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Symptoms-based Phenotypes among Women with Dysmenorrhea: A Latent Class Analysis

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Abstract

Dysmenorrhea is highly prevalent and may increase women's risk for developing other chronic pain conditions. Although it is highly variable, symptom-based dysmenorrhea phenotypes have not been identified. The study aims were to identify symptom-based dysmenorrhea phenotypes and examine their relationships with demographic and clinical characteristics. In a cross-sectional study, 762 women with dysmenorrhea rated severity of 14 dysmenorrhea-related symptoms. Using latent class analysis, we identified three distinctive phenotypes. Women in the "mild localized pain" phenotype (n=202, 26.51%) had mild abdominal cramps and dull abdominal pain/ discomfort. Women in the "severe localized pain" phenotype (n=412 54.07%) had severe abdominal cramps. Women in the "multiple severe symptoms" phenotype (n=148, 19.42%) had severe pain at multiple locations and multiple gastrointestinal symptoms. Race, ethnicity, age, and comorbid chronic pain conditions were significantly associated with phenotypes. Identification of these symptom-based phenotypes provides a foundation for research examining genotype-phenotype associations, etiologic mechanisms, and/or variability in treatment responses.

Keywords

Dysmenorrhea; chronic pain; pelvic pain; menstruation; phenotype

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Dysmenorrhea is a prevailing pain condition affecting 45% to 95% of women of reproductive age (Iacovides, Avidon, & Baker, 2015). On a monthly basis, it contributes to lost work/study hours, reduced physical activity, and lower quality of life (Iacovides et al., 2015). Commonly occurring with other chronic pain conditions (e.g., irritable bowel syndrome, noncyclic pelvic pain), dysmenorrhea can exacerbate other pain conditions (Giamberardino et al., 2010) or increase women's risk for future chronic pain (Berkley, 2013; Iacovides et al., 2015; Westling, Tu, Griffith, & Hellman, 2013). Given its significant short- and long- term impact on women's lives, scientists have called for more research into dysmenorrhea mechanisms and treatment options (Berkley, 2013; Iacovides et al., 2015).

Symptom–based dysmenorrhea phenotypes have not been identified, which impedes mechanistic investigation and precision-based treatment development. Based on the National Institute of Health Symptom Science Model, phenotypic characterization is fundamental to discovering biomarkers and illuminating precision-based symptom management (Cashion & Grady, 2015). A symptom-based phenotype is a subgroup of individuals with a given condition who share similar symptom characteristics. Symptom-based phenotypes exist in other groups. For example, among women experiencing menopausal symptoms, five different symptom phenotypes were identified that varied in the type and severity of symptoms experienced (Woods et al., 2016). Such phenotypes can be valuable in understanding mechanisms underlying symptoms (Tu & As-Sanie, 2016; Turk, 2005), linking genotypes to phenotypes (Anttila et al., 2006), differentiating treatment effects (Turk, 2005), and tailoring treatments based on phenotypes (Turk, 2005).

Earlier studies suggested that women's dysmenorrhea symptoms vary. For example, women have described variability in whether they experience gastrointestinal symptoms along with painful cramps (Heitkemper, Shaver, & Mitchell, 1988), and whether they experience menstrual pain as severe or excruciating (Ju, Jones, & Mishra, 2014). It is unclear, however, if women form distinctive subgroups based on dysmenorrhea symptom experience.

Factors that differentiate phenotypes are also unknown and these may include demographic and clinical variables. For demographic variables, older age and higher education levels have been related to lower dysmenorrhea prevalence (Ju et al., 2014; Woods, Most, & Dery, 1982). Ethnicity may also have an impact on the dysmenorrhea experience. In a pilot comparative study, Chinese women reported milder menstrual pain than Australian women (mainly Caucasian) (Zhu et al., 2010). Years with dysmenorrhea could affect perceived symptom severity.

Clinical characteristics are also important potential factors to consider. Clinically, dysmenorrhea is commonly classified into two types: primary, when symptoms occur in absence of underlying pathology; and secondary, when symptoms are caused by underlying pathology (e.g., endometriosis and uterine fibroids) (International Association for the Study of Pain (IASP) Taxonomy Working Group, 2011). It is commonly believed that dysmenorrhea symptoms are more severe among women with pelvic pathology than women without pelvic pathology. Research findings, however, have been equivocal. While some research suggests women with endometriosis are more likely to report severe menstrual pain than those without (Apostolopoulos, Alexandraki, Gorry, & Coker, 2016), others suggest

women with and without pelvic pathology experience similar dysmenorrhea symptoms (Nguyen, Humphrey, Kitchen, Rehman, & Norquist, 2015), and the symptom severity is not well correlated with pathology (Gruppo Italiano per lo Studio dell'Endometriosi, 2001). In addition to this pathology-based clinical classification, comorbid pain conditions are important to consider given their high co-occurrence with dysmenorrhea (Berkley, 2013; Giamberardino et al., 2010; Iacovides et al., 2015; Westling et al., 2013).

In this study, our aims were to (1) identify symptom-based dysmenorrhea phenotypes and (2) investigate their relationships with demographic and clinical variables.

Methods

Design and Participants

This was a cross-sectional descriptive study. Using a web-based survey, data were collected from 762 women with dysmenorrhea in the United States (Chen, Kwekkeboom, & Ward, 2016). The University Health Sciences Institutional Review Boards approved this anonymous survey study and granted a waiver of written informed consent. Survey completion implied informed consent. Data collection occurred during January and February of 2015.

Women eligible for the study were (1) at least 18 years old, (2) living in the United States, (3) able to read and write in English, and (4) self-identified as having had dysmenorrhea symptoms in the last 6 months. Participants were recruited through established online survey panels (Qualtrics, UT). Those online panels consisted of individuals who were willing to be contacted for internet surveys. Participants of the panels are usually recruited by banner ads on websites, direct mail or emails, or by word of mouth (Baker et al., 2010). Online survey panels have been used in large studies, including the development of Patient-Reported Outcome Measurement Information System (PROMIS®) funded by the National Institutes of Health (Liu et al., 2010) and flu vaccination coverage study sponsored by the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention (CDC), 2013). The panel provider informed us that panel registrants were of diverse race/ethnicity, thus, we did not make a special effort to oversample a particular race/ethnicity. The panel provider emailed study invitations to panel registrants who met the first three eligibility criteria. Interested women were directed to the survey website, and a screening question further identified those who met the fourth eligibility criterion. The screening question read "Some women experience abdominal cramps and other symptoms just before or during a menstrual period (for example, low back pain, nausea, vomiting, change in the number and type of bowel movements, change in appetite). The medical term for these symptoms is "dysmenorrhea" (pronounced dis-men-uh-ree-uh). Think about the last 6 months. During this time, have you had any of these dysmenorrhea symptoms?" Among 1384 women who responded to the screening question, 977 women indicated that they had experienced symptoms (i.e., met the fourth eligibility criterion) and were invited to complete the study. Participants received compensation ($3.50 USD), as arranged with the panel provider. To safeguard data quality, we excluded the following respondents before data analysis: respondents who clicked the same answer every time; respondents who spent less than one-third the median time to complete the survey; and respondents who failed one or more

attention filters that were embedded in the survey. Attention filters were questions that required a specific response, which was provided within the question (e.g., “mark answer B”). Among the 977 women who met eligibility criteria, 762 (78.0%) completed the survey with valid responses. The median time for survey completion was 14 minutes. Details on the flow of participants through the study are published elsewhere (Chen et al., 2016).

Measures

Dysmenorrhea Symptoms—Participants rated the severity and bother of 14 dysmenorrhea-related symptoms (listed in Table 1). The choice of symptoms was based on a review of dysmenorrhea measures (Chen, Kwekkeboom, & Ward, 2015). Instructions for each symptom were: “Think about the past 6 months. Before or during your period, how severe was [symptom] usually? Before or during your period, how bothersome was [symptom] usually?” Participants rated severity and bother on 0 “not present/no bother” to 10 “extremely severe/extreme bother” scales. Because severity and bother had significant correlation (r’s = 0.92 to 0.99; p’s < 0.001), we used only severity scores in the current data analysis. Each severity rating was further grouped into one of four categories based on established cut-offs: no symptom (0), mild (1–4), moderate (5–6), and severe (7–10) (Oldenmenger, de Raaf, de Klerk, & van der Rijt, 2013; Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995).

Demographics and Clinical Characteristics—As potential covariates for subgroup membership, we collected data on the demographic and clinical characteristics that we identified in the literature (Apostolopoulos et al., 2016; Berkley, 2013; Ju et al., 2014; Zhu et al., 2010). Women provided demographic information including current age, age at dysmenorrhea symptom onset, race, ethnicity, and highest level of education. By subtracting symptom-onset age from chronological age, we calculated “years with dysmenorrhea”.

Women provided relevant clinical information including history of gynecological conditions that are related to secondary dysmenorrhea and comorbid chronic pain conditions. Specifically, participants were asked if a health care provider had ever diagnosed them with any of the following conditions: endometriosis, adenomyosis, uterine fibroids/myomas, and pelvic inflammatory disease. Participants were also asked to select if they had any of the following common chronic pain conditions: back pain, irritable bowel syndrome, migraine headaches, non-migraine headaches, fibromyalgia, neck pain, pelvic pain occurring outside of the menstrual period, and painful sexual intercourse (dyspareunia).

Statistical Analysis

We used all responses that were determined as valid (N=762). Descriptive statistics were used to summarize demographics and clinical characteristics. Latent class analysis (LCA) was performed to identify symptom-based phenotypes. LCA is an established statistical method that is used to find subgroups or phenotypes (i.e., latent classes) of individuals based on response patterns that are not directly observed (Hagenaars & McCutcheon, 2002). In LCA analysis, women with similar dysmenorrhea symptom profiles were classified into the same subgroup based on conditional probabilities. Specifically, women were classified based on severity (no, mild, moderate, severe) of the 14 dysmenorrhea-related symptoms.

The final number of phenotypes (i.e., latent classes) was determined based on model fit and model usefulness. Model fit was determined by inspecting values of Bayesian information criterion (BIC, lower value, better fit) and Akaike information criterion (AIC, lower value, better fit). Model usefulness was determined by the measure of entropy (>0.8 suggesting satisfactory classification of individual participants) and interpretability of the latent class solution. Among solutions with entropy values above 0.8 (see Table 2), we chose the solution with lowest AIC (i.e., three-class solution), as opposed to the solution with lowest BIC (i.e., two-class solution) because models selected based on the BIC tend to be overly simplified (Woods et al., 2016). The three-class solution represented a finer and more interpretable classification of individual participants.

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 at least 0.4, the symptom was unevenly distributed across the four severity categories (none, mild, moderate, severe). For these symptoms, the severity category with the greatest probability was used to derive an interpretation of the latent class.

To investigate associations between phenotypes and covariates (i.e., demographic and clinical characteristics), we used the one-step latent class model estimation approach, in which, the phenotypes were estimated and regressed on covariates simultaneously (Bolck, Croon, & Hagenaars, 2004). This one-step approach overcomes the biased-estimation issue associated with the traditional three-step approach (Bolck et al., 2004). Asian, Mixed races, and those without race information were combined into a category of “Other” race for modeling. Because having a large number of covariates would decrease the precision of the parameter estimates, we reduced the number of covariates by grouping chronic pain conditions. We used the following categories: back pain, neck pain, headaches (including migraine and non-migraine headaches), irritable bowel syndrome, fibromyalgia, and pelvic pain other than dysmenorrhea (including pelvic pain occurring outside of menstrual period and dyspareunia/painful sexual intercourse). These categories are based on the diagnostic clusters for population pain research recommended by the United States National Pain Strategy (Interagency Pain Research Coordinating Committee, 2015). In addition, only covariates with prevalence higher than 5% were entered into the model, as less frequent covariates would result in unstable and imprecise estimates. Multicollinearity issues were not observed among covariates. The variance inflation factor (VIFs) values were all below 10, which indicated that the covariates were not highly inter-correlated. Strengths and directions of associations between covariates and latent class membership were quantified with relative risk ratios (RRR) and 95% confidence intervals. MPlus (V6.1) was used for the latent class analysis. Other analyses were conducted using SAS/STAT (V9.4) software (Cary, NC).

Results

Sample Characteristics

The mean age of the sample was 34.1 years (SD =6.6, Range: 18–49). The majority were White (73.4% White, 13.1% African American, 4.7% Asian, 2.2% mixed race) and non-

Hispanic (89.8%). Slightly more than half (53.7%) had an Associate Degree or higher education. The majority (69.7%) had at least one comorbid chronic pain condition, with the most frequent comorbid pain conditions being lower back pain (46.9%), migraine headaches (29.8%), non-migraine headaches (23.9%), neck pain (17.3%), irritable bowel syndrome (12.9%), painful sexual intercourse/dyspareunia (11.0%), and pelvic pain occurring outside of menstruation (10.5%). Some (18.0%) reported being diagnosed with a gynecological condition that could have contributed to secondary dysmenorrhea, including uterine fibroids (7.7%), endometriosis (5.6%), pelvic inflammatory disease (3.4%), adenomyosis (0.8%), and other miscellaneous conditions (3.9%). On average, women reported 6.0 (SD=2.5) symptoms (range 1 to 14). The five most commonly reported symptoms were abdominal cramps (86.1%), low back pain (75.2%), bloating (73.9%), dull abdominal pain or discomfort (65.0%), and headache or migraine (61.2%). The five least commonly reported symptoms were vomiting (7.2%), fewer bowel movements than usual (9.1%), pain in the upper thighs (21.5%), constipation (22.7%), and reduced appetite (27.0%).

Identification of Symptom-based Phenotypes

Three distinct phenotypes of women with dysmenorrhea were identified as shown in Table 1. Phenotype 1 (n= 202, 26.5% of the total sample) was named “mild localized pain” as women in this group reported mild abdominal cramps and dull abdominal pain/discomfort, and few other symptoms. Phenotype 2 (n= 412, 54.1%) was named “severe localized pain” as women in this group reported severe abdominal cramps. Some participants in this phenotype also experience a few other symptoms such as low back pain, headache or migraine, and bloating. However, those symptoms were about evenly distributed across the severity categories (i.e., none, mild, moderate, severe). These symptoms, thus, did not characterize this phenotype. Phenotype 3 (n=148, 19.4%) was named “multiple severe symptoms” as women in this group reported severe pain at multiple locations (including abdominal cramps, dull abdominal pain/discomfort, lower back pain, headaches, and aches all over) and multiple gastrointestinal symptoms (including bloating, nausea, diarrhea, and more bowel movements than usual). The pain at multiple locations and gastrointestinal symptoms were all distributed toward the severe category. These symptoms, thus, did characterize Phenotype 3. The five least commonly reported symptoms (vomiting, fewer bowel movements than usual, pain in the upper thighs, constipation, and reduced appetite) did not discriminate across the phenotypes.

Relationship Between Phenotypes and Demographic and Clinical Characteristics

Age, race/ethnicity, years with dysmenorrhea, and certain comorbid chronic pain conditions were significantly associated with phenotype (see Table 3). Relative to the “mild localized pain” phenotype, women in the “severe localized pain” phenotype were more likely to have migraine or non-migraine headaches (RRR=1.99, p=0.019). Relative to the “mild localized pain” phenotype, women in the “multiple severe symptoms” phenotype were significantly more likely to be older (RRR=1.10, p=0.001), Black (RRR=3.68, p=0.004), Hispanic (RRR=4.23, p=0.007), have fewer years with dysmenorrhea (RRR=.95, p=0.014), have migraine or non-migraine headaches (RRR=3.08, p<0.001), have neck pain (RRR=2.23, p=0.037), or have pelvic pain other than dysmenorrhea (i.e., pelvic pain outside of menstruation or dyspareunia) (RRR=2.74, p=0.008). Compared to women in the “severe

localized pain" phenotype, women in the "multiple severe symptoms" phenotype were more likely to be older (RRR=1.06, p=0.014), Black (RRR=2.72, p=0.005), Hispanic (RRR=2.76, p=0.015), have fewer years with dysmenorrhea (RRR=.96, p=0.042), have neck pain (RRR=2.09, p=0.015), or have pelvic pain other than dysmenorrhea (RRR=2.90, p<0.001). Diagnosis of endometriosis or uterine fibroids were not significantly associated with any phenotype. Because race data was missing for some participants (n=50, 6.56%), we repeated analyses excluding these cases, but findings were unchanged. Table 4 provides a descriptive summary of the demographic and clinical characteristics by three phenotypes.

Discussion

The identified phenotypes support dysmenorrhea as a heterogeneous condition where symptom severity varies (Ju et al., 2014) and some women experience multiple symptoms (Heitkemper et al., 1988). Our study makes a new contribution in empirically identifying distinct symptom-based phenotypes to elucidate this heterogeneity.

While previous studies have identified relationships between demographics and dysmenorrhea prevalence (Ju et al., 2014; Woods et al., 1982), our study differed in that we identified relationships between demographics and phenotypes. Adding to the limited literature on race/ethnicity differences in dysmenorrhea symptomology (Zhu et al., 2010), we found that Black women and Hispanic women were more likely to be in the "multiple severe symptom" phenotype. Black and Hispanic women also have earlier menarche than White women (Wu, Mendola, & Buck, 2002); Black women also have higher heavy bleeding episodes than White women (Harlow & Campbell, 1996). Race and ethnicity are also associated with prevalence, progression, and outcomes of various pain conditions (Campbell & Edwards, 2012). Clinicians should be aware of the potential race and ethnicity differences in dysmenorrhea and improve treatment outcomes for minority patients. Although older age is associated with lower dysmenorrhea prevalence (Ju et al., 2014), we found that older age was associated with the "multiple severe symptoms" phenotype. One explanation may be increased pain sensitivity with aging (Yezierski, 2012). However, the age difference (<2.2 years) and effect size estimates (RRRs<1.1) were small, and it remains unclear whether the age difference is clinically meaningful. To reduce potential race/ethnicity/age disparities in dysmenorrhea, it is essential to elucidate the biopsychosocial mechanisms underlying these associations.

Findings support the growing literature linking dysmenorrhea to other pain conditions (Berkley, 2013; Giamberardino et al., 2010; Iacovides et al., 2015; Westling et al., 2013). The novelty in our findings is that the likelihood of having comorbid pain differed based on phenotypes. The high prevalence of comorbid pain in the "multiple severe symptoms" phenotype could be explained by persistent central sensitization, because a heightened sensitivity of the central nervous system (CNS) characterizes many chronic pain syndromes (Woolf, 2011). We did not find significant association between phenotypes and certain gynecological conditions. Wide confidence intervals were noted likely due to few participants reporting endometriosis or uterine fibroids diagnosis (n= 43 and 59, respectively) and/or lack of laparoscopic confirmation of some diagnosis. Previous research also showed little association between pelvic pathology and symptomatology (Fedele,

Bianchi, Bocciolone, Di Nola, & Parazzini, 1992; Gruppo Italiano per lo Studio dell'Endometriosi, 2001). Therefore, it can be problematic to assume pelvic pathologies as the primary determinant of dysmenorrhea symptomology.

We acknowledge study limitations. First, because the literature on covariates of dysmenorrhea symptomology is limited, we may have omitted factors that discriminate phenotypes. Future research could consider biopsychosocial factors that are known to impact pain and central pain mechanisms (e.g., genetics, estrogen, inflammation, sleep, and psychological distress) (Phillips, & Clauw, 2011). Second, there could be recall bias in survey responses. Third, due to logistical challenges in parental consent, we did not include adolescents younger than 18. Fourth, there could be self-selection bias and coverage bias and associated with our sampling method. Only internet users were surveyed. Researchers using other sampling methods can further assess consistency and reproducibility of the findings.

Our findings have implications for future research. Findings may provide precise and individualized insights into the mechanistic underpinnings of dysmenorrhea, as phenotypes may involve different mechanisms. A main etiology of dysmenorrhea is elevated prostaglandins (Dawood, 2006; Iacovides et al., 2015). However, other mechanisms may also underlie dysmenorrhea, such as central sensitization that involves hypersensitivity to pain in multiple sites (Iacovides et al., 2015). Severe central sensitization may particularly affect the "multiple severe symptoms" phenotype, but needs further research. Similarly, genetic polymorphisms are linked to dysmenorrhea (Jones et al., 2016) and may explain specific phenotypes. Future research on biomarkers, genetics, and symptoms could provide insight into the mechanisms underlying phenotypes.

Our findings have relevance for research on personalizing, enhancing, and developing novel dysmenorrhea treatments. Individuals with different phenotypes may respond to the same treatment differently, as shown in depression (Uher et al., 2012). It is currently unclear if prostaglandin inhibitors work equally in women with localized pain and women with widespread pain and gastrointestinal symptoms. Incorporating phenotypes as a potential moderator of intervention effects will allow us to determine what treatment is effective for whom. Similarly, the "multiple severe symptoms" phenotype may require more intensive, comprehensive, or novel treatments that address multiple symptoms. For example, if strong CNS involvement is confirmed in this group, novel use of treatments targeting central sensitization (e.g., gabapentin and tricyclic antidepressants) (Woolf, 2011) may be promising especially for women refractory to conventional treatment. Instead of treating women as a homogeneous group, treatments could be matched to specific phenotypes to improve cost-effectiveness.

Our findings have implications for clinical practice. First, it is essential to acknowledge symptom heterogeneity to accurately assess and treat women with dysmenorrhea. Second, clinicians should be mindful of the associations between dysmenorrhea and other pain conditions. It is important to screen for dysmenorrhea among women with chronic pain, and vice versa, to screen for chronic pain among women with significant dysmenorrhea symptom burden. Effective dysmenorrhea treatment has been shown to decrease pain and symptoms from other organs (Giamberardino et al., 2010). Third, it is vital to take a

symptom-based rather than a solely pathology-based approach in managing dysmenorrhea to avoid discounting symptomatology in those without pelvic pathology. Traditional dysmenorrhea classification based on pathology is inadequate (Stratton, Khachikyan, Sinaii, Ortiz, & Shah, 2015; Tu & As-Sanie, 2016). Growing evidence supports that women with pelvic pain likely share common symptom mechanisms, regardless of pathology (Tu & As-Sanie, 2016).

In conclusion, we have identified three symptom-based dysmenorrhea phenotypes and explored demographic and clinical correlates. This phenotype characterization is a foundational step for conducting research designed to uncover etiologic mechanisms underlying women's variability in dysmenorrhea symptoms and, ultimately, to guide precision-based treatments.

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References

Anttila V, Kallela M, Oswell G, Kaunisto MA, Nyholt DR, Hämäläinen E, Palotie A. Trait components provide tools to dissect the genetic susceptibility of migraine. The American Journal of Human Genetics. 2006; 79(1):85–99. DOI: 10.1086/504814 [PubMed: 16773568]

Apostolopoulos NV, Alexandraki KI, Gorry A, Coker A. Association between chronic pelvic pain symptoms and the presence of endometriosis. Archives Gynecology and Obstetrics. 2016; 293(2): 439–445. DOI: 10.1007/s00404-015-3855-2

Baker R, Blumberg SJ, Brick JM, Couper MP, Courtright M, Dennis JM, Krosnick J. Research synthesis: AAPOR report on online panels. Public Opinion Quarterly. 2010; 74(4):711–781.

Berkley KJ. Primary dysmenorrhea: An urgent mandate. Pain: Clinical Updates. 2013; 21(3):1–7.

Bolck A, Croon M, Hagenaars J. Estimating latent structure models with categorical variables: One-step versus three-step estimators. Political Analysis. 2004; 12(1):3–27. DOI: 10.1093/pan/mph001

Campbell CM, Edwards RR. Ethnic differences in pain and pain management. Pain Management. 2012; 2(3):219–230. DOI: 10.2217/pmt.12.7 [PubMed: 23687518]

Cashion AK, Grady PA. The National Institutes of Health/National Institutes of Nursing Research intramural research program and the development of the National Institutes of Health Symptom Science Model. Nursing Outlook. 2015; 63(4):484–487. DOI: 10.1016/j.outlook.2015.03.001 [PubMed: 26187087]

Centers for Disease Control and Prevention (CDC). Health care personnel and flu vaccination, internet panel survey, United States. 2013. Retrieved from https://www.cdc.gov/flu/fluvaxview/hcp-ips-nov2013.htm

Chen CX, Kwekkeboom KL, Ward SE. Self-report pain and symptom measures for primary dysmenorrhoea: A critical review. European Journal of Pain. 2015; 19(3):377–391. DOI: 10.1002/ejp.556 [PubMed: 25059384]

Chen CX, Kwekkeboom KL, Ward SE. Beliefs about dysmenorrhea and their relationship to self-management. Research in Nursing & Health. 2016; 39(4):263–276. DOI: 10.1002/nur.21726 [PubMed: 27177093]

Dawood MY. Primary dysmenorrhea: Advances in pathogenesis and management. Obstetrics and Gynecology. 2006; 108(2):428–441. DOI: 10.1097/01.AOG.0000230214.26638.0c [PubMed: 16880317]

Fedele L, Bianchi S, Bocciolone L, Di Nola G, Parazzini F. Pain symptoms associated with endometriosis. Obstetrics and Gynecology. 1992; 79(5 Pt 1):767–769. [PubMed: 1565363]

Giamberardino MA, Costantini R, Affaitati G, Fabrizio A, Lapenna D, Tafuri E, Mezzetti A. Viscero-visceral hyperalgesia: Characterization in different clinical models. Pain. 2010; 151(2):307–322. DOI: 10.1016/j.pain.2010.06.023 [PubMed: 20638177]

Gruppo Italiano per lo Studio dell'Endometriosi. Relationship between stage, site and morphological characteristics of pelvic endometriosis and pain. Human Reproduction. 2001; 16(12):2668–2671. DOI: 10.1093/humrep/16.12.2668 [PubMed: 11726593]

Hagenaars JA, McCutcheon AL. Applied latent class analysis. Cambridge, UK: Cambridge University Press; 2002.

Harlow SD, Campbell B. Ethnic differences in the duration and amount of menstrual bleeding during the postmenarcheal period. American Journal of Epidemiology. 1996; 144(10):980–988. [PubMed: 8916509]

Heitkemper MM, Shaver JF, Mitchell ES. Gastrointestinal symptoms and bowel patterns across the menstrual-cycle in dysmenorrhea. Nursing Research. 1988; 37(2):108–113. [PubMed: 3347518]

Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: A critical review. Human Reproduction Update. 2015; 21(6):762–778. DOI: 10.1093/humupd/dmv039 [PubMed: 26346058]

Interagency Pain Research Coordinating Committee. National Pain Strategy: A comprehensive population health-level strategy for pain. Washington, DC: Department of Health and Human Services; 2015.

International Association for the Study of Pain (IASP) Taxonomy Working Group. Classification of Chronic Pain. 2011. Retrieved from http://www.iasp-pain.org/PublicationsNews/Content.aspx?ItemNumber=1673

Jones AV, Hockley JR, Hyde C, Gorman D, Sredic-Rhodes A, Bilsland J, Scollen S. Genome-wide association analysis of pain severity in dysmenorrhea identifies association at chromosome 1p13.2, near the nerve growth factor locus. Pain. 2016; 157(11):2571–2581. DOI: 10.1097/j.pain.0000000000000678 [PubMed: 27454463]

Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. Epidemiologic Reviews. 2014; 36:104–113. DOI: 10.1093/epirev/mxt009 [PubMed: 24284871]

Liu H, Cella D, Gershon R, Shen J, Morales LS, Riley W, Hays RD. Representativeness of the Patient-Reported Outcomes Measurement Information System Internet panel. Journal of Clinical Epidemiology. 2010; 63(11):1169–1178. DOI: 10.1016/j.jclinepi.2009.11.021 [PubMed: 20688473]

Nguyen AM, Humphrey L, Kitchen H, Rehman T, Norquist JM. A qualitative study to develop a patient-reported outcome for dysmenorrhea. Quality of Life Research. 2015; 24(1):181–191. DOI: 10.1007/s11136-014-0755-z [PubMed: 25048731]

Oldenmenger WH, de Raaf PJ, de Klerk C, van der Rijt CC. Cut points on 0–10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: A systematic review. Journal of Pain and Symptom Management. 2013; 45(6):1083–1093. DOI: 10.1016/j.jpainsymman.2012.06.007 [PubMed: 23017617]

Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states – maybe it is all in their head. *Best Practice & Research.* Clinical Rheumatology. 2011; 25(2):141–154. DOI: 10.1016/j.berh.2011.02.005 [PubMed: 22094191]

Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain. 1995; 61(2):277–284. DOI: 10.1016/0304-3959(94)00178-h [PubMed: 7659438]

Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. Obstetrics and Gynecology. 2015; 125(3):719–728. DOI: 10.1097/aog.0000000000000663 [PubMed: 25730237]

Tu FF, As-Sanie S. A modest proposal to investigate chronic uterine pain. BJOG: An International Journal of Obstetrics and Gynaecology. 2016; 124:182–184. DOI: 10.1111/1471-0528.14393 [PubMed: 27813232]

Turk DC. The potential of treatment matching for subgroups of patients with chronic pain: Lumping versus splitting. Clinical Journal of Pain. 2005; 21(1):44–55. discussion 69-72. [PubMed: 15599131]

Uher R, Perlis RH, Henigsberg N, Zobel A, Rietschel M, Mors O, McGuffin P. Depression symptom dimensions as predictors of antidepressant treatment outcome: Replicable evidence for interest-activity symptoms. Psychological Medicine. 2012; 42(5):967–980. DOI: 10.1017/s0033291711001905 [PubMed: 21929846]

Westling AM, Tu FF, Griffith JW, Hellman KM. The association of dysmenorrhea with noncyclic pelvic pain accounting for psychological factors. American Journal of Obstetrics and Gynecology. 2013; 209(5):422.e421–422.e410. DOI: 10.1016/j.ajog.2013.08.020 [PubMed: 23973396]

Woods NF, Hohensee C, Carpenter JS, Cohen L, Ensrud K, Freeman EW, Otte JL. Symptom clusters among MsFLASH clinical trial participants. Menopause. 2016; 23(2):158–165. DOI: 10.1097/gme.0000000000000516 [PubMed: 26506500]

Woods NF, Most A, Dery GK. Prevalene of perimenstrual symptoms. American Journal of Public Health. 1982; 72(11):1257–1264. [PubMed: 6889817]

Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2011; 152(3 Suppl):S2–15. DOI: 10.1016/j.pain.2010.09.030 [PubMed: 20961685]

Wu T, Mendola P, Buck GM. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: The Third National Health and Nutrition Examination Survey, 1988–1994. Pediatrics. 2002; 110(4):752–757. [PubMed: 12359790]

Yezierski RP. The effects of age on pain sensitivity: Preclinical studies. Pain Medicine. 2012; 13(Suppl 2):S27–S36. DOI: 10.1111/j.1526-4637.2011.01311.x [PubMed: 22497745]

Zhu X, Wong F, Bensoussan A, Lo SK, Zhou C, Yu J. Are there any cross-ethnic differences in menstrual profiles? A pilot comparative study on Australian and Chinese women with primary dysmenorrhea. The Journal of Obstetrics and Gynaecology Research. 2010; 36(5):1093–1101. DOI: 10.1111/j.1447-0756.2010.01250.x [PubMed: 20846252]

Table 1

Latent Class Analysis: Posterior Probabilities of Phenotype Membership

	Mild Localized Pain Group				Severe Localized Pain Group				Severe Multiple Symptom Group			
	None	**Mild**	**Mod**	**Severe**	**None**	**Mild**	**Mod**	**Severe**	**None**	**Mild**	**Mod**	**Severe**
Symptoms differentiating group membership												
Abdominal cramps	0.222	**0.381**	0.318	0.079	0.140	0.042	0.332	**0.486**	0.028	0.007	0.031	**0.934**
Dull abdominal pain or discomfort	0.353	**0.443**	0.204	0.000	0.350	0.070	0.301	0.278	0.348	0.000	0.065	**0.588**
Low back pain	**0.408**	0.378	0.184	0.030	0.213	0.136	0.329	0.322	0.133	0.000	0.075	**0.791**
Headache or migraine	**0.606**	0.165	0.111	0.119	0.328	0.090	0.242	0.340	0.269	0.020	0.077	**0.634**
Aches all over	**0.848**	0.092	0.048	0.011	**0.747**	0.058	0.126	0.069	0.417	0.007	0.057	**0.519**
Bloating	**0.431**	0.292	0.213	.064	0.234	0.113	0.268	0.385	0.113	0.022	0.078	**0.788**
Nausea	**0.865**	0.109	0.019	0.007	**0.659**	0.156	0.134	0.051	0.325	0.016	0.212	**0.448**
Diarrhea	**0.684**	0.233	0.082	0.000	**0.566**	0.112	0.161	0.160	0.357	0.029	0.121	**0.493**
More bowel movements	**0.692**	0.236	0.049	0.023	**0.649**	0.085	0.153	0.113	**0.466**	0.000	0.075	**0.459**
Symptoms not differentiating group membership												
Pain in the upper thighs	**0.914**	0.069	0.012	0.005	**0.803**	0.059	0.067	0.071	**0.569**	0.013	0.144	0.275
Vomiting	**0.996**	0.000	0.004	0.000	**0.957**	0.026	0.013	0.003	**0.761**	0.027	0.069	0.143
Reduced appetite	**0.837**	0.152	0.000	0.011	**0.764**	0.104	0.106	0.026	**0.497**	0.041	0.180	0.282
Constipation	**0.841**	0.087	0.072	0.000	**0.805**	0.050	0.067	0.078	**0.598**	0.021	0.093	0.288
Fewer bowel movement	**0.889**	0.076	0.013	0.023	**0.936**	0.007	0.015	0.042	**0.866**	0.007	0.055	0.073

Note: Mod = moderate, Identification of symptoms with potential distinguishing ability: the sum of the Manhattan distance between the posterior probabilities and 0.25 was above 0.4. Severity class with highest posterior probability is bolded for ease of latent class interpretation

Table 2

Latent Class Analyses Model Fit and Usefulness Indices

Number of Classes	Log Likelihood	BIC	AIC	Entropy
1	−19050.43	38552.10	38236.86	
2	−9891.71	20433.74	19979.42	0.82
3	**−9722.36**	**20466.66**	**19752.73**	**0.81**
4	−9574.496	20542.541	19568.99	0.79

Note: BIC: Bayesian information criterion; AIC: Akaike information criterion. The model of selection is bolded.

Table 3

Associations Between Phenotype and Demographic and Clinical Variables

Demographic and Clinical Variables	"Mild localized pain" phenotype[a] vs. "Multiple severe symptoms" phenotype		"Mild localized pain" phenotype[a] vs. "Severe localized pain" phenotype		"Severe localized pain" phenotype[a] vs. "Multiple severe symptoms" phenotype	
	RRR	95% CI	RRR	95% CI	RRR	95% CI
Age	1.095[‡]	(1.038–1.154)	1.032	(0.984–1.083)	1.061[*]	(1.012–1.112)
Black	3.680[†]	(1.507–8.987)	1.355	(0.548–3.351)	2.716[†]	(1.341–5.499)
Other Races	1.755	(0.673–4.582)	1.182	(0.563–2.484)	1.484	(0.582–3.788)
Hispanic	4.230[†]	(1.496–11.96)	1.533	(0.582–4.038)	2.759[*]	(1.214–6.273)
Associate Degree or More	0.589	(0.336–1.033)	0.792	(0.502–1.248)	0.744	(0.451–1.226)
Years with Dysmenorrhea	0.949[*]	(0.910–0.989)	0.983	(0.944–1.024)	0.965[*]	(0.931–0.999)
Migraine or Headache	3.080[‡]	(1.627–5.796)	1.988[*]	(1.117–3.537)	1.550	(0.881–2.725)
Neck Pain	2.234[*]	(1.049–4.758)	1.067	(0.495–2.302)	2.094[*]	(1.156–3.792)
Pelvic Pain Other Than Dysmenorrhea	2.745[†]	(1.305–5.775)	0.946	(0.442–2.024)	2.901[‡]	(1.630–5.162)
Back Pain	1.314	(0.698–2.473)	1.025	(0.570–1.844)	1.281	(0.734–2.236)
Irritable Bowel Syndrome	2.428	(0.982–6.003)	1.513	(0.647–3.539)	1.605	(0.823–3.131)
Endometriosis	9.003	(0.625–129.602)	6.303	(0.459–86.486)	1.429	(0.529–3.860)
Uterine Fibroids	2.560	(0.559–11.727)	2.327	(0.507–10.677)	1.101	(0.479–2.527)

Note.

[a] referent category,

[*] $p<0.05$,

[†] $p<0.01$,

[‡] $p\leq0.001$, RRR: relative risk ratio, CI: Confidence Interval.

Table 4

Demographic and Clinical Characteristics by Symptom-based Phenotypes (N=762)

	"Mild-localized pain" phenotype (n=202)	"Severe localized pain" phenotype (n=412)	"Multiple severe symptoms" phenotype (n=148)
Age (y) *	33.1 ± 6.4	34.2 ± 6.7	35.3 ± 6.3
Years with Dysmenorrhea *	16.6 ± 7.5	16.6 ± 8.3	15.9 ± 8.7
Race			
Black	20 (9.9)	50 (12.1)	30 (20.3)
White	159 (78.7)	310 (75.2)	90 (60.8)
Other	23 (11.4)	52 (12.6)	28 (18.9)
Hispanic	12 (5.9)	37 (9.0)	29 (19.6)
Education			
Less than Associate Degree	82 (40.6)	189 (45.9)	82 (55.4)
Associate Degree or More	120 (59.4)	223 (54.1)	66 (44.6)
Back Pain	76 (37.6)	182 (44.2)	99 (66.9)
Irritable Bowel Syndrome	14 (6.9)	48 (11.7)	36 (24.3)
Migraine Headaches	33 (16.3)	122 (29.6)	72 (48.6)
Non-Migraine Headaches	29 (14.4)	96 (23.3)	57 (38.5)
Fibromyalgia	5 (2.5)	16 (3.9)	18 (12.2)
Neck Pain	21 (10.4)	58 (14.1)	53 (35.8)
Pelvic Pain Occurring Outside of Menstrual Period	6 (3.0)	33 (8.0)	41 (27.7)
Dyspareunia/Painful Sexual Intercourse	17 (8.4)	34 (8.3)	33 (22.3)
Endometriosis	2 (1.0)	25 (6.1)	16 (10.8)
Adenomyosis	2 (1.0)	3 (0.7)	1 (0.7)
Uterine Fibroids/Myomas	5 (2.5)	34 (8.3)	20 (13.5)
Pelvic Inflammatory Disease	4 (2.0)	12 (2.9)	10 (6.8)

Note.

* Data are mean ± standard deviation (SD). All other data are n (%).