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The Association Between Immune-Related Conditions Across the Life-Course and Provoked Vulvodynia

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Abstract: **Vulvodynia, impacts up to 8% of women by age 40, and is hypothesized to manifest through an altered immune-inflammatory response. To test this hypothesis, we identified all women born in Sweden between 1973 and 1996 diagnosed with localized provoked vulvodynia (N76.3) and/or vaginismus (N94.2 or F52.5) between 2001 and 2018. We matched each case to two women from the same birth year with no vulvar pain ICD codes. As a proxy for immune dysfunction, we used Swedish Registry data to capture 1) immunodeficiencies, 2) single organ and multiorgan autoimmune conditions, 3) allergy and atopies, and 4) malignancies involving immune cells across the life course. Women with vulvodynia, vaginismus or both were more likely to experience immune deficiencies (OR 1.8, 95% CI, 1.2–2.8), single organ (OR 1.4, 95% CI, 1.2–1.6) and/or multi-organ (OR 1.6, 95% CI, 1.3–1.9) immune disorders, and allergy/atopy conditions (OR 1.7, 95% CI, 1.6–1.8) compared to controls. We observed greater risk with increasing numbers of unique immune related conditions (1 code: OR = 1.6, 95% CI, 1.5–1.7; 2 codes: OR = 2.4, 95% CI, 2.1–2.9; 3 or more codes: OR = 2.9, 1.6–5.4). These findings suggest that 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.**

Perspective: ***Women with vulvodynia are substantially more likely to experience a spectrum of immune related conditions across the life course. These findings lend support to the hypothesis that chronic inflammation initiates the hyperinnervation that causes the debilitating pain in women with vulvodynia.***

Key words: *Vulvodynia, immune dysfunction, risk factors, inflammation, life course.*

Vulvodynia is a debilitating and stigmatizing condition that has been shown to impact up to 8% of women by the age of 40.[1,2] We have shown that women with vulvodynia begin to experience signs suggestive of subsequent vulvar pain as early as menarche, where women with vulvodynia were 8 times more likely to experience pain and difficulty with their first use of tampons compared to those without.[13] Although the etiology of vulvodynia remains unclear, *in vivo* studies suggest that sensitization of vestibular nerve fibers may occur as a consequence of various immune-inflammatory response mechanisms. One example suggests that immune activation of vestibule-associated lymphoid tissue (VALT) induces the sprouting of nociceptive nerve fibers.[24] Other immune related hypotheses focus on macrophages, which can promote inflammation and contribute to hyperinnervation and nociceptor sensitization.[1] Further support for immune inflammatory precursors comes from the increased presence of mast cells in vestibular tissue which can also modulate pain and excitation of nerve fibers.[2,4,22] Another important inflammatory precursor is recurrent vulvovaginal yeast infections, which has been suggested to be a trigger of

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provoked vulvodynia both in epidemiological and experimental studies.[7,9,13] Thus, there is suggestive evidence that the pathogenic mechanism behind vulvodynia is through an altered immune-inflammatory response. Related to these findings, children born preterm are at higher risk of developing immune dysfunction and a previous study found that women born prematurely (<37 weeks of gestation), with low birth weight or small for their gestational age exhibit a higher risk of developing vulvodynia compared to women at term with normal birth weight.[14,19]

We have shown that women with vulvodynia are substantially more likely to have experienced hypersensitivity to insect bites and urticaria indicative of hyper-allergenic immune activation.[11] We also found that women with vulvodynia had higher thymic output more proximate to the first onset of their vulvar pain compared to a comparable time period among controls with no vulvar pain history.[25] However, it is unclear to what extent women who go on to develop vulvodynia are more or less likely than others to experience immune-related conditions across the life course. It is also unclear at what point in a woman's life an altered immune profile impacts the onset of vulvar pain.

Although our etiologic hypothesis of interest is the extent to which immune dysregulation impacts provoked vulvar pain, we are limited by the inability to directly examine immune dysregulation. Therefore, we chose to identify a) events that could impact immune dysfunction as early as birth and b) the onset of immune-related conditions across a woman's life course. We then assessed whether these events were associated with the onset of provoked vulvodynia (PVD) diagnoses. This allowed us to use immune related events and conditions as a proxy for immune dysregulation to test our etiologic hypothesis.

Methods

Data Sources, Sampling Frame, and Study Design

We used Swedish administrative data for the period 1973 to 2018 after approval by the Swedish Ethical 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 administrative registers. These registers document all medical conditions and procedures and are used to guide health care policy, utilization, and support research. Several studies have assessed the validity of inpatient and outpatient registry data showing strong validity.[16,17,6] We included all women in Sweden during this time period except those who emigrated into the country 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 was obtained from the Swedish Medical Birth Register, which includes detailed information on conditions during pregnancy, delivery, and postpartum for stillbirths and live births. It also contains detailed information on maternal characteristics including age, parity and previous and current health conditions. The Medical Birth Register also includes extensive information on infants, including growth indicators (birth weight, height, and length), gestational age and information on health conditions and medical procedures during delivery.

The Swedish National Board of Health and Welfare maintains the National Patient Register, from which we obtained all in-patient visits between 1987 and 2018 (1987 is when the register became nationwide) and >80% of out-patient visits to hospital-based specialized health care physicians between 2001 and 2018 (this register became active in 2001). The National Patient Register contains information on diagnoses, date of admission and discharge, procedures, and treatments. Deaths were identified via the Swedish National Board of Health and Welfare's Causes of Death Register. We excluded women who died at 15 years of age or younger or who were not alive in 2001. Information on education was obtained from Statistics Sweden's Longitudinal Integration Database for Health Insurance and Labor Market Studies. This data contains annual information on education for all individuals older than 16 years, between 1990 and 2018. For each individual, we collected information on the highest level of education attained by the end of 2018.

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 chose to include only 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 = 4,787), vaginismus (n = 2,063), or both (n = 867) based on ICD codes recorded in the National Patient Register between 2001 and 2018 (see below). Each case was matched on 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.[18,19] By including both conditions, we increase the sensitivity of our outcome and maximize the likelihood of capturing 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 is that this code is not valid for the assessment of localized provoked vulvodynia. Therefore, we conservatively chose to exclude 372 women with vulvodynia only, 126 with vaginismus only, and 118 with vulvodynia and vaginismus due to the presence of the N90.8 code. Thus, our final sample of cases included 4,415 women with vulvodynia only, 1,937 with vaginismus only, and 749 with both (total N of cases = 7,101). We also excluded 102 women with N90.8 codes from our sample of controls leaving a total of 15,332 for our analyses. Fig 1 illustrates how we obtained our final sample of cases and controls.

Description of Exposures—Events that Could Impact Immune Dysfunction

We used the Medical Birth Register and the National Patient Register to identify events at birth that could impact immune function later in life, and clinical diagnoses of immune-related conditions from birth through 2018. We created categories of immune related conditions across the life course, including: 1) disorders involving the immune system (immunodeficiencies), 2) single organ autoimmune conditions, 3) multi-organ autoimmune conditions, 4) allergy and atopy conditions, and 5) malignancies involving immune cells (codes detailed in Supplemental Table 1). In Fig 2, we illustrate the conceptual model that guided our analyses. In addition, we assessed the distribution of all other ICD diagnoses not directly considered immune-related conditions to determine whether women with vulvodynia, vaginismus or both were more likely to have greater rates of other diagnoses relative to controls.

For events at birth, we limited our assessments to mode of delivery, gestational age at birth and birthweight. Although participant mother's use of antibiotics, infections, and choice to breastfeed could impact offspring immune function, we were unable to link these maternal events to the women included in our study. Thus, ICD-9 and ICD-10 codes associated with mode of delivery, gestational age, preterm birth, and birthweight were identified and used to classify participants. We also assessed whether individuals had multiple ICD codes across the 5 different immune categories listed above.

Statistical Analyses

We assessed the distributions of demographic characteristics including birth year, history of live births, region of residency, and education among cases and controls stratified by those with vulvodynia only, vaginismus only, and both vulvodynia and vaginismus. We further assessed categories of birth related events and immune conditions reported across the life course in controls, and the three stratified case groups. After comparing the distributions between the three vulvar pain categories we found them to be similar across the demographics, birth related events and immune conditions and thus combined all vulvar pain categories in our analyses.

We used multivariable conditional logistic regression methods to calculate odds ratios (OR) and 95% confidence intervals (CIs) that estimated associations of the various birth events and immune conditions across the life course with vulvar pain. We adjusted for birth year, parity, education, and region of residence at birth in all analyses. When assessing immune specific conditions, we additionally adjusted for mode of delivery, gestational age, low birthweight and preterm birth. We also assessed the association between immune related conditions and vulvar pain among those who did and did not have any of the birth related exposures assessed (cesarean section, preterm delivery, small for gestational age,

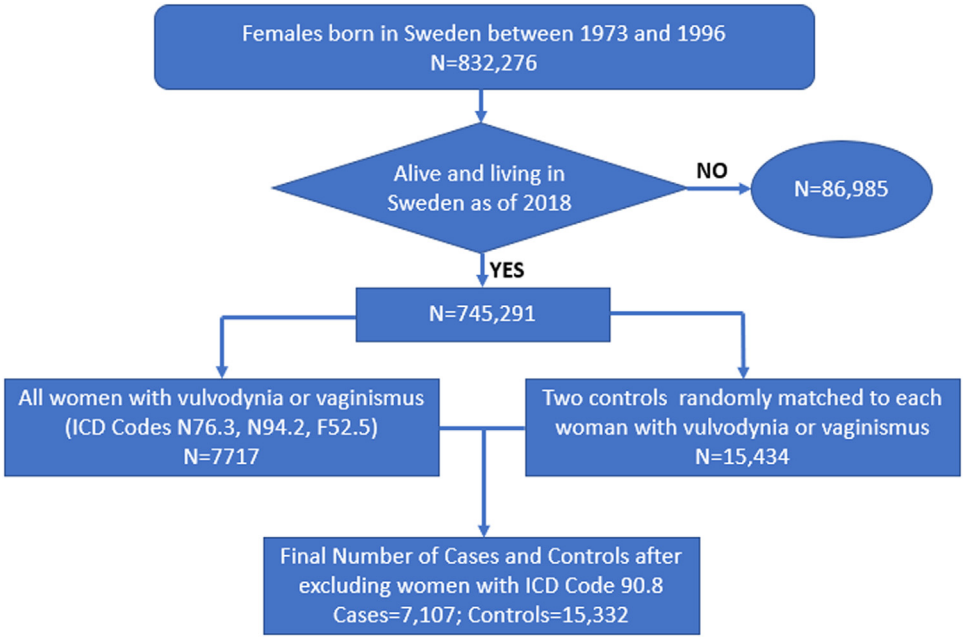

Figure 1. Process by which cases and controls were identified.

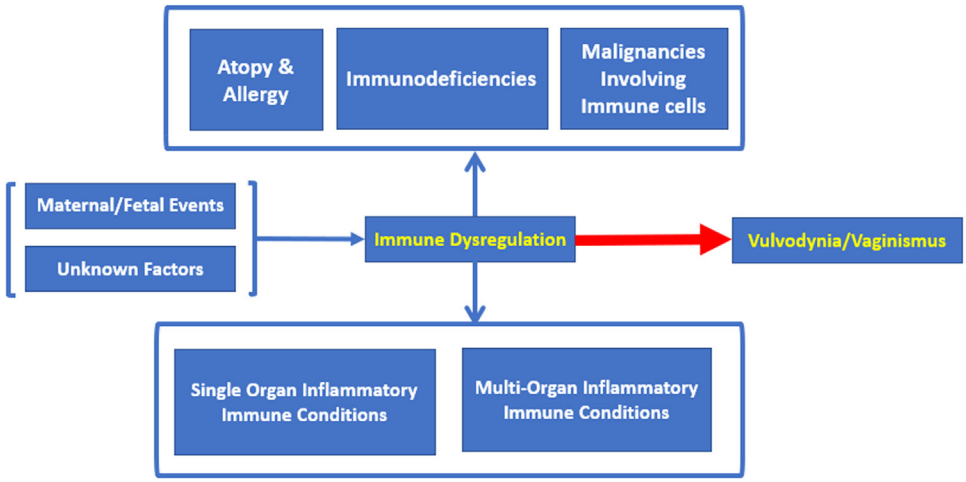

Figure 2. Conceptual model illustrating our analytic approach.

and low birthweight) to evaluate the effect modification of these birth events on our immune conditions' associations. Additionally, we assessed the associations in those who had one versus two versus three or more different immune related codes in relation to vulvar pain.

Results

Women with vulvodynia, vaginismus, or both had a median age of 23 at their first vulvar pain code in the registry. Fewer than 10% were entered at age 18 or younger, or 30 years of age or older. The distribution of women with no vulvar pain, vulvodynia only, vaginismus only, or both was similar by birth year compared to controls (Table 1). 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 being by region of residence.

Compared to women with no vulvar pain history, women with vulvodynia, vaginismus or both were more likely to have been born by cesarean section, delivered before 37 weeks, and/or as a small-for-gestational-age baby, and/or <2500 grams at birth (Table 2). Women with vulvodynia, vaginismus or both were more commonly diagnosed with immunodeficiency conditions,

Table 1. Demographic Characteristics of Women With and Without Vulvodynia, Vaginismus or Both by Birth Year, Parity, Region of Birth and Education

	No Vulvar Pain (N = 15,332)	*Vulvodynia Only (N = 4415)*	*Vaginismus Only (N = 1937)*	*Vulvodynia and Vaginismus (N = 749)*
	N (%)	*N (%)*	*N (%)*	*N (%)*
Birth year				
1980–1984	3742 (24.4)	1065 (24.1)	496 (25.6)	169 (22.6)
1985–1989	5571 (36.3)	1550 (35.1)	702 (36.2)	305 (40.7)
1990–1994	4989 (32.5)	1487 (33.7)	609 (31.4)	226 (30.2)
1995–1999	1030 (6.7)	313 (7.1)	130 (6.7)	49 (6.5)
Parity				
0	8770 (57.2)	2793 (63.3)	1173 (60.6)	511 (68.2)
1	2613 (17.0)	753 (17.1)	350 (18.1)	116 (15.5)
2 or more	3949 (25.8)	869 (19.7)	414 (21.4)	122 (16.3)
Region of residence at birth				
South	3491 (22.8)	754 (17.1)	418 (21.6)	170 (22.7)
Middle	8694 (56.7)	2566 (58.1)	1159 (59.8)	392 (52.3)
North	3146 (20.5)	1095 (24.8)	360 (18.6)	187 (25.0)
Missing	1			
Highest education				
<High school (<9 y)	1119 (7.3)	152 (3.4)	111 (5.7)	25 (3.3)
High school (9 y)	6436 (42.0)	1432 (32.4)	751 (38.8)	247 (33.0)
>High school (>9 y)	7775 (50.7)	2831 (64.1)	1075 (55.5)	477 (63.7)
Missing	2			

Table 2. Distribution of Maternal/Neonatal Events at Birth and Immune Conditions Across the Life Course by Vulvar Pain Diagnoses

Birth Events and Immune Conditions	*No Vulvar Pain (N = 15,332)*	*Vulvodynia Only (N = 4415)*	*Vaginismus Only (N = 1937)*	*Vulvodynia & Vaginismus (N = 749)*
	N (%)	*N (%)*	*N (%)*	*N (%)*
Delivered by cesarean section	1733 (11.3)	547 (12.4)	244 (12.6)	93 (12.4)
Gestational age				
Mod-aevere SGA	1757 (11.5)	545 (12.3)	273 (14.1)	88 (11.7)
Appropriate for GA	11,947 (79.9)	3456 (78.3)	1491(77.0)	590 (78.8)
Mod-severe LGA	1371 (8.9)	354 (8.0)	141 (7.3)	61 (8.1)
Unknown	257 (1.7)	60 (1.4)	32 (1.7)	10 (1.3)
Preterm birth (<37 weeks)	914 (6.0)	294 (6.7)	161 (8.3)	54 (7.2)
Low birthweight (<2500 grams)	657 (4.3)	220 (5.0)	130 (6.7)	43 (5.7)
Immunodeficiencies	52 (0.3)	29 (0.7)	12 (0.6)	2 (0.3)
Single organ inflammatory autoimmune disorders	590 (3.8)	228 (5.2)	111 (5.7)	38 (5.1)
Multiorgan inflammatory autoimmune disorders	299 (2.0)	129 (2.9)	62 (3.2)	22 (2.9)
Malignancies involving immune cells	26 (0.2)	8 (0.2)	10 (0.5)	1 (0.1)
Allergy or atopy conditions	3306 (21.6)	1374 (31.1)	617 (31.9)	236 (31.5)

Table 3. The Association between Immune Conditions across the Life Course with Vulvodynia and or Vaginismus Diagnoses*

Immune Conditions	*All Women*		*No Adverse Birth Events*		*Any Maternal Fetal Conditions*	
	Crude OR (95% CI)	*Adjusted† OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted‡ OR (95% CI)*	*Crude OR (95% CI)*	*Adjusted‡ OR (95% CI)*
Immunodeficiencies	1.8 (1.2–2.7)	1.8 (1.2–2.8)	2.1 (1.3–3.2)	2.0 (1.3–3.2)	1.1 (0.5–2.6)	1.3 (0.5–3.1)
Single organ auto-immune disorders	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.7)	1.3 (0.9–1.8)	1.3 (0.9–1.8)
Multi organ auto-immune disorders	1.6 (1.3–1.9)	1.6 (1.3–1.9)	1.5 (1.2–1.9)	1.6 (1.3–1.9)	1.7 (1.1–2.6)	1.8 (1.2–2.8)
Immune cell malignancies	1.6 (0.9–2.9)	1.7 (0.9–3.1)	1.7 (0.9–3.2)	1.8 (1.0–3.4)	0.9 (0.2–5.2)	1.2 (0.2–7.7)
Allergy/atopy conditions	1.7 (1.6–1.8)	1.7 (1.6–1.8)	1.6 (1.5–1.8)	1.7 (1.6–1.8)	1.7 (1.5–2.0)	1.7 (1.5–2.0)

*Women with vulvodynia only, vaginismus only, and both vulvodynia and vaginismus were combined as cases.
†Adjusted for birthyear, parity, education, residential location, and history of cesarean section, preterm birth or low birth weight at delivery.
‡Adjusted for birthyear, parity, education, and residential location.

single and multiorgan autoimmune disorders, malignancies involving immune cells, and allergy or atopy conditions compared to controls.

We combined women with vulvodynia, vaginismus or both together as "cases" to assess our risk estimates in comparison to controls. Cases were 40 to 80 percent more likely to experience one of these immune-related conditions compared to controls after adjustment for birth year, education, parity, region of residence and history of cesarean section, preterm birth or low birth weight at delivery (Table 3). These associations were largely unchanged when the study population was restricted to *those who did not have* the events at birth listed above. When the study population was restricted to *those with the birth related events listed above*, we did not see a substantial attenuation of these findings other than in the categories of immunodeficiencies and immune related malignancies which was relatively rare within this population.

We further assessed the association between increasing numbers of unique immune-related conditions and our outcome (Table 4). We observed a dose-response increase in the association with increasing numbers of independent immune conditions, with 3 or more conditions associated with 2.4-fold greater odds of having vulvodynia, vaginismus or both compared to those with no history of vulvar pain, after adjustment for covariates.

Lastly, we assessed the proportion of cases and controls aligned with all other ICD codes across their lifetime excluding the vulvar pain codes used to classify cases, and all the codes used to classify cases and

Table 4. The Association Between Immune Related Conditions and Vulvodynia and or Vaginismus

Number of Unique Immune Related Conditions	*Crude OR (95% CI)*	*Adjusted* OR (95% CI)*
None	1.0	1.0
1. Code only	1.6 (1.5–1.7)	1.6 (1.5–1.7)
2. Different codes	2.3 (2.0–2.8)	2.4 (2.1–2.9)
3. or more different codes	3.0 (1.7–5.6)	2.9 (1.6–5.4)

*Adjusted for birthyear, parity, education, residential location, and history of cesarean section, preterm birth or low birth weight at delivery.

Table 5. Distribution of ICD-10 Overall Global Categories of Diseases by Vulvar Pain Diagnoses, Excluding Immune Related Conditions, Vvulvodynia, and Vaginismus Used in Tables Above, Ordered by Percent Differences

ICD-10 Codes (Overall Global Categories of Diseases)	*No Vulvar Pain (N = 15,332)*	*Vulvodynia, Vaginismus, or Both (N = 7,101)*	*Percent Difference*
	N (%)	*N (%)*	*%*
N80-N99.9 (Noninflammatory disorders of female genital tract)	5,596 (36.5)	4,288 (60.4)	23.9
L00-L99 (Skin conditions)	3,221 (21.0)	2,393 (33.7)	12.7
A00-B99 (Infectious and parasitic diseases)	9,583 (62.5)	5,278 (74.3)	11.8
K20-K99 (Digestive diseases, Appendix, hernias, liver)	3,264 (21.3)	2,276 (32.1)	10.8
F00-F99 (Mental health and behavioral disorders)	4003 (26.1)	2602 (36.6)	10.5
Z00-Z99 (Health care screenings and counselling)	9,678 (62.7)	5,648 (73.2)	10.5
M00-M99 (Arthropathies, orthopedic, bone conditions)	4,456 (29.1)	2,693 (37.9)	8.8
H00-H99 (Disorders of the eye and ear)	3,641 (23.7)	2,142 (30.2)	6.5
N00—N39.9 (Kidney and bladder conditions)	2,009 (13.1)	1,364 (19.2)	6.1
G00-G99 (CNS Inflammatory disorders)	2,100 (13.7)	1,408 (19.8)	6.1
V00-X99 (Collisions, falls, accidents, assaults)	2,156 (14.0)	1,452 (18.8)	4.8
C00-D49.9 (Benign/malignant neoplasms)	4,527 (29.5)	2,424 (34.1)	4.6
J00-J99 (Respiratory conditions)	3,166 (20.6)	1,729 (24.3)	3.7
S00-T99 (Injuries, trauma, poisonings, maltreatment)	7,758 (50.3)	4,132 (53.5)	3.2
N60-N64.9 (Benign breast related conditions)	617 (4.0)	420 (5.9)	1.9
E00-E99 (Endocrine organ disorders)	2245 (14.6)	1168 (16.4)	1.8
K00-K19.9 (Oral cavity, salivary glands, mouth and jaw)	732 (4.8)	471 (6.6)	1.8
I00-I99 (CVD disorders and diseases)	974 (6.4)	577 (8.1)	1.7
D50-D99 (Anemias, spleen, blood disorders)	565 (3.7)	305 (4.3)	0.6

controls with key immune-related conditions (Table 5). We sorted the ICD global categories of diseases by those with the greatest differences between cases and controls. Across all categories, cases had higher percentages of ICD codes compared to controls. Most notably, cases showed the greatest percent differences in having other comorbid noninflammatory disorders of the female genital tract. Other conditions notably higher among cases included skin conditions, infectious diseases, digestive diseases, mental health disorders, and ICD codes aligned with health care screening, respectively.

Conclusions

Using the nationwide Swedish register data, we found that women with localized provoked vulvodynia, vaginismus or both were more likely to experience a wide spectrum of other immune related conditions throughout their life course compared to women who had never been diagnosed with a vulvar pain syndrome. This association became stronger with increasing numbers of unique immune related conditions relative to women with no vulvar pain history. In this analysis and in our earlier publication,[19] we observed that women born through cesarean section, or as a preterm birth, small for gestational age, or low birth weight baby were more likely to be vulvodynia cases. However, the absence of these events at birth did not alter the associations between immune related conditions and vulvar pain.

A number of studies have now suggested that vulvodynia is a consequence of a persistent immune-inflammatory process with a greater abundance of proinflammatory and anti-inflammatory immune proteins,[26] mast cells, lymphocytes and T-Cells[23] than that observed in women with no vulvar pain histories. This clearly aligns with the knowledge that there is substantial crosstalk between the immune and neuronal systems. Neuropeptides are known to activate immune cell function, and inflammatory mediators produced by immune cells enhance neuronal activation.[5,15,21] Thus, the pathogenic mechanism that leads to the development of vulvar pain is becoming better understood.

However, what is less understood and studied is why certain women exposed to events that lead to hyperimmune activated responses go on to develop vulvodynia while many who experience the same exposures do not. Our findings bring forth the hypothesis that women who develop vulvar pain later in life may be more likely to have experienced immune-compromising health conditions, perhaps as early as birth.[19] We and others have shown that women with vulvodynia are prone to greater numbers of yeast and other sexually transmitted infections[10,20] but it is unclear whether these women are more susceptible due to a compromised immune system. There is an ongoing discussion in the scientific literature whether changes in local vaginal immune factors are responsible for the recurrent infections,[3] but it is unclear whether women with recurrent vulvovaginal candidiasis also have a general immune deficiency.

It is clear from Table 5, that women with vulvar pain are more likely to be diagnosed with a wide range of conditions beyond those that we specifically targeted as disorders involving the immune system (immunodeficiencies), single organ and multiorgan autoimmune conditions, allergy and atopy conditions, and malignancies involving immune cells. It's possible that the

conditions listed in Table 5 with the greatest differences between cases and controls could be indirectly related to cases being more susceptible to disorders involving the immune system and thus more susceptible to illnesses in general. We can also not rule out that the differences between cases and controls that are smaller (perhaps less than 5%) may be due to cases being more likely to seek care for a wide range of conditions and therefore more likely to be diagnosed with conditions that otherwise might not be identified among controls who seek care less often. This is particularly relevant given we observed that our cases were more highly educated than controls, and education is associated with greater health care seeking behaviors.[8] Although we did adjust for education in all our analyses, if women with vulvodynia do seek care more often because immune disorders require more health care visits, then further adjusting for health care visits would spuriously attenuate the findings.

To further address this issue of health care seeking behavior, we restricted our immune related conditions to only those that had in-patient assessments. Given that in-patient assessments need to be arranged by the health care provider, and not the patient, we sought to determine whether our associations remained. Although the numbers were substantially smaller, and some of our findings did in fact attenuate, we still observed significant adjusted associations with single-organ immune conditions (aOR 1.3, 1.1−1.6), and allergy and atopy conditions (aOR = 1.3, 1.1−1.5).

We further assessed the differences in our Table 5 prevalence estimates among those with higher education (post high school) versus lower education (high school or lower). Regardless of whether the conditions are immune or nonimmune related, we see that women with vulvar pain have higher rates regardless of education. This suggests that women with vulvar pain, are in general a less healthy population. Whether that is due to our hypothesis of immune dysfunction, or some other reason, it's hard to disentangle health care seeking within a population that is in general, less healthy.

There are numerous strengths associated with our study including the fact that we used a data source that represents 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. However, we recognize that our study is not without limitations. Because the first onset of vulvar pain cannot truly be documented by the date of entry into the Swedish register system, 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 immune related events across the life course in those with the outcome of vulvodynia, vaginismus, or both at some point in their lifetime in comparison to those with no such vulvar pain history. Although this does not allow us to do a comparison of incidence, it does allow us to assess the odds of vulvar pain in relation to the various immune conditions. Thus, we cannot be sure of the temporal assessments of when the immune conditions occurred in relation to the true first onset of vulvar pain. However, since we are not testing whether these immune related conditions "cause" the onset of vulvar pain, but rather, assessing their association with the development of vulvar pain, we believe these findings are quite compelling.

Another limitation stems from the minimal number of 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 the onset of immune related conditions. In addition, we and others have shown that a large proportion of women fail to seek care for their vulvar pain. Also, 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. Thus, we recognize that our cases of vulvodynia, vaginismus and both captured within the Swedish registers may not represent all women who suffer from these conditions. In fact, it is possible that our "cases" may represent only those with the most severe symptoms. However, many women in the registers that served as controls could have in truth been cases given this misclassification and thus we believe that our associations observed may in fact be an attenuation of the true associations given this potential misclassification.

In conclusion, we found that women with vulvodynia appear more likely to experience a spectrum of immune related conditions across the life course suggesting that women with vulvodynia may have a more compromised immune system that puts them at risk of developing this debilitating condition. Given that other chronic pain conditions such as interstitial cystitis, irritable bowel syndrome, and fibromyalgia are often observed comorbidly with vulvar pain, assessing the degree to which immune dysfunction occurs more or less so in those with multiple chronic overlapping pain conditions would be of interest.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2023.03.007.

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