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# Latent class analysis of comorbidity patterns among women with generalized and localized vulvodynia: preliminary findings

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**Background:** The pattern and extent of clustering of comorbid pain conditions with vulvodynia is largely unknown. However, elucidating such patterns may improve our understanding of the underlying mechanisms involved in these common causes of chronic pain. We sought to describe the pattern of comorbid pain clustering in a population-based sample of women with diagnosed vulvodynia.

**Methods:** A total of 1457 women with diagnosed vulvodynia self-reported their type of vulvar pain as localized, generalized, or both. Respondents were also surveyed about the presence of comorbid pain conditions, including temporomandibular joint and muscle disorders, interstitial cystitis, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, endometriosis, and chronic headache. Age-adjusted latent class analysis modeled extant patterns of comorbidity by vulvar pain type, and a multigroup model was used to test for the equality of comorbidity patterns using a comparison of prevalence. A two-class model (no/single comorbidity versus multiple comorbidities) had the best fit in individual and multigroup models.

**Results:** For the no/single comorbidity class, the posterior probability prevalence of item endorsement ranged from 0.9% to 24.4%, indicating a low probability of presence. Conversely, the multiple comorbidity class showed that at least two comorbid conditions were likely to be endorsed by at least 50% of women in that class, and irritable bowel syndrome and fibromyalgia were the most common comorbidities regardless of type of vulvar pain. Prevalence of the multiple comorbidity class differed by type of vulvar pain: both (37.6% prevalence, referent), generalized (21.6% prevalence, adjusted odds ratio 0.41, 95% confidence interval 0.27–0.61), or localized (12.5% prevalence, adjusted odds ratio 0.31, 95% confidence interval 0.21–0.47).

**Conclusion:** This novel work provides insight into potential shared mechanisms of vulvodynia by describing that a prominent comorbidity pattern involves having both irritable bowel syndrome and fibromyalgia. In addition, the prevalence of a multiple comorbidity class pattern increases with increasing severity of vulvar pain.

**Keywords:** vulvodynia, generalized, localized, comorbidity

## Introduction

Approximately 8%–18% of American women at some point in their lives have had chronic vulvar pain symptoms consistent with a diagnosis of vulvodynia.[1–4] As defined by the International Society for the Study of Vulvovaginal Disorders, vulvodynia is characterized by vulvar discomfort in the absence of gross anatomical and neurological findings.[3] This condition can be further subdivided into multiple classifications, highlighting its heterogeneous nature. Classifications of vulvar pain may include localized or generalized pain, with the ability to have both,[5,6] provoked or nonprovoked,[5,7] and primary or secondary.[8] Among the estimated 110 million

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chronic pain sufferers in the US, women with vulvodynia may be unique due to their high rate of comorbidity,[9–12] the psychosocial impact of this condition,[13–15] the young age at which the peak incidence occurs,[16,17] and the potential for reproductive consequences.[18,19]

Pain conditions such as fibromyalgia, irritable bowel syndrome, interstitial cystitis, temporomandibular joint and muscle disorders, and chronic fatigue syndrome are common among women with vulvodynia.[2,9–12,20] Reed et al recently reported that women with vulvodynia were 2–3 times more likely to have one of these conditions.[10] Our own recent work has found that women with vulvodynia were more likely to feel isolated and that their pain was invalidated if they had a comorbid pain condition, and that this association was greater in the presence of multiple comorbid pain conditions.[9] It is unknown how these feelings could affect the presence of vulvar pain. However, there is evidence suggesting that the pain from one condition may influence the presence of pain from another condition. In a recent study of women with interstitial cystitis, it was concluded that specific sensitivities are associated with differing patterns of comorbid pain conditions,[21] perhaps indicating a unique biological mechanism for certain clusters of pain conditions. In a separate study of individuals with interstitial cystitis, the presence of comorbid pain conditions was a significant predictor of the prognosis of interstitial cystitis.[22] These studies suggest that the presence of comorbid pain disorders could either worsen disease or be a marker of more severe pathology.

Despite our knowledge that pain conditions often co-occur, previous studies have not identified patterns of comorbid clustering with vulvodynia, and identification of such patterns would be highly beneficial to future studies of the underlying biological mechanisms of these common chronic pain conditions. The purpose of this study was to describe the clustering patterns of comorbid pain in women with vulvodynia. If significant clustering patterns existed, we determined whether the cluster patterns differed in prevalence by the extent of vulvar pain, ie, localized, generalized, or both.

# Materials and methods

## Study design and sample

The data used in this study were from an online cross-sectional study (the Coexisting Conditions Survey) conducted by the National Vulvodynia Association (NVA) using a convenience sample of its membership. The NVA is the leading patient advocacy organization representing women with vulvodynia and those affected by the condition. The NVA has collaborated with research institutions on research studies using its membership, as well as having initiated research of its own. The Coexisting Conditions Survey was initiated by the NVA and is available on the NVA website (http://www.nva.org). In January 2009, the NVA notified its patient membership of the survey. Women were asked to refrain from completing the survey if they had yet to be diagnosed with vulvodynia. Therefore, the only inclusion criterion was a formal diagnosis of vulvodynia. Responses were anonymous and there was no compensation given for completing the survey. Data for this study represent participants recruited from January 2009 to April 2011. Originally 1460 women responded to the survey, with three dropouts due to incomplete responses. Therefore, our analytical dataset included 1457 women.

## Survey

The survey is a 13-item instrument assessing age, basic information about a woman's history of vulvodynia, and history of a physician diagnosis of any of the following comorbid pain conditions: interstitial cystitis, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, endometriosis, temporomandibular joint and muscle disorders, chronic headache, and burning mouth syndrome. If a woman reported that she had been diagnosed with a comorbid condition from the list, she was asked to report if the symptoms of the other condition began before, around the same time, or after the onset of symptoms of vulvodynia. Women were also asked whether their diagnosis of vulvodynia included a subtype; women could report if they had been diagnosed with generalized vulvodynia, vulvar vestibulitis syndrome/vestibulodynia, or both.

## Statistical analysis

We used a multigroup latent class analysis[23] to identify and compare patterns of comorbidity between women with localized, generalized, or both forms of vulvodynia; a woman could only be classified into one of these types of vulvar pain categories. In the first stage of the analysis, we estimated iterative latent classes separately for each of the three vulvar pain categories. We compared the fit of the iterative models using the Akaike information criterion, the Bayes information criterion, and the Lo-Mendel-Rubin likelihood ratio test.[24] A model with one additional class was considered an improvement in fit with lower Akaike information criterion and Bayes information criterion values and a statistically significant ($P < 0.05$) likelihood ratio test. We also evaluated

the absolute fit of each model using the $G^2$ statistic and its associated degrees of freedom.[23] A nonsignificant ($P > 0.05$) $G^2$ value indicated a close approximation between the model-implied contingency table and the empirical contingency table of the indicator items used in the latent class analysis. All models were adjusted for age, which was entered as continuous after natural logarithm transformation.

After identifying the optimal solution for each outcome, we tested a series of multigroup models that placed increasing constraints on parameter equality between the groups.[23] In the first model, we freely estimated the item thresholds and the participant classification for all three vulvar pain types. We then constrained the thresholds to equality for comparison of the equivalence of the latent class structure. A final model restricted the classification distribution of participants to equality across the outcome groups. We used the difference in $G^2$ estimates between each model and the difference in degrees of freedom as a likelihood ratio test of the worsening of model fit with the imposed constraints. Posterior probabilities were reported after rescaling to a percentage (ie, multiplying the probability by 100%). We estimated all latent class models in Mplus version 6.1.[25]

## Research ethics

No identifying information was collected in the Coexisting Conditions Survey. Therefore, the institutional review board at the University of Minnesota exempted this secondary data analysis from human subjects approval because no identifying information was collected or transferred to the University of Minnesota by investigators from the NVA.

# Results

The mean age of the 1457 women who completed the survey was 41.5 ± 14 years and they had a mean duration of vulvodynia of 48 ± 63 months. In total, 32.1% had generalized vulvodynia, 43.9% had localized vulvodynia, and 24.1% had both types of vulvodynia present at the time of the survey.

Table 1 shows the distribution of the eight comorbid conditions in each of the vulvodynia outcome groups. For all three groups, the most common conditions were temporomandibular muscle and joint disorders, interstitial cystitis, and irritable bowel syndrome. Overall, participants with both generalized and site-specific vulvodynia reported a greater prevalence of comorbid conditions. Burning mouth syndrome had the lowest prevalence overall, and was omitted from the latent class analysis because of low variability.

Outcome-specific latent class models (Table 2) indicated that a two-class solution was optimal for each vulvodynia outcome (Lo-Mendel-Rubin likelihood ratio test [LMR-LRT], $P < 0.001$). For generalized vulvodynia, the three-class model had a lower Bayesian information criterion, but the LMR-LRT was not statistically significant, indicating that the increase in model complexity with the three classes did not produce a strong improvement in the model fit. For the other two types of vulvodynia, the information criterion values for the three-class solutions were larger than for the two-class solutions, and differences in the likelihood ratio tests were not statistically significant, thus leading us to prefer the two-class solution. For all three outcomes, interpretation of the two-class model was considered superior to that of the three-class model, further supporting selection of the two-class model for each type of vulvodynia.

Table 3 shows the posterior probabilities of item endorsement within each latent class identified and the distribution of women in each class according to vulvodynia outcome. For women with generalized vulvodynia, the multiple comorbidity class was defined by an endorsement of over 50% for both fibromyalgia and irritable bowel syndrome. Women with localized vulvodynia assigned to the multiple comorbidity class were more likely to endorse both temporomandibular muscle and joint disorders and fibromyalgia using the same threshold. Finally, women with both types of vulvodynia who were assigned to the multiple comorbidity class were more likely to endorse all of the

**Table 1** Frequency of endorsement of each of eight possible comorbidities by type of vulvodynia in 1457 women with self-reported vulvodynia

| | Type of vulvodynia | | | *P* value |
|---|---|---|---|---|
| | Generalized n = 467 (%) | Localized n = 639 (%) | Both n = 351 (%) | |
| **Comorbidity** | | | | |
| TMD | 20.1 | 19.9 | 29.6 | 0.001 |
| Interstitial cystitis | 18.8 | 14.7 | 27.9 | <0.001 |
| Fibromyalgia | 17.3 | 8.9 | 24.2 | <0.001 |
| Chronic fatigue syndrome | 7.9 | 4.7 | 10.5 | 0.002 |
| Irritable bowel syndrome | 29.3 | 29.4 | 37.3 | 0.02 |
| Endometriosis | 12.6 | 11.1 | 14.5 | 0.29 |
| Chronic headache | 18.0 | 17.4 | 19.9 | 0.60 |
| Burning mouth syndrome | 6.4 | 2.0 | 6.0 | 0.001 |
| **Number of comorbidities** | | | | |
| 0 | 37.9 | 41.5 | 28.2 | <0.001 |
| 1 | 27.4 | 31.1 | 26.8 | |
| 2 | 15.6 | 13.5 | 17.9 | |
| ≥3 | 19.1 | 13.9 | 27.1 | |

**Abbreviation:** TMD, temporomandibular joint and muscle disorders.

**Table 2** Fit estimates for iterative latent class models, stratified by three types of vulvodynia

| Classes (n) | LL | AIC | BIC | $G^2$, df | *P* | Entropy | LMR-LRT | *P* |
|---|---|---|---|---|---|---|---|---|
| **Generalized** | | | | | | | | |
| 2 | −1397.57 | 2827.14 | 2842.71 | 129.79, 112 | 0.12 | 0.69 | 171.89 | <0.001 |
| 3 | −1381.66 | 2813.32 | 2837.64 | 99.65, 104 | 0.60 | 0.79 | 31.26 | 0.27 |
| **Localized** | | | | | | | | |
| 2 | −1710.60 | 3453.19 | 3473.72 | 111.31, 112 | 0.50 | 0.72 | 177.88 | <0.001 |
| 3 | −1698.18 | 3446.37 | 3478.45 | 90.69, 104 | 0.82 | 0.84 | 24.41 | 0.06 |
| **Both** | | | | | | | | |
| 2 | −1213.05 | 2458.10 | 2469.12 | 143.39, 112 | 0.02 | 0.63 | 144.00 | <0.001 |
| 3 | −1204.14 | 2458.28 | 2475.49 | 126.01, 104 | 0.07 | 0.76 | 17.49 | 0.56 |

**Abbreviations:** LL, log likelihood; AIC, Akaike information criterion; BIC, Bayes information criterion; LMR-LRT, Lo-Mendel-Rubin likelihood ratio test.

outcomes, except chronic fatigue syndrome and endometriosis. The distribution of women into the assigned latent classes was similar for both generalized vulvodynia and women with both forms of vulvodynia; the proportion of women assigned to the multiple comorbidity class was lower for women with site-specific vulvodynia. Overall, the average probabilities for most-likely latent class membership were high, indicating acceptable quality of classification using the model.

In multigroup assessment, the model which constrained the pattern of item thresholds to equality across the three vulvodynia types did not worsen the model fit (Table 4), indicating that the two-class model had the same structure for all three groups. An additional constraint of equidistribution of women across the latent classes produced a worsening of model fit, indicating that distribution of women was heterogeneous by type of vulvodynia.

The final two-class model showed that the most likely comorbid pattern for all three vulvar pain types was fibromyalgia, irritable bowel syndrome, and temporomandibular muscle and joint disorders, with irritable bowel syndrome having the strongest endorsement in the posterior probabilities (Table 5). We did not observe a statistically significant difference between women with localized vulvodynia and those with generalized vulvodynia in terms of classification into comorbidity patterns when compared with women who reported both forms of vulvodynia. However, women with either localized or generalized vulvodynia were significantly less likely to show the dominant comorbidity pattern than women with both types of vulvodynia (adjusted odds ratio 0.31 compared to having both, 95% confidence interval 0.21–0.47, and adjusted odds ratio 0.41 compared to having both, 95% confidence interval 0.27–0.61, respectively).

## Discussion

To our knowledge, this is the first study to describe comorbid cluster patterns in women with diagnosed vulvodynia. Using latent class analyses, we found that the most common presentation of comorbid clustering with vulvodynia was three comorbid pain conditions, ie, fibromyalgia, irritable bowel syndrome, and temporomandibular muscle and joint disorders, with the least certainty about the last comorbidity. This finding may be useful for classifying women with

**Table 3** Single-group latent class posterior probabilities* and participant classification

| | Generalized | | Localized | | Both | |
|---|---|---|---|---|---|---|
| | No/single comorbidity (%) | Multiple comorbidity (%) | No/single comorbidity (%) | Multiple comorbidity (%) | No/single comorbidity (%) | Multiple comorbidity (%) |
| Comorbidity | | | | | | |
| TMD | 12.2 | 45.6 | 11.7 | 58.7 | 18.8 | 54.6 |
| Interstitial cystitis | 11.8 | 41.4 | 10.3 | 35.7 | 17.9 | 50.9 |
| Fibromyalgia | 4.3 | 59.2 | 2.2 | 41.0 | 8.7 | 59.9 |
| Chronic fatigue syndrome | 1.4 | 28.9 | 0.9 | 22.7 | 2.2 | 29.8 |
| Irritable bowel syndrome | 19.5 | 60.8 | 21.8 | 65.5 | 24.4 | 67.2 |
| Endometriosis | 8.6 | 25.7 | 7.5 | 28.1 | 10.1 | 24.7 |
| Chronic headache | 9.2 | 46.1 | 11.5 | 44.6 | 6.9 | 50.1 |
| Prevalence | 76.2 | 23.8 | 85.3 | 14.7 | 72.4 | 27.6 |
| Average probability of correct classification | 93.2 | 85.4 | 94.1 | 84.7 | 90.5 | 84.7 |

**Note:** *Posterior probabilities reported after rescaling to a percent.
**Abbreviation:** TMD, temporomandibular joint and muscle disorders.

**Table 4** Multigroup comparison of latent class parameters across three types of vulvodynia

| | LL | AIC | BIC | $G^2$, df | $\Delta G^2$, df | *P* |
|---|---|---|---|---|---|---|
| All parameters freely estimated | −5878.55 | 11853.10 | 11954.22 | 384.62, 336 | | |
| Thresholds constrained to equality | −5895.97 | 11831.95 | 11874.08 | 422.08, 364 | 37.46, 28 | 0.11 |
| Classification distributions | −5914.66 | 11865.33 | 11903.25 | 457.90, 365 | 35.82, 1 | <0.001 |

**Abbreviations:** LL, log likelihood; AIC, Akaike information criterion; BIC, Bayes information criterion.

vulvodynia into two distinct etiologic groups, ie, those with no or just one comorbidity and those with multiple comorbidities. We also found that the prevalence of this clustering differed according to type of vulvar pain. Women who had both localized and generalized vulvodynia were significantly more likely to exhibit multiple comorbidities.

Our finding that fibromyalgia and irritable bowel syndrome are highly prevalent among women with vulvodynia is consistent with a previous study examining individual comorbidities. Arnold et al found that fibromyalgia and irritable bowel syndrome were each strongly and significantly associated with vulvodynia.[11] This study did not determine the effect of clustering, and no previous study to our knowledge has determined the association of comorbidity with type of vulvar pain.

We considered what may be contributing to the differences observed according to the severity of vulvar pain. While localized vulvodynia involves a portion or component of the vulva, generalized vulvodynia involves the entire vulva.[26] A woman may be classified as having both types if, for example, she has a burning pain throughout the vulva but there is one portion of the vulva that experiences knife-like pain upon contact. Although hypothesized, it is not known whether women who experience both localized and generalized vulvar pain have a more severe or advanced pathology. Our data cannot directly address the issue of severity of vulvodynia among these women, but they do contribute novel evidence of the heterogeneity of the types of vulvodynia as they relate to comorbid pain conditions, importantly highlighting that if severity in some manner incorporates the presence of comorbid pain conditions, then those women who have both types could be considered to have more severe vulvodynia and an increased likelihood of comorbid pain. An example of the underlying biological mechanism between severe vulvodynia and comorbid conditions could be that women with severe vulvodynia could have a greater level of shared neuronal processing or augmentation with that present with fibromyalgia or irritable bowel syndrome.[27–29]

**Table 5** Latent class posterior probabilities* of item endorsement and distribution of classification of type of vulvodynia in women with a diagnosis of the condition

| | Latent class | | |
|---|---|---|---|
| | No or single comorbidity (%) | Multiple comorbidity (%) | Adjusted OR (95% CI) |
| **Comorbidity** | | | |
| TMD | 13.3 | 50.9 | |
| Interstitial cystitis | 11.7 | 43.0 | |
| Fibromyalgia | 3.3 | 53.5 | |
| Chronic fatigue syndrome | 1.2 | 25.9 | |
| Irritable bowel syndrome | 21.5 | 62.5 | |
| Endometriosis | 8.3 | 25.6 | |
| Chronic headache | 10.0 | 43.7 | |
| **Distribution** | | | |
| Both | 62.4 | 37.6 | 1 (Ref) |
| Generalized | 78.4 | 21.6 | 0.41 (0.27, 0.61) |
| Localized | 87.1 | 12.5 | 0.31 (0.21, 0.47) |

**Note:** *Posterior probabilities reported after rescaling to a percentage.
**Abbreviations:** OR, odds ratio; CI, confidence interval; TMD, temporomandibular joint and muscle disorders; Ref, reference.

## Strengths and limitations

The results of this study could contribute to elucidation of the shared biological mechanisms involved in these types of chronic pain, but our findings should be interpreted in light of the following strengths and limitations. First, the convenience sample cross-sectional design enabled recruitment of a large number of women diagnosed with vulvodynia, and perhaps represents the largest sample to date of women with the condition. Therefore, it is possible that women who had suspected that they had vulvodynia may have also suspected another comorbidity and presented for care, thus potentially inflating our prevalence estimates of comorbidity in women with diagnosed vulvodynia. However, the online survey necessary to capture this number and representation of women from across the US made it impossible to confirm the presence of comorbid pain clinically. It is likely that a self-reported history of diagnosed chronic pain comorbidities in women with vulvodynia may be valid, because previous survey-based population studies have found a high validity between self-reported vulvar pain and clinical confirmation.[30,31] Although not a direct assessment, given that there are no published reports on the validity of self-reported diagnosis of multiple chronic pain conditions, the previous validation studies of vulvar pain indicate that women

with vulvodynia are able to discern specific types of pain. Our survey took the additional measure of requesting that only women with diagnosed vulvodynia complete the survey, and similarly, women were asked to report only diagnosed comorbid conditions. It should be noted that approximately half of women with symptoms of vulvodynia do not seek care for their vulvar pain,[1,4] hence our restriction to those who received a diagnosis is representative only of those women who sought care.

Further, aside from the woman's age, which is a common confounder, we were limited in our ability to account for other potentially confounding variables that may influence the prevalence of prominent comorbidity and type of vulvodynia. Adjustment for confounders typically attenuates an estimate, so if in fact we have missed other important confounders, these prevalence estimates could be overestimated. Future studies should consider collecting information on demographic characteristics and access to health services, which may affect diagnosis of comorbid conditions.[32]

Finally, as reported in the previous literature on vulvodynia and comorbidity, we have not corrected for length of time with vulvodynia. Emerging evidence suggests that underlying mechanisms influencing the development of comorbid conditions could follow a temporal pattern,[33] suggesting that including the duration of vulvodynia may be important in such research. However, at this point, there is no evidence suggesting that certain comorbid conditions precede or result from vulvodynia. Future prospective cohort studies will need to document the onset of comorbid pain conditions following vulvodynia.

## Conclusion

Women with vulvodynia, regardless of type, are likely to have at least two additional pain conditions, and are most likely to have comorbid fibromyalgia and irritable bowel syndrome. Women with both localized and generalized vulvodynia have the highest prevalence of this cluster pattern compared with the other types, indicating that more severe vulvar pain is significantly associated with multiple comorbidities.

Our study demonstrates that there may be both investigational and clinical value in categorizing women with vulvodynia into two groups, ie, those who have no or just one comorbidity and those who have multiple comorbidities. Our findings should be considered when planning future research and adopting screening policies for identifying chronic pain conditions in women with vulvodynia.

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## Disclosure

The authors have no conflicts of interest to report in this work.

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