Dysmenorrhea Symptom-Based Phenotypes: A Replication and Extension Study

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Abstract

***Background*:** Dysmenorrhea is a prevalent pain condition among women and a risk factor for other chronic pain conditions. Individuals vary in dysmenorrhea pain severity, the number of painful sites, and co-occurring gastrointestinal symptoms. Three dysmenorrhea symptom-based phenotypes were previously identified using latent class analysis; however, there is a need to validate these in an independent sample, so they can be used in mechanistic and interventional research. There also is a need to further characterize dysmenorrhea symptom-based phenotypes in terms of demographic, clinical, and psychobehavioral characteristics so they can be used to inform precision dysmenorrhea treatment.

***Objectives*:** The study objectives were to: (a) determine whether the same dysmenorrhea symptom-based phenotypes would be found in a new sample; (b) determine whether including demographic, clinical, and psychobehavioral covariates in latent class analyses would change individuals' phenotype memberships; and (c) investigate relationships between dysmenorrhea symptom-based phenotypes and demographic, clinical, and psychobehavioral characteristics.

***Methods*:** This cross-sectional survey study included 678 women (aged 14 to 42 years) with dysmenorrhea. Participants reported dysmenorrhea symptom severity, demographic, clinical (comorbid chronic pain and gynecological conditions), and psychobehavioral characteristics (perceived stress, anxiety, depression, sleep disturbance, and pain catastrophizing). We used latent class analysis to identify symptom-based phenotypes. We compared analyses with and without covariates (i.e., demographic, clinical, and psychobehavioral characteristics) to determine if individuals' phenotype memberships changed. We then examined associations between phenotypes and demographic, clinical, and psychobehavioral characteristics.

***Results*:** We reproduced three dysmenorrhea symptom-based phenotypes: the "mild localized pain" phenotype (characterized by mild abdominal cramps), the "severe localized pain" phenotype (characterized by severe abdominal cramps), and the "multiple severe symptoms" phenotype (characterized by severe pain at multiple locations and gastrointestinal symptoms). Analyses with and without covariates had little effect on individuals' phenotype membership. Race, comorbid chronic pain condition, endometriosis, and pain catastrophizing were significantly associated with the dysmenorrhea phenotypes.

***Discussion*:** Findings provide a foundation to further study mechanisms of dysmenorrhea symptom heterogeneity and develop dysmenorrhea precision treatments. The three dysmenorrhea symptom-based phenotypes were validated in a second sample. Demographic, clinical, and psychobehavioral factors were associated with dysmenorrhea symptom-based phenotypes.

Keywords: chronic pain, dysmenorrhea, menstruation, pelvic pain, phenotype

Dysmenorrhea Symptom-Based Phenotypes: A Replication and Extension Study

Dysmenorrhea affects 45% to 95% of women of reproductive age or approximately 855 million women worldwide (Iacovides et al., 2015; United Nations, Department of Economic and Social Affairs, Population Division, 2015). It can negatively affect women's physical activity, sleep, and quality of life (Iacovides et al., 2015). Dysmenorrhea commonly occurs with other chronic pain conditions (e.g., irritable bowel syndrome [IBS], migraine, and noncyclic pelvic pain), can worsen other pain conditions, and may even increase women's risk for developing other chronic pain conditions (Altman et al., 2006; Giamberardino, 2008; Olafsdottir et al., 2012; Vincent et al., 2011; Westling et al., 2013).

Although dysmenorrhea is characterized by menstrual pain, significant inter-individual variability exists. Women have described variability in menstrual pain severity, the number of painful sites, and co-occurring gastrointestinal (GI) symptoms (Chen, Draucker et al., 2018; Heitkemper et al., 1988). Using latent class analysis, three distinct dysmenorrhea symptom-based phenotypes have been identified (Chen, Ofner et al., 2018). The first phenotype was "mild localized pain," characterized by mild abdominal cramps and dull pain. The second phenotype was "severe localized pain," wherein women experience severe abdominal cramps. The third phenotype was "multiple severe symptoms," characterized by severe pain at multiple sites and severe GI symptoms (Chen, Ofner et al., 2018). In that study, women in different symptom-based dysmenorrhea phenotypes varied in age, race/ethnicity, and the existence of comorbid chronic pain conditions.

Despite progress in identifying and characterizing individual differences in dysmenorrhea symptomology, three gaps exist. First, it is unclear if prior findings regarding the existence of

three dysmenorrhea symptom-based phenotypes are reproducible. The previous study (Chen, Ofner et al., 2018) included only adult women aged 18 and above; thus, results need to be validated in samples that include younger women. Replication studies are needed in symptom phenotype research(Miaskowski et al.2007). Validating the previous findings in an independent sample is necessary so future research can use these phenotypes to study mechanisms and test differential treatment response.

Second, it is unclear if individuals' phenotype membership varies based on whether covariates (i.e., demographic, clinical, and psychobehavioral characteristics) are included in latent class analysis. Latent class analysis is increasingly used in symptom research to subgroup individuals (Miaskowski et al., 2007; Woods et al., 2016). While latent class analysis can be conducted with and without covariates, it is unclear whether including covariates affects individuals' phenotype classification. In other words, it is unknown whether individual participants will be classified into different phenotype groups when covariates are included in the analysis. Are only the symptom data or both the symptom *and* other covariates data needed to phenotype individuals? Knowing the answer to this question can help researchers understand how best to measure phenotypes in the future.

Third, psychobehavioral correlates of dysmenorrhea symptom-based phenotypes are unknown. Research suggests psychobehavioral characteristics (e.g., perceived stress, depression, anxiety, sleep disturbance, and pain catastrophizing) may be associated with individual differences in chronic pain (Edwards et al., 2006; Fillingim, 2017; Phillips & Clauw, 2011). Individuals with widespread pain commonly reported high levels of perceived stress (Lai et al., 2017). Depression and anxiety commonly co-occur with chronic pain—especially widespread pain (Phillips & Clauw, 2011). Sleep disturbance has a bidirectional relationship with chronic

pain; it can be the result of chronic pain as well as a risk factor for chronic pain (Finan et al., 2013). Lastly, pain catastrophizing, or maladaptive thoughts and feelings about pain characterized by catastrophic thinking and feeling helpless, predicts the severity and number of pain locations in other pain conditions (Schanberg et al., 1997; Sullivan et al., 2001). In the context of dysmenorrhea, research suggests psychobehavioral characteristics are associated with individual differences in menstrual pain severity (Payne et al., 2016; Sahin et al., 2018; Walsh et al., 2003). For example, Walsh et al. (2003) found that high pain catastrophizers reported more severe menstrual pain compared to low pain catastrophizers. However, the association between symptom-based dysmenorrhea phenotypes and psychobehavioral characteristics has yet to be explored. Further characterizing symptom-based dysmenorrhea phenotypes in terms of demographic, clinical, and psychobehavioral variables is a prerequisite to using phenotypes to guide precision dysmenorrhea treatment.

The aims of this study were to: (a) replicate prior study findings in an independent sample that included younger women; (b) compare analyses with and without covariates to determine if individuals' phenotype memberships changed; and (c) investigate associations between symptom-based dysmenorrhea phenotypes and demographic, clinical, and psychobehavioral characteristics.

Methods

Design and Participants

This was a cross-sectional descriptive study. We used data from 678 participants with dysmenorrhea who participated in an online survey. Data collection occurred between January and March of 2019.

Eligibility criteria were: (a) female; (b) age 14–42 years old; (c) living in the United

States; (d) able to read and write English; and (d) self-identified as having had abdominal cramps and other symptoms just before or during a menstrual period (e.g., low back pain, headache, bloating, nausea, diarrhea, or more bowel movements than usual) in the last 6 months. Participants were recruited from online survey panels maintained by the panel provider, Qualtrics (Qualtrics, Provo, UT). Online survey panels consisted of individuals willing to be contacted for internet surveys. The online survey panel providers typically recruited panel participants through internet banner ads, mail or emails, or by word of mouth (Baker et al., 2010).

Procedures

The institutional review board at the Indiana University approved this study. The survey panel provider used registrants' demographic data on file to select potential participants and sent an email notification about the study to this pre-identified group. For those interested in participating, they proceeded by clicking the hyperlink to the survey embedded in the email message. Potential participants were further screened and those who met eligibility criteria were directed to the study information page (i.e., the implied consent form). Those who agreed to participate proceeded to the survey questionnaires.

To ensure data quality, we used three attention filters (i.e., "trap questions") buried in the online survey. We excluded data from those who failed any of the attention filters. In addition, we excluded data from respondents who spent less than one third of the overall group's median time to complete the survey.

Measurement

Dysmenorrhea Symptom Severity

Participants rated the severity of 14 dysmenorrhea-related symptoms: abdominal cramps,

dull abdominal pain or discomfort, low back pain, pain in the upper thighs, headache or migraines, pain when the bladder was full, aches all over, bloating, nausea, vomiting, diarrhea (loose stools), constipation (hard stools), more bowel movements than usual, and fewer bowel movements than usual. The list of symptoms was based on a literature review of dysmenorrhea symptom measures (Chen et al., 2015). Participants rated the severity of each symptom on a 0 ("not present") to 10 ("extremely severe") scale. Each severity rating was then categorized into one of four groups based on established cut points: no symptom (0), mild (1–4), moderate (5–6), and severe (7–10; Serlin et al., 1995). Table 1 summarizes the covariates we used in the latent class analyses and provides descriptions of their corresponding measures.

Demographic and Clinical Covariates

We collected demographic (age, race, ethnicity) and self-reported clinical data on comorbid chronic pain and gynecological conditions. For comorbid chronic pain conditions, participants reported if they had any of the following: back pain, IBS, migraines, nonmigraine headaches, fibromyalgia, neck pain, pelvic pain outside of the menstrual period, interstitial cystitis, and/or other chronic pain. For gynecological conditions, participants reported whether a health provider had ever diagnosed them with endometriosis, uterine fibroids, bacterial vaginosis, and/or polycystic ovary syndrome. These conditions have been linked to dysmenorrhea (Berkley, 2013; Li et al., 2014).

Psychobehavioral Covariates

We assessed psychobehavioral characteristics, including perceived stress, depression, anxiety, sleep disturbance, and pain catastrophizing. Each of the measures described below has demonstrated appropriate reliability and validity.

Perceived stress was measured with the Perceived Stress Scale (Cohen et al., 1983). The

questions in the scale asked participants about their thoughts and feelings during the last month. Participants rated each of 10-items on a 5-point (0–4) scale, with higher scores indicating higher perceived stress.

The Patient-Reported Outcomes Measurement Information System (PROMIS) depression, anxiety, and sleep disturbance short-form scales were used to measure these respective symptoms (Pilkonis et al., 2011; Yu et al., 2012). On each 8-item measure, participants rated the severity of their symptoms during the past seven days on a 5-point (1–5) scale. Raw scale scores were converted to T-scores using a conversion table (more information can be found at www.healthmeasures.net). A score of 50 is the average for the United States general population, and 10 is the standard deviation. Higher T-scores indicated more severe depression, anxiety, or sleep disturbance. Table 1 lists the range of each PROMIS short form.

Pain catastrophizing was measured with the 13-item Pain Catastrophizing Scale (Sullivan et al., 1995). On a scale from 0–4, participants rated the extent to which they worry, amplify, and feel helpless about the experience of pain. Higher scores suggested greater pain catastrophizing.

Data Analysis

Descriptive statistics were used to summarize participants' demographic, clinical, and psychobehavioral characteristics.

Aim 1: Reproducing Dysmenorrhea Symptom-Based Phenotypes

We used latent class analysis to replicate previous research (Chen, Ofner, et al., 2018). Similar to the prior study, we fit the latent class model using the one-step method—in which we regressed the latent variable (i.e., symptom-based phenotypes) on the covariates (i.e., demographic, clinical, and psychobehavioral variables)—while simultaneously estimating the latent class using the dysmenorrhea symptom severity data.

The number of phenotypes (i.e., latent classes) was determined based on model fit and model usefulness. We assessed model fit by inspecting values of the Bayesian information criterion ([BIC], lower value, better fit) and Akaike information criterion ([AIC], lower value, better fit). We assessed model usefulness by inspecting the measure of entropy (with a goal of 0.8 or above) and the interpretability of the latent class solution. Among solutions with entropy values of 0.8 and above, the solution with the lowest AIC and lowest BIC was selected. The interpretation of each phenotype was based on examining posterior probabilities. Specifically, for each symptom, the sum of Manhattan distances between the posterior probabilities and 0.25 was calculated. When the sum is 0.4 and above, the symptom was unevenly distributed across the four severity categories (none, mild, moderate, severe; Chen, Ofner, et al., 2018). For these symptoms, the severity category with the largest probability was used to interpret the phenotype.

Aim 2: Comparing Analyses With and Without Covariates to Determine if Individuals' Phenotype Memberships Changed

We constructed three latent class models: empty model (i.e., model without covariates); partial model (i.e., with demographic and clinical covariates); and full model (i.e., with demographic, clinical, and psychobehavioral covariates). For each model, individual participants were assigned to a phenotype based on probabilities. To determine if three models would result in different phenotype assignment for a given individual, we compared individuals' phenotype memberships across three models. Specifically, we checked the consistency among models for phenotype assignment by calculating the percentage of perfect agreement in latent class membership among models.

Aim 3: Associations Between Phenotypes and Demographic, Clinical, and Psychobehavioral Characteristics

To examine associations between phenotypes and covariates (i.e., demographic, clinical, and psychobehavioral characteristics), we used the one-step latent class model estimation approach in which the phenotypes were estimated and regressed on covariates simultaneously (Bolck et al., 2004). This one-step approach overcomes the biased-estimation issue associated with the traditional three-step approach (Bolck et al., 2004). Strengths and directions of associations between covariates and latent class membership were quantified with odds ratios (ORs) and 95% confidence intervals. We used Mplus (V6.1) for the latent class analysis and SAS/STAT (V9.4) software (Cary, NC) for other analyses.

Results

Sample Characteristics

Table 2 shows the demographic, clinical, and psychobehavioral characteristics of the sample. The mean age of the sample was 28.0 years (*SD* = 7.6; range = 14–42). Among the participants, 71(10.5%) were adolescents younger than 18 years old. Most were White (67.7%) and non-Hispanic/non-Latino (87.9%). More than half (57.2%) had another chronic pain condition, including low back pain (31.7%), migraine headaches (28.8%), neck pain (13.9%), nonmigraine headaches (10.2%), pelvic pain occurring outside of menstrual period (9.7%), and IBS (8.3%). Some participants had been diagnosed with one or more gynecological conditions, including bacterial vaginosis (9.1%), endometriosis (4.9%), polycystic ovary syndrome (4.9%), and uterine fibroids (3.1%).

Aim 1: Reproducing Dysmenorrhea Symptom-Based Phenotypes

For the latent class model with demographic and clinical covariates, the three-class solution had a better model fit (lowest BIC and AIC) and represented a more interpretable classification of individual participants (entropy = 0.8). Based on the posterior probabilities, the

interpretation of the three phenotypes was largely consistent with previous research (Chen, Ofner, et al., 2018). The “mild localized pain” phenotype was characterized by mild abdominal cramps (posterior probabilities = 0.4 for the mild category) with few other symptoms. The “severe localized pain” phenotype was characterized by severe abdominal cramps (posterior probability = 0.5 for the severe category). The “multiple severe symptoms” phenotype was characterized by severe symptoms at multiple sites, including severe abdominal cramps (posterior probability = 0.8 for the severe category), severe menstrual low back pain (posterior probability = 0.6 for the severe category), severe menstrual headache or migraine (posterior probability = 0.6 for the severe category), and severe bloating (posterior probability = 0.6 for the severe category).

Aim 2: Comparing Analyses With and Without Covariates to Determine if Individuals’ Phenotype Memberships Changed

As shown in Table 3, the phenotype membership assignment was largely consistent across the three latent class models (i.e., empty, partial, and full). Among the three models, perfect agreement for phenotype membership assignment was above 94%. Therefore, individuals’ phenotype memberships rarely differed when covariates were included or excluded, suggesting that using only symptom data for defining phenotype membership (i.e., the most parsimonious model) was an appropriate choice.

Aim 3: Associations Between Phenotypes and Demographic, Clinical, and Psychobehavioral Characteristics

As shown in Table 4, certain demographic, clinical, and psychobehavioral characteristics were significantly associated with phenotypes. With regard to demographic characteristics, race was significantly associated with phenotype groups. The odds of Black/African American

women being in the “multiple severe symptoms” phenotype group versus the “mild localized pain” phenotype group were 2.43 times greater than those of White women ($p = 0.041$). Similarly, the odds of Black/African American women being in the “multiple severe symptoms” phenotype group versus the “severe localized pain” phenotype group were 3.78 times greater ($p = .005$).

For clinical characteristics, the number of comorbid chronic pain conditions and a diagnosis of endometriosis were associated with dysmenorrhea phenotypes. For every additional increase in the number of chronic pain conditions, the odds of being in the “multiple severe symptoms” phenotype group versus the “mild localized pain” phenotype group increased by 59% (OR = 1.59, $p = .001$). A diagnosis of endometriosis increased the odds of being in the “multiple severe symptoms” phenotype group versus the “mild localized pain” phenotype 14.8 times (OR = 14.78, $p = .018$).

For psychobehavioral characteristics, pain catastrophizing was associated with dysmenorrhea phenotypes. For a one unit increase in pain catastrophizing score, the odds of being in the “multiple severe symptoms” phenotype group versus the “mild localized pain” phenotype group increased by 6% (OR = 1.06, $p < .001$). Similarly, the odds of being in the “multiple severe symptoms” phenotype group versus the “severe localized pain” phenotype group increased by 4% for each unit increase in the pain catastrophizing score (OR = 1.04, $p = .002$).

Discussion

In this study of 678 women with dysmenorrhea, we replicated and extended previous research on dysmenorrhea symptom-based phenotypes. Specifically, we reproduced previous findings on three dysmenorrhea symptom-based phenotypes, compared analyses with and

without covariates to determine if individuals' phenotype memberships changed, and investigated the associations between dysmenorrhea symptom-based phenotypes and demographic, clinical, and psychobehavioral characteristics.

Following the recommendation of symptom scientists (Miaskowski et al., 2007) and the National Institute of Health initiative to enhance the reproducibility of scientific findings (Colins & Tabak, 2014), we used an independent sample that included younger women to replicate the previous study on dysmenorrhea symptom-based phenotypes. Consistent with a previous study (Chen, Ofner, et al., 2018), we identified three dysmenorrhea symptom-based phenotypes, which were consistent with the previous findings. The previous study included only adult women, while this study included adolescents aged 14 to 17. In addition, there were higher percentages of women who were Asian, Black/African American, and Hispanic in the current study. This study provides additional evidence for the validity of dysmenorrhea symptom-based phenotypes. We encourage other researchers to independently replicate the study. Cumulative evidence will allow researchers to incorporate symptom-based phenotypes to study dysmenorrhea mechanisms and examine differential treatment responsiveness.

We also found that including demographic, clinical, and psychobehavioral covariates in the latent class analysis did not significantly affect individuals' phenotype classification. In other words, including covariates in the latent class analysis did not significantly affect how individual participants were grouped. Latent class analysis has been increasingly used in symptom research to subgroup individuals (Miaskowski et al., 2007). There has been little discussion about whether including covariates in latent class analysis affects participants' classification. Based on this study, symptom severity data alone, without covariates, can be used to classify individuals into different symptom-based phenotypes, which simplifies the measurement of the phenotypes.

These findings should be further replicated in populations with other health conditions.

This study expands upon previous research on dysmenorrhea symptom heterogeneity (Chen, Ofner et al., 2018; Heitkemper et al., 1991) and elucidates demographic, clinical, and psychobehavioral correlates of dysmenorrhea phenotypes. While including these correlates in latent class analysis did not change individuals' phenotype classification, demographic, clinical, and psychobehavioral factors were associated with symptom-based dysmenorrhea phenotypes. Specifically, we found that race, the number of comorbid chronic pain conditions, diagnosis of endometriosis, and pain catastrophizing were significantly associated with symptom-based dysmenorrhea phenotypes. These data can help target and tailor treatments.

The literature on racial and ethnic differences in dysmenorrhea has been limited. We found that women who were Black or African American were less likely to be in the "mild localized pain" phenotype group. Racial differences in menstruation have been reported in previous research. Black or African American women have higher heavy bleeding episodes than White women (Harlow & Campbell, 1996). In various pain conditions, race differences in prevalence and outcomes of chronic pain also have been reported (Campbell & Edwards, 2012). African Americans, compared to non-Hispanic Whites, suffer a greater burden of pain (Campbell & Edwards, 2012). The racial differences could be attributed to biological (e.g., genetic factors influencing pain sensitivity), psychological (e.g., depression and other psychological stress), and social factors (discrimination, access to effective treatments; Campbell & Edwards, 2012). Future research is needed to understand biopsychosocial mechanisms underlying the racial differences in dysmenorrhea symptomology.

Our findings provide additional evidence that dysmenorrhea is associated with other chronic pain conditions (Altman et al., 2006; Hellman et al., 2018; Iacovides et al., 2015;

Olafsdottir et al., 2012; Westling et al., 2013). Consistent with a previous study (Chen, Ofner et al., 2018), we found that having comorbid pain was associated with a greater likelihood of a more severe dysmenorrhea phenotype. Increasing evidence suggests that women with dysmenorrhea have elevated pain sensitivity (Iacovides et al., 2015). Multiple studies have shown that women with moderate-to-severe dysmenorrhea exhibit abnormal structural and functional changes in the areas of the brain involved in pain processing (Tu et al., 2010; Vincent et al., 2011). These changes may increase women's risk of developing chronic pain (Iacovides et al., 2015). Throughout the menstrual cycle, women with dysmenorrhea have increased pain sensitivity; therefore, dysmenorrhea has been classified as a type of central sensitivity syndrome (Iacovides et al., 2015). Central sensitization—characterized by heightened sensitivity to pain in multiple sites—may explain the higher prevalence and number of chronic pain conditions among participants in the "multiple severe symptoms" phenotype group.

A diagnosis of endometriosis was associated with symptom-based dysmenorrhea phenotypes. Previous research has suggested that women with endometriosis were more likely to report severe menstrual pain than those without (Apostolopoulos et al., 2016). It is likely that endometriosis results in inflammation, which in turn exacerbates dysmenorrhea symptoms (Apostolopoulos et al., 2016). It is important to note that the association between endometriosis and dysmenorrhea symptomology has not always been supported. In a previous study, having endometriosis did not differentiate symptom-based dysmenorrhea phenotypes (Chen, Ofner et al., 2018). Other studies have shown little association between endometriosis pelvic pathology and dysmenorrhea symptoms (Gruppo Italiano per lo Studio dell'Endometriosi, 2001; Vercellini et al., 2007). Different study populations and different levels of diagnostic certainties may explain the inconsistent findings.

Our study showed that symptom-based dysmenorrhea phenotypes were associated with psychobehavioral factors, specifically pain catastrophizing. The effect sizes of the association were small, which is likely due to the small unit of measurement for the pain catastrophizing scale. In our analysis, instead of dichotomizing the pain catastrophizing variable, we treated it as a continuous variable with a possible range of 0–52. It also remains unclear whether the association is clinically meaningful. In a previous study by Walsh et al. (2003), high pain catastrophizers reported more severe menstrual pain compared to low pain catastrophizers. The relationship between psychological factors and dysmenorrhea symptomology likely is bidirectional. Psychological factors, such as pain catastrophizing, have been shown to increase the risk of developing chronic pain (Edwards et al., 2016). At the same time, repeated severe menstrual pain may increase women's risk for negative cognitive and affective responses to pain (Liu et al., 2016), as imaging studies have shown that women with dysmenorrhea have abnormal connectivity between brain regions (e.g., hippocampus, medial prefrontal cortex, amygdala) involved in emotional processing (Liu et al., 2016; Tu et al., 2010).

This study has several implications for future research. First, our findings have implications for identifying and characterizing symptom-based phenotypes in other health conditions. Including covariates in a latent class analysis will result in more reliable estimates for covariates and phenotype associations without significantly altering individuals' phenotype membership. Second, longitudinal studies are needed to elucidate the relationships between dysmenorrhea phenotypes and other chronic pain conditions. For example, women in the "multiple severe symptoms" phenotype group may have a higher risk of developing future pain and might be appropriately targeted for more comprehensive and intensive treatment. Similarly, longitudinal studies may shed light on the relationship between dysmenorrhea phenotypes and

psychobehavioral factors. Second, exploring other factors that explain dysmenorrhea symptom heterogeneity is warranted. Researchers can consider additional biopsychosocial processes known to contribute to individual differences in pain (e.g., genetics, traumatic experiences; Fillingim, 2017) and explore interactions between those factors. The knowledge gained from this research could serve as the basis for developing precision treatment for dysmenorrhea.

This study also has implications for clinical practice. First, individual differences in dysmenorrhea suggest a "one-size-fits-all" approach to dysmenorrhea treatment could be inefficient and ineffective. Clinicians mostly treat dysmenorrhea with pharmacotherapy, such as nonsteroidal inflammatory drugs, while 18% of women with dysmenorrhea do not respond to nonsteroidal inflammatory drugs (Owen, 1984). Data in this paper suggest that, for individuals with severe dysmenorrhea symptoms, a more complex combination of therapies may be promising. Second, clinicians need to be aware of the racial differences in dysmenorrhea and its likely multifactorial mechanisms. Research suggests that perceptions of discrimination is prevalent among African Americans with chronic pain and contributes to negative outcomes of chronic pain (Campbell & Edwards, 2012). Clinicians need to make an effort to reflect implicit bias when treating patients and reduce disparity in outcomes of dysmenorrhea and other chronic pain conditions. Third, clinicians should be aware of the linkage between dysmenorrhea and other chronic pain conditions so that they can screen for pain conditions and treat women appropriately. It is important to screen for other chronic pain conditions among women with dysmenorrhea, especially those with more systematic symptoms (menstrual pain at multiple sites and menstrual GI symptoms). In so doing, clinicians can treat conditions that might improve dysmenorrhea management. Conversely, treating dysmenorrhea may reduce symptoms associated with other chronic pain conditions (Giamberardino, 2008). Fourth, the associations

between dysmenorrhea phenotypes and psychobehavioral factors suggest the need to screen for dysmenorrhea among women with high pain catastrophizing. Likewise, among women who have more severe, widespread menstrual pain and menstrual GI symptoms, it can be valuable to screen for pain catastrophizing. Interventions targeting pain catastrophizing may help relieve dysmenorrhea symptoms for some women.

Limitations

This study had limitations. First, the study was cross-sectional, preventing conclusions about causality. We do not know with certainty if specific dysmenorrhea phenotypes increase women's risk for future pain or if having another chronic pain condition exacerbates dysmenorrhea symptoms. The same uncertainty is true for the relationship between dysmenorrhea phenotypes and pain catastrophizing. Second, there could be recall bias in survey responses. Third, clinical data were self-reported; gynecological conditions were not verified. The gold standard for confirmatory diagnosis of endometriosis is laparoscopic inspection with histologic confirmation after biopsy, making confirmatory diagnosis ethically and logistically challenging for a large population-based study. Despite these limitations, we recruited a relatively large and diverse sample in terms of age, race, and ethnicity, and we enhanced data quality by excluding participants who had failed attention filters or took less than one third of the group's median time to complete the survey.

Conclusion

We reproduced the three dysmenorrhea symptom-based phenotypes and found certain demographic, clinical, and psychobehavioral factors were associated with dysmenorrhea symptom-based phenotypes. Findings provide a foundation to further study mechanisms of dysmenorrhea symptom heterogeneity and develop dysmenorrhea precision treatments.

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Table 1

Summary of Demographic, Clinical, and Psycho-behavioral Covariates

Types of Variables	Variable Name	Item Options	Scale	Summary Score
Demographic	Age		Interval	
	Race	1) White 2) Black or African American 3) American Indian or Alaska Native 4) Asian 5) Native Hawaiian or Pacific Islander 6) Other	Nominal	
	Ethnicity	1) Hispanic (Spanish or Latino) 2) Non-Hispanic	Binary	
Clinical	Comorbid chronic pain conditions	1) back pain 2) irritable bowel syndrome 3) migraine 4) non-migraine headaches 5) fibromyalgia 6) neck pain 7) pelvic pain occurring outside of menstrual period 8) interstitial cystitis 9) other chronic pain not listed above	Interval	Number of comorbid chronic pain conditions
	Comorbid gynecological conditions	1) endometriosis 2) uterine fibroids 3) bacterial vaginosis 4) polycystic ovary syndrome	Binary	Existence of each comorbid gynecological condition
Psycho-behavioral	Perceived Stress Scale	10 items each with 6-point ordinal (0-5)	Interval	Total score (Possible range: 0-50)
	PROMIS Depression Short Form	8 items each with 5-point ordinal (1-5)	Interval	PROMIS T Score (Possible range: 35-82)
	PROMIS Anxiety Short Form	8 items each with 5-point ordinal (1-5)	Interval	PROMIS T Score (Possible range: 37-83)
	PROMIS Sleep Disturbance Short Form	8 items each with 5-point ordinal (1-5)	Interval	PROMIS T Score (Possible Range: 29-77)

	Pain Catastrophizing Scale	13 Items each with 5-point ordinal (0-4)	Interval	Total score (Possible range: 0-52)

Table 2

Sample Demographic, Clinical, and Psycho-behavioral Characteristics (N=678)

	Mean ± *SD*	*n* (%)
Age (Mean ± SD)	28.0 ± 7.6	
Years with dysmenorrhea	15.8 ± 7.7	
Race		
White		459 (67.7%)
Black or African American		90 (13.3%)
Asian		53 (7.8%)
Other		76 (11.2%)
Ethnicity Hispanic		82 (12.1%)
Number of Comorbid Chronic Pain Conditions	1.1 ± 1.4	
Bacterial Vaginosis		62 (9.1%)
Endometriosis		33 (4.9%)
Polycystic Ovary Syndrome		33 (4.9%)
Uterine Fibroids		21 (3.1%)
Perceived Stress	22.4 ± 6.4	
Anxiety T-score	62.3 ± 8.8	
Depression T-score	57.1 ± 9.7	
Sleep Disturbance T-score	51.6 ± 4.0	
Pain Catastrophizing	18.3 ± 12.8	

Table 3

Comparing Phenotype Membership for Latent Class Models With and Without Covariates (N=678)

Model Without Covariate	Model with Demographic and Clinical Covariates n (%)			Model with Demographic, Clinical, and Psycho-behavioral Covariates n (%)		
	"Severe Multiple Symptoms" Phenotype	"Severe Localized Pain" Phenotype	"Mild Localized Pain" Phenotype	"Severe Multiple Symptoms" Phenotype	"Severe Localized Pain" Phenotype	"Mild Localized Pain" Phenotype
"Severe Multiple Symptoms" Phenotype	175 (25.8)	4 (0.6)	1 (0.1)	170 (25.1)	3 (0.4)	7 (1.0)
"Severe Localized Pain" Phenotype	7 (1.0)	202 (29.8)	10 (1.5)	5 (0.7)	198 (29.2)	16 (2.4)
"Mild Localized Pain" Phenotype	9 (1.3)	8 (1.2)	262 (38.6)	5 (0.7)	4 (0.6)	270 (39.8)

Note. Perfect agreement between model without covariate and model with demographic and clinical covariates = 94.2%. Perfect Agreement between model without covariate and model with demographic, clinical, and psycho-behavioral covariates=94.1%

Table 4

Associations between Dysmenorrhea Symptom-based Phenotypes and Demographic, Clinical, and Psycho-behavioral Variables Using Latent Class Analysis with Covariates (N=678)

	"Severe Multiple Symptoms" vs "Mild Localized Pain"		"Severe Localized Pain" vs "Mild Localized Pain"		"Severe Multiple Symptoms" vs "Severe Localized Pain"	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age	0.960	(0.810, 1.137)	0.905	(0.773, 1.060)	1.060	(0.883, 1.272)
Black	2.427*	(1.036 5.683)	0.641	(0.258, 1.595)	3.785**	(1.495, 9.583)
Asian	0.778	(0.288 2.100)	0.444	(0.144, 1.366)	1.751	(0.492, 6.234)
Other race	1.035	(0.417 2.569)	1.240	(0.534, 2.880)	0.835	(0.320, 2.182)
Associates degree or Higher	1.130	(0.638 2.002)	1.096	(0.628, 1.915)	1.030	(0.567, 1.873)
Hispanic	1.633	(0.721 3.699)	0.551	(0.203, 1.494)	2.962	(0.910, 9.640)
Years Dysmenorrhea	1.077	(0.913 1.271)	1.130	(0.966, 1.322)	0.953	(0.794, 1.144)
Number of chronic pain conditions	1.592**	(1.216 2.086)	1.438*	(1.088, 1.900)	1.107	(0.912, 1.345)
Bacterial Vaginosis	0.410	(0.162 1.040)	0.624	(0.263, 1.483)	0.656	(0.274, 1.570)
Endometriosis	14.775*	(1.594 136.967)	9.814	(0.972, 99.060)	1.505	(0.575, 3.941)
Polycystic Ovary Syndrome	0.559	(0.139 2.250)	0.516	(0.140, 1.905)	1.083	(0.254, 4.629)
Uterine fibroids	0.830	(0.218 3.166)	1.161	(0.275, 4.911)	0.715	(0.190, 2.696)
PSS Total	0.982	(0.920 1.048)	1.030	(0.968, 1.095)	0.954	(0.891, 1.022)
PROMIS Anxiety T-score	1.036	(0.980 1.095)	1.042	(0.990, 1.098)	0.994	(0.937, 1.054)
PROMIS Depression T-score	0.966	(0.927 1.008)	0.981	(0.938, 1.025)	0.985	(0.940, 1.033)
PROMIS Sleep T-score	1.061	(0.987 1.140)	1.006	(0.938, 1.080)	1.054	(0.981, 1.134)

Pain Catastrophizing total	1.062***	(1.035 1.090)	1.017	(0.992, 1.043)	1.044**	(1.016, 1.073)

Note, *p-value < .05, **p-value < .01, ***p-value < .001