiatric conditions occurred in relation to first onset of vulvar pain. Therefore, we cannot test whether these psychiatric conditions "cause" the onset of vulvar pain, but rather, we can only observe their association with the development of vulvar pain. However, earlier research has shown depression to be bidirectionally associated with vulvodynia.[3]

There are also few potential confounders available within the Swedish registers. Lifestyle, behavioral, and anthropomorphic factors such as smoking, diet, physical activity, obesity, etc., are not available and we cannot determine how these factors might have impacted psychiatric morbidity. In addition, a large proportion of women fail to seek care for their vulvar pain.[20] Adolescent girls with vulvar pain symptoms being seen in youth clinics or women with vulvar pain symptoms being seen by general practitioners may not use the traditional ICD codes for vulvodynia or vaginismus. Likewise, many women with depression and anxiety fail to seek treatment. Thus, we recognize that our participants with vulvodynia, vaginismus, and both, as well as the psychiatric morbidity captured within the Swedish registers, may not represent all women who suffer from these conditions. Thus, we expect misclassification has occurred in both our exposures and outcomes, and that participants with psychiatric conditions and vulvar pain may represent those with the most severe symptoms. In addition, women who served as controls could have actually been cases and/or also living with psychiatric morbidity. Therefore, we believe that the associations we observed may in fact be an attenuation of the true associations given this potential nondifferential misclassification.

Regardless of psychiatric impairment as a cause or consequence of vulvodynia, in clinical practice it is important to be aware of potential comorbidities among these women. Using validated screening instruments for anxiety and depression is the standard of practice in Swedish specialized centers for vulvar care since the psychiatric conditions may impact treatment efficacy. In some cases, a patient with ongoing depression needs to be treated before specific treatment for vulvodynia can be addressed, and collaboration with a psychiatrist or psychologist is highly recommended.

In conclusion, we found that a wide spectrum of psychiatric disorders is more commonly present in women with vulvodynia, vaginismus, or both compared to women with no history of vulvar pain, and that this excess risk is not due to the prevalence of immune-related disorders that we have shown to be more commonly observed in women with vulvodynia. This finding suggests that the stress immune pathways by which women may develop vulvar pain could be independent from those of other immune pathways shown in our earlier report.

Author contributions

B.L.H.: Design, oversight of data acquisition, analytic approach, interpretation of findings, writing of the manuscript. H.M.: Design, oversight of data acquisition, analytic approach, interpretation of findings, writing of the manuscript. J.Y.: Analytic approach, interpretation of findings. E.L.: Oversight of data acquisition, analytic approach. D.L.: Analytic approach, interpretation of findings, writing of manuscript. M.P.F.: Design, analytic approach, interpretation of findings, writing of manuscript. N.B.B.L.H.: Design, oversight of data acquisition, analytic approach, interpretation of findings, writing of the manuscript.

CRediT taxonomy

B.H. (Conceptualization [Equal], Funding acquisition [Equal], Methodology [Equal], Project administration [Equal], Supervision [Equal], Writing – original draft [Equal]), H.M. (Data curation [Equal], Investigation [Equal], Methodology [Equal], Resources [Equal], Writing – review & editing [Equal]), J.Y. (Data curation [Equal], Formal analysis [Equal], Writing – review & editing [Equal]), E.L. (Data curation [Equal], Writing – review & editing [Equal]), D.L. (Data curation [Equal], Formal analysis [Equal], Methodology [Equal], Supervision [Equal], Writing – review & editing [Equal]), M.F. (Methodology [Equal], Writing – review & editing [Equal]), N.B.-S. (Funding acquisition [Equal], Investigation [Equal], Methodology [Equal], Project administration [Equal], Resources [Equal], Writing – review & editing [Equal]).

Supplementary material

Supplementary material is available at *The Journal of Sexual Medicine* online.

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Conflict of interest

All authors declare no conflicts of interest.

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