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Prospective Association between Dysmenorrhea and Chronic Pain Development in Community-Dwelling Women

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Abstract: Despite emerging evidence of associations between dysmenorrhea, enhanced pain sensitivity, and functional neuroimaging patterns consistent with chronic pain, it is unknown whether dysmenorrhea is prospectively associated with chronic pain development. Gaining a better understanding of this relationship could inform efforts in prevention of chronic pain. Using data from the national Midlife in the United States cohort, we examined the prospective association between dysmenorrhea and chronic pain development during a 10-year follow-up (starting 10 years after dysmenorrhea was measured) among 874 community-dwelling women aged 25-74 at baseline (when dysmenorrhea was measured). We fit modified Poisson regression models adjusting for sociodemographic, lifestyle and psychosocial factors. Among women who were menstruating at baseline, self-reported dysmenorrhea was associated with a 41% greater (95% confidence interval [CI] = 6%-88%) risk of developing chronic pain. Women with dysmenorrhea also developed chronic pain in more body regions (≥3 regions vs 1-2 regions vs none, odds ratio [OR] = 1.77, 95% CI = 1.18-2.64) and experienced greater pain interference (high-interference vs low-interference vs none, OR = 1.73, 95% CI = 1.15-2.59). Among women who had stopped menstruation at baseline, we did not find evidence of an association between their history of dysmenorrhea and subsequent risk of chronic pain development. Results suggest dysmenorrhea may be a general risk factor for chronic pain development among menstruating women.

***Perspective:** This study supports the temporality of dysmenorrhea and chronic pain development in a national female sample. Dysmenorrhea was also associated with developing more widespread and disabling pain among women who were still menstruating. Early management of dysmenorrhea may reduce the development and severity of chronic pain in women, although further research is required to determine whether dysmenorrhea is a causal risk factor or a risk marker of chronic pain.*

***Key Words:** Dysmenorrhea, chronic pain, pain region, pain interference, cohort study.*

Introduction

Dysmenorrhea, or painful menstrual cramps, is the most common gynecological condition among women of reproductive age,[13] with severe dysmenorrhea affecting 2-29% of menstruating women.[36] Dysmenorrhea is associated with significant academic impact worldwide,[1] and has been identified as the leading cause of lost work hours for women in the United State (US).[18] Despite substantially decreasing women's physical and psychosocial well-being,[63] dysmenorrhea is

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undertreated and its etiology and long-term impact understudied.[30,54] Recent evidence has suggested that dysmenorrhea may be a risk factor for chronic pain given its associations with chronic pain mechanisms.[10,11,28,30,31,33,35,41,45,51,65,66,69,70,75] Given the tremendous economic toll of chronic pain[23] and the recognized limitations of current treatment,[64] the identification of risk factors for chronic pain development, such as dysmenorrhea, could provide an opportunity for prevention of chronic pain among at-risk women.

Evidence supporting a role for dysmenorrhea in the etiology of chronic pain mainly comes from laboratory-based studies. Neuroimaging studies have found structural and functional brain changes in women with dysmenorrhea that may mimic individuals with chronic pain. Changes in grey and white matter,[45,65] in spectrum features and brain asymmetry,[31] in cerebral metabolism,[66] in central processing of experimental noxious stimuli,[69] and in functional connectivity,[70] have been reported. Quantitative sensory testing also demonstrated enhanced pain sensitivity in women with dysmenorrhea both in areas of referred pain and remote body regions.[11,28,30,50] Despite this evidence potentially linking dysmenorrhea to mechanisms related to pain chronicity, the temporal association between dysmenorrhea and the development of chronic pain in the general female population is currently unknown. Evidence of a prospective association between dysmenorrhea and chronic pain development in a large, population-based sample is needed to determine whether dysmenorrhea is an etiologically relevant risk factor for chronic pain development.

From both a clinical and economic perspective, the degree of functional limitation due to pain is more significant than whether or not an individual develops chronic pain. A strong linear relationship between the number of pain sites and functional limitations has been reported in musculoskeletal pain.[37] Pain at multiple body sites is also associated with worse health-related quality of life.[39] Pain that significantly interferes with life is associated with greater mortality than pain per se, and the degree of pain interference is monotonically associated with increased mortality.[59] It was estimated that mild, moderate, and severe chronic pain-related interference were associated with a \$2,498, \$3,707, and \$5,804 increase in annual health care expenditures, respectively, compared to no pain interference.[61] Therefore, in addition to understanding the temporal association between dysmenorrhea and chronic pain development, it is important to examine whether the experience of dysmenorrhea is associated with more widespread and disabling chronic pain symptoms later in life. This may shed light on the potential to prevent significant morbidity and mortality through effective management of dysmenorrhea.

Using data from the large, population-based, longitudinal Midlife in the United States (MIDUS) study,[67] we examined the prospective association between dysmenorrhea and chronic pain development among community-dwelling women aged 25-74 years at baseline. We hypothesized that dysmenorrhea would be associated with a greater risk of chronic pain development during a 10-year follow-up. We also examined the number of reported chronic pain body regions and the level of chronic pain-related interference, to determine whether dysmenorrhea would be prospectively associated with more widespread and disabling chronic pain.

Methods

Dataset and Study Population

The MIDUS study is a national, longitudinal study of psychosocial, behavioral, and sociodemographic determinants of healthy aging.[67] The main baseline survey (MIDUS 1) was conducted from 1995-1996 and recruited non-institutionalized, English-speaking adults aged 25-74 years across the country, collecting extensive information through phone interviews and self-administered questionnaires (SAQs). In addition to a national probability sample (n = 3,487), the study also included oversamples in selected metropolitan areas (n = 757), a sample of siblings (n = 950) of the main respondents, and a national sample of twin pairs (n = 1,914), constituting a total baseline sample of 7,108 U.S. adults. The MIDUS 2 main study was a follow-up of the MIDUS 1 main study participants that was conducted from 2004-2006 through phone interviews and SAQs, with data collection largely repeating the baseline assessments. The average follow-up interval from MIDUS 1 was 9 years (range = 7.8−10.4 years). The third wave of MIDUS (MIDUS 3) is a longitudinal follow-up of MIDUS 2 participants conducted from 2013-2014 through phone interviews and SAQs, with measures largely repeating baseline assessments. The average longitudinal follow-up interval from MIDUS 2 to MIDUS 3 was 9 years (range = 7.9−10.3 years).

Self-reported questions about menstrual periods were asked of women at baseline in MIDUS 1 SAQs, while self-reported questions about chronic pain were asked in MIDUS 2 and MIDUS 3 SAQs. Because we were not able to ascertain women's chronic pain status at baseline, the risk of developing chronic pain from baseline to MIDUS 2 was not estimable. Instead, we were able to quantify the risk of developing chronic pain from MIDUS 2 to MIDUS 3 among women free of chronic pain at MIDUS 2. In order to compare the risk of developing chronic pain among women with and without dysmenorrhea, for our study, we examined the association between baseline dysmenorrhea and the development of chronic pain during the approximately 10-year follow-up period between MIDUS 2 and MIDUS 3, among the cohort of women who did not report chronic pain at MIDUS 2. The diagram for cohort construction is provided in **Fig 1**. Detailed information about the MIDUS study design can be found on (http://midus.wisc.edu/) and the publicly available MIDUS data were downloaded from ICPSR (https://www.icpsr.umich.edu/icpsrweb/). The current secondary analysis was reviewed and approved by the Institutional Review Board at University of Rochester School of Medicine and Dentistry

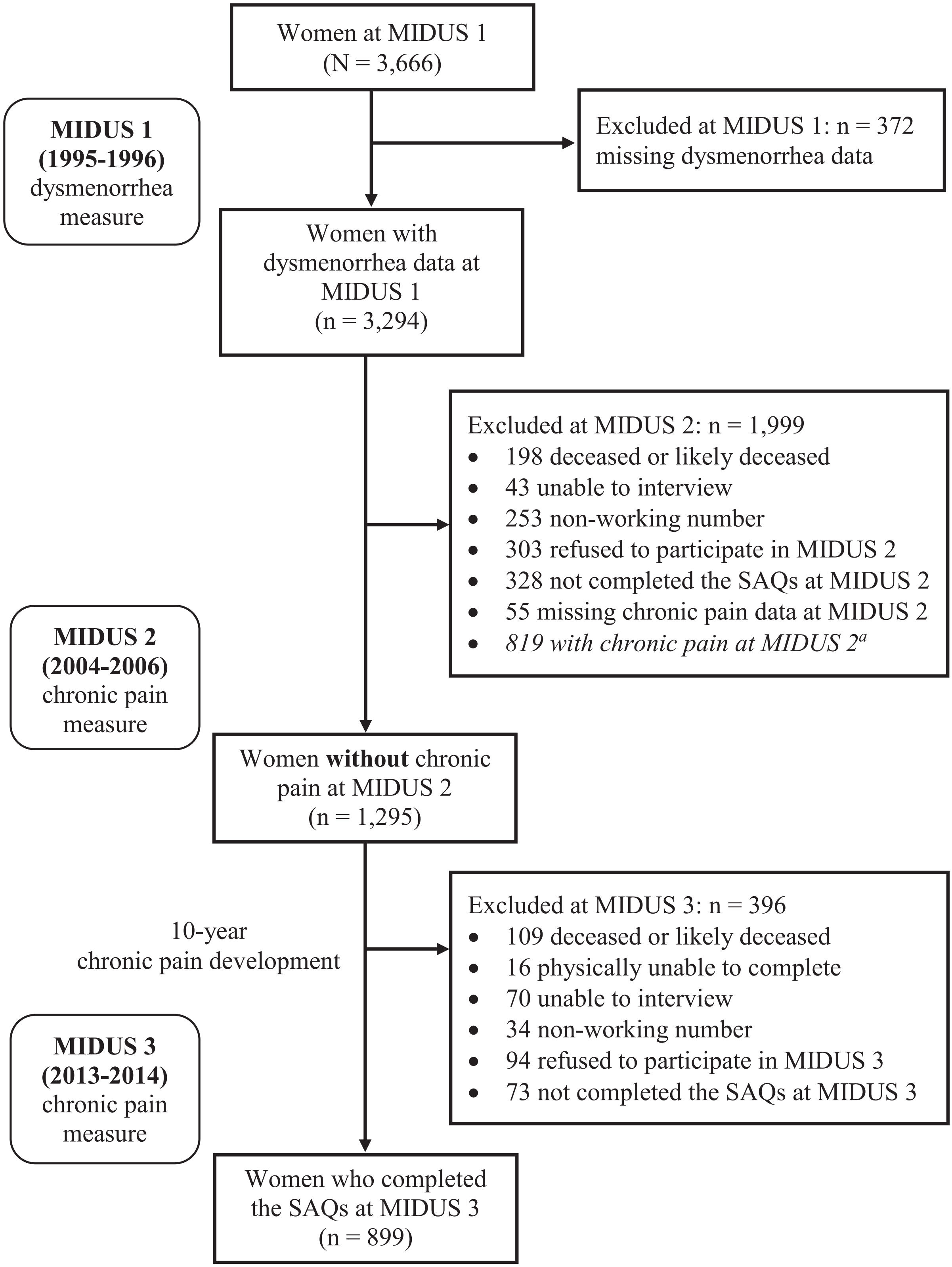

Figure 1. Flow diagram for the study cohort. MIDUS, midlife in the united states; SAQ, self-administered questionnaire. [a]Women who self-reported with chronic pain at MIDUS 2 were excluded because they were not at "risk" for developing chronic pain at MIDUS 3.

(STUDY00004387). All participants provided informed consent when they participated in the MIDUS study.

Measures

Dysmenorrhea

Dysmenorrhea was constructed from the menstruation-related questions in MIDUS 1, where we used reports of menstrual discomfort as a proxy for dysmenorrhea status. Women were asked to rate how much discomfort they usually experienced during their menstrual periods, by the question: "When you have a menstrual period (or when you had them in the past), how much discomfort do (or did) you usually experience during your periods?" Answer choices were "a lot", "some", "a little" and "none at all". For the main analysis, women who reported having "a lot" and "some" discomfort during their periods were classified as having dysmenorrhea, while those who reported "a little" and "none at all" were classified as not having dysmenorrhea. In sensitivity analyses, we also used the linear (ranging from 0-3) and ordinal (0, 1, 2, 3) forms as the exposure variables to indicate the severity of dysmenorrhea.

We determined dysmenorrhea status based on self-reported menstrual discomfort because dysmenorrhea is frequently expressed as pain or discomfort,[29] and discomfort may better capture the diverse symptoms associated with dysmenorrhea. In addition, we assessed the validity of menstrual discomfort as a proxy for dysmenorrhea in our data by estimating the correlations of the menstrual discomfort measures with women's self-reported attitudes toward the permanent stop of their menstrual periods. We expected women with more menstrual discomfort would report more relief in the stop of their periods.

Menstruation Status

We determined women's menstruation status at MIDUS 1 based on their self-report answers to the question "Have your menstrual periods stopped permanently - not counting a temporary stop because of such things as pregnancy, birth control, extreme dieting, or medications?", as well as their gynecological surgery history. Women who reported "yes" to the above question, or women who reported having hysterectomy, removal of uterus and 1 or 2 ovaries, or removal of 2 ovaries, were classified as having their menstrual periods permanently stopped. For women who did not answer the above question and with no information on surgical history, we set their menstruation status as missing.

Chronic Pain

The outcome of chronic pain was based on the same question asked at both MIDUS 2 and MIDUS 3: "Do you have chronic pain, that is do you have pain that persists beyond the time of normal healing and has lasted anywhere from a few months to many years?" Women reporting "yes" to the question were classified as having chronic pain (those reporting "no" were classified as not having it). Although this question does not specify the duration of pain, it is consistent with the official definition of chronic pain as "pain that persists past normal healing time ".[9] Women who reported not having chronic pain at MIDUS 2 and then reported having chronic pain at MIDUS 3 were classified as developing chronic pain during the approximately 10-year follow up period.

In addition to chronic pain incidence, we also studied the number of body regions involved and pain-related interference as secondary outcomes. Women who endorsed chronic pain were asked: "Where is your pain primarily located? (Check all that apply.)", with the locations including head, neck, back, shoulders, arms/hands, hips, legs/feet, knees, and others. We constructed a count variable summing pain regions and categorized it into none (women without chronic pain), 1-2 regions, and 3 or more regions. Women with chronic pain were also asked to rate from 0 ("did not interfere") to 10 ("completely interfered") how their chronic pain (without referring to a specific body region) interfered with their general activity, mood, relationships with other people, sleep, and enjoyment of life. We constructed the level of chronic pain interference based on the mean score of the 5 questions, and categorized it into none (women without chronic pain), low-interference (mean score $\leq$4), and high-interference (mean score >4) pain, according to the suggested cutoff value for the Pain Interference Subscale.[34]

Covariates

Confounder selection was based on the existing knowledge of the risk factors of chronic pain and the correlates of dysmenorrhea that are not on the hypothesized causal pathway between dysmenorrhea and chronic pain, as indicated by published literature. The selected confounders include age,[17] race and ethnicity,[8,47-49] education,[26] body mass index (BMI), smoking status, physical activity,[19,36,40] regular fish oil intake,[53] childhood emotional abuse, childhood physical abuse, depression, anxiety,[4,20,21,55] and the degree of somatic amplification (ie, a tendency to perceive normal somatic and visceral sensations as being relatively intense, disturbing and noxious).[40] The confounders were mainly selected from MIDUS 1, except fish oil intake which was only measured at MIDUS 2. Although physical activity, depression and anxiety could be on the causal pathway between dysmenorrhea and chronic pain,[2,22] they can also be risk factors for dysmenorrhea.[40] We decided on a conservative approach and included them as confounders.

Age and BMI were coded as continuous variables. Race and ethnicity were based on self-report and categorized into non-Hispanic White, non-Hispanic Black, and others. Education was classified as high school or less, some college, bachelor's degree or above. Smoking status was classified into with a history (previous or current) of daily smoking or not. Physical activity level was constructed based on self-reported answers to the questions about the frequency ("several times a week or more", "once a week", "several times a month", "once a month", "less than once a month", or "never", each coded from 5 to 0) of moderate and vigorous physical activity, during summer and winter respectively. We calculated the mean of moderate physical activity across summer and winter, as well as the mean of vigorous physical activity across summer and winter. We used the higher score from the calculated moderate and vigorous physical activity as an indicator for the overall level of physical activity, consistent with previous practice.[16] Regular fish oil intake was classified as yes vs no.

Childhood abuse questions were taken from the commonly used Conflict Tactics Scale.[62] In the literature, childhood abuse has been operationalized as a combination of physical and emotional abuse as an overall abuse frequency,[6] a binary indicator of frequent abuse experience,[32] or a score derived from latent class models.[56] In this paper we considered average childhood physical abuse severity and average childhood emotional abuse severity across individuals' mothers and fathers, with the following classification approach. For childhood physical abuse, women were asked during childhood, how often their mother/the women who raised them, and father/the man who raised them did the following: moderate physical abuse (ie, pushed, grabbed or shoved; slapped; or threw something at them), and severe physical abuse (ie, kicked, bit, or hit with a fist; tried to hit with an object; beat up; choked; burned or scalded). Frequency responses included "often", "sometimes", "rarely" and "never", each coded from 3 to 0. We calculated the mean of *moderate* parental physical abuse score by averaging the maternal and paternal moderate physical abuse scores. We calculated the mean of *severe* parental physical abuse score by averaging the maternal and paternal severe physical abuse scores. We then calculated an overall parental physical abuse score by adding the *moderate* physical abuse score and two times the *severe* physical abuse score, with the assumption that severe physical abuse is more impactful than moderate physical abuse. For childhood emotional abuse, women were asked during childhood, how often their mother/the women who raised them, and father/the man who raised them did the following: insulted them; sulked or refused to talk to them; stomped away; did or said something to spite them; threatened to hit them; smashed or kicked something in anger. Responses included "often", "sometimes", "rarely" and "never", coded from 3 to 0. We created a mean score of childhood parental emotional abuse by averaging the maternal and paternal emotional abuse scores.

Diagnoses within the past 12 months of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Panic Disorder based on the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; 1987) were assessed with World Mental Health Organization's Composite International Diagnostic Interview Short Form (WHO CIDI-SF).[38,74] WHO CIDI-SF has shown good validity to the full CIDI diagnoses and clinician diagnoses, and has been widely used in epidemiological studies.[7,38,72] We combined the GAD and Panic Disorder measures into a single, binary anxiety disorder indicator. Somatic amplification was measured using the 5-question Somatic Amplification Scale,[5] which includes the following 5 items: "I am often aware of various things happening within my body", "Sudden loud noises really bother me", "I hate to be too hot or too cold", "I am quick to sense hunger contractions in my stomach", and "I have a low tolerance for pain"; responses included "not at all true", "a little bit true", "moderately true", and "extremely true", each coded from 0 to 3. We used the mean score computed from the 5 items as a continuous variable indicating somatization.

Statistical Analyses

We compared baseline characteristics between the analytic sample and those lost to follow-up (women free of chronic pain at MIDUS 2 but did not participate in the MIDUS 3 SAQs). Continuous variables were compared using the two-sample t-test or the Wilcoxon Rank-Sum test, and categorical variables using the Chi-Square test. We then stratified based on whether women's menstrual periods were stopped permanently at MIDUS 1 throughout the subsequent analyses, because both the recall for dysmenorrhea and the association between dysmenorrhea and chronic pain may be different between menstruating women and women who already stopped their menstrual periods. We excluded 25 women who we were not able to ascertain their menstruation status, leaving 523 menstruating women, and 351 non-menstruating women for the following analyses.

For estimating the risk ratio (RR) of chronic pain development associated with dysmenorrhea between MIDUS 2 and MIDUS 3, we fit a stratified clustered modified Poisson regression model with the sandwich variance estimator, which is suitable for modeling a non-rare individual binary outcome and can also account for the clustering effects due to the correlated outcomes among siblings and twins in our sample.[77,78] We adjusted for baseline confounders (measured at MIDUS 1) including age, racial and ethnic group, education level, marital status, BMI, smoking status, physical activity level, regular fish oil intake (measured at MIDUS 2), childhood physical abuse by parents, childhood emotional abuse by parents, and somatic amplification score (our main model). About 5% (26/523) of menstruating women and 11% (39/351) of non-menstruating women missed covariates or outcome information (including 1% and 2% missing the chronic pain outcome, respectively).

We conducted sensitivity analyses to examine potential bias due to selection, missing data, residual confounding, and dysmenorrhea definition, for the above dysmenorrhea–chronic pain association, all stratified based on the menstruation status. First, we gauged potential selection bias due to loss to follow-up by fitting an inverse probability-of-response weighted, clustered modified Poisson regression model, with weight calculated as the inverse of the probability of responding in MIDUS 3. The weights were derived from a multinomial logistic regression with 4 outcomes that included participation in MIDUS 3 and then 3 reasons for attrition from MIDUS 2 to MIDUS 3: not reachable (eg, a nonworking number), unable to participate due to health concerns (physically or mentally unable to participate or deceased), and refusal to participate or SAQs not returned in MIDUS 3. Independent variables in the multinomial logistic regression model included self-rated health (poor, fair, good, very good, excellent, coded from 1 to 5), the number of chronic conditions (a count of common chronic conditions), in addition to dysmenorrhea and all covariates in our main model. Second, to address potential bias due to missing data in our primary model estimates, we used a fully conditional, multiple-imputation approach with 10 imputations to deal with anticipated missing values for both the covariates and the outcome variable within our analytic sample (not including those lost to follow-up), assuming missing at random. Third, to account for potential residual confounding from several controversial variables, we additionally controlled for the number of chronic conditions, age of menarche (years), the total number of years of female hormone use, the total number of years of birth control medication use, and parity (ie, the number of biological children). Disease burden is generally associated with chronic pain but has not been associated with dysmenorrhea. Age of menarche is associated with dysmenorrhea but has not been associated with chronic pain. Hormonal treatment is commonly used by women to manage their dysmenorrhea, but its effect on relieving dysmenorrhea may result in self-report of lower dysmenorrhea severity (acting as a confounder). Although evidence have shown that dysmenorrhea improves after giving birth,[71] the association between parity and chronic pain is less clear. Lastly, to assess whether the association persisted with different operationalization of the exposure variable, we used the continuous (0−3) and ordinal (0, 1, 2, 3) forms of dysmenorrhea, respectively, and repeated our main model to examine whether higher severity of dysmenorrhea was associated with a higher risk for developing chronic pain.

To examine the association between dysmenorrhea and chronic pain-related functional impairment, we regressed the number of chronic pain regions (none, 1-2, ≥3) and the degree of pain interference (none, low-interference, high-interference), respectively, on dysmenorrhea (binary), using clustered ordinal or multinomial (if the proportional odds assumption was not met) logistic regressions, adjusting for the same set of covariates as the main model. All data management and statistical analyses were conducted in SAS v.9.4 (SAS Inc., Cary, NC, USA).

Results

Sample Description

A flow diagram for the study cohort is presented in Fig 1. Among a total of 3,666 female participants at MIDUS 1, 1,295 had information about their dysmenorrhea history and were self-reported chronic pain-free at MIDUS 2, among whom 899 were alive MIDUS 3 participants who completed the SAQs for ascertaining chronic pain development. The baseline characteristics between the analytic sample and those lost to follow-up at MIDUS 3 are compared in Table 1. The analytic sample was slightly younger, more educated, more likely to be married, and less likely to smoke compared to women who were lost to follow-up at MIDUS 3. There was no difference in the prevalence or severity of self-reported dysmenorrhea. The rest of the MIDUS sample were older and less healthy compared to these 2 groups (data not shown). Overall, 48% of women reported dysmenorrhea at baseline among our analytic sample.

Among the analytic sample, 523 women were menstruating at baseline, who were aged between 25-62 years (95.4% were aged 25−50 years). Women who had stopped menstruation at baseline (n = 351) were aged between 34-74 years (72.6% were aged over 50 years).

Chronic Pain Outcomes

Table 2 shows the incidence of chronic pain overall, the incidence of chronic pain at each body region, the number of chronic pain body regions, and chronic pain interference at MIDUS 3, by history of dysmenorrhea at baseline (ie, at the time of the MIDUS 1 interview). Among women who were menstruating at baseline, the 10-year cumulative incidence of chronic pain from MIDUS 2 to MIDUS 3 was 35.3% for women with dysmenorrhea and 23.2% for women without. Menstruating women with dysmenorrhea also developed chronic pain in more body regions and experienced greater pain-related interference. Among women who had stopped their menstrual periods permanently at baseline, there were no differences in the 10-year cumulative incidence of chronic pain, the number of chronic pain body regions, or the degree of pain interference between women with and without a history of dysmenorrhea.

Dysmenorrhea and Chronic Pain Development

Table 3 shows the adjusted associations between dysmenorrhea and chronic pain development at MIDUS 3. Dysmenorrhea was associated with a 41% greater risk (95% CI = 6%−88%) of developing chronic pain during the 10-year follow-up (between MIDUS 2 and MIDUS 3). Inverse probability-of-response weighting (RR = 1.44), multiple imputation (RR = 1.43), or additional covariates adjustment (RR = 1.44) did not appreciably change the effect estimate. Each unit increase in dysmenorrhea severity was associated with a 22% greater risk of chronic pain, with marginally significant (P= 0.067) linear trend for categorical dysmenorrhea severity. We did not find evidence of an association between dysmenorrhea and chronic pain development among non-menstruating women (RR = 0.90, 95% CI = 0.59−1.37). The results did not change considerably with weighting, imputation, additional covariates adjustment, or linear/categorical operationalization of dysmenorrhea.

Table 1. **Baseline Sample Characteristics**

Characteristics	Analytic Sample (n = 899) mean (SD) / median (5^{TH}-95^{TH}) / n (%)	Lost to Follow-up (n = 396) mean (SD) / median (5^{TH}-95^{TH}) / n (%)	P
Age (Ys): mean (SD)	45.0 (11.5)	46.9 (14.1)	0.017
25-35	217 (24.1%)	108 (27.3%)	<0.001
36-55	487 (54.2%)	165 (41.7%)	
56-74	195 (21.7%)	123 (31.1%)	
Race and ethnicity			
Non-Hispanic White	821 (91.3%)	352 (88.9%)	0.127
Non-Hispanic Black	31 (3.5%)	24 (6.1%)	
Hispanic	19 (2.1%)	6 (1.5%)	
Other	28 (3.1%)	14 (3.5%)	
Highest education†			
High school or less	283 (31.6%)	154 (38.9%)	<0.001
Some college	273 (30.4%)	137 (34.6%)	
Bachelor's degree or more	341 (38.0%)	105 (26.5%)	
Marital status			
Married	649 (72.2%)	254 (64.1%)	0.004
Not married	250 (27.8%)	142 (35.9%)	
Parity			
0	192 (21.4%)	86 (21.7%)	0.514
1-2	424 (47.2%)	174 (43.9%)	
≥ 3	283 (31.5%)	136 (34.3%)	
BMI*: mean (SD)	25.4 (5.0)	25.5 (5.3)	0.846
<18.5 kg/m^2	26 (2.9%)	17 (4.3%)	0.375
18.5-24.9 kg/m^2	452 (50.3%)	197 (49.7%)	
25-29.9 kg/m^2	256 (28.5%)	98 (24.7%)	
>30 kg/m^2	137 (15.2%)	69 (17.4%)	
Smoking status			
Non-smoker	543 (60.4%)	196 (49.5%)	<0.001
Past daily smoker	222 (24.7%)	100 (25.3%)	
Current daily smoker	134 (14.9%)	100 (25.3%)	
Physical activity level**	5.0 (3.0−5.0)	5.0 (2.0−5.0)	0.353
Childhood physical abuse by parents‡	0.5 (0−4)	0.5 (0−3.5)	0.448
Childhood emotional abuse by parents§	0.5 (0−2)	0.5 (0−2)	0.226
MDD	95 (10.6%)	43 (10.9%)	0.876
GAD	18 (2.0%)	9 (2.3%)	0.754
Panic Disorder	55 (6.1%)	20 (5.1%)	0.449
Somatic amplification score¶	2.5 (0.5)	2.5 (0.5)	0.692
Binary dysmenorrhea	429 (47.7%)	193 (48.7%)	0.736
Dysmenorrhea severity			
None at all	144 (16.0%)	62 (15.7%)	0.979
A little	326 (36.3%)	141 (35.6%)	
Some	296 (32.9%)	131 (33.1%)	
A lot	133 (14.8%)	62 (15.7%)	

Abbreviations: SD, standard deviation; BMI, body mass index; MDD, major depressive disorder; GAD, generalized anxiety disorder.
*BMI was missing in 28 among the analytic sample and 15 among those loss to follow-up.
†Highest education was missing in 2 among the analytic sample.
‡A higher score indicates a higher frequency of childhood physical abuse by parents; the score was missing in 13 among the analytic sample and 15 among those loss to follow-up.
§A higher score indicates a higher frequency of childhood emotional abuse by parents; the score was missing in 23 among the analytic sample and 22 among those loss to follow-up.
¶Somatic amplification score was missing in 1 among the analytic sample and 1 among those loss to follow-up.
** A higher score indicates a higher level of physical activity; the score was missing in 2 among those loss to follow-up.

To explore the impact of time lapse between exposure and outcome measurement, we replicated our primary analysis in a cross-sectional model using chronic pain presence at MIDUS 2 as the outcome (it was deemed cross-sectional because the chronic pain status at baseline was unknown). Dysmenorrhea was associated with greater "risk" of chronic pain presence at MIDUS 2 among both menstruating women (n = 1,032, RR = 1.39, 95% CI = 1.16−1.67) and non-menstruating women (n = 868, RR = 1.25, 95% CI = 1.08−1.45).

Dysmenorrhea and Chronic Pain-Related Functional Impairment

Table 4 shows the adjusted associations between dysmenorrhea and chronic pain-related functional

Table 2. Chronic Pain Incidence, Number of Chronic Pain Body Regions, and Chronic Pain Interference, by History of Dysmenorrhea, Stratified by Menstruating Status at Baseline

	Menstruating Women†		Non-menstruating Women†	
	With dysmenorrhea (n = 232)	Without dysmenorrhea (285)	With dysmenorrhea (n = 175)	Without dysmenorrhea (n = 168)
Chronic pain development: yes	82 (35.3%)	66 (23.2%)*	45 (25.7%)	39 (23.2%)
Chronic pain body regions‡				
Head	10 (4.3%)	2 (0.7%)*	4 (2.3%)	3 (1.8%)
Neck	17 (7.3%)	10 (3.5%)	12 (6.9%)	4 (2.4%)*
Back	31 (13.4%)	29 (10.2%)	26 (14.9%)	20 (11.9%)
Arms/hands	25 (10.8%)	13 (4.6%)*	11 (6.3%)	2 (1.2%)*
Legs/feet	37 (15.9%)	22 (7.7%)*	22 (12.6%)	18 (10.7%)
Shoulders	18 (7.8%)	8 (2.8%)*	14 (8.1%)	6 (3.6%)
Hips	15 (6.5%)	11 (3.9%)	15 (8.6%)	11 (6.5%)
Knees	21 (9.1%)	21 (7.4%)	18 (10.3%)	13 (7.7%)
Others§	3 (1.3%)	3 (1.1%)	3 (1.7%)	6 (3.6%)
No pain	*150 (64.7%)*	*219 (76.8%)*	*130 (74.7%)*	*129 (76.8%)*
Pain in 1-2 body regions	*55 (23.7%)*	*56 (19.6%)*	*23 (13.2%)*	*25 (14.9%)*
Pain in ≥3 body regions	*27 (11.6%)*	*10 (3.5%)*	*21 (12.1%)*	*14 (8.3%)*
Chronic pain interference¶				
No pain	*150 (64.7%)*	*219 (77.1%)*	*130 (75.1%)*	*129 (76.8%)*
Pain with low interference	*55 (23.7%)*	*50 (17.6%)*	*30 (17.3%)*	*26 (15.5%)*
Pain with high interference	*27 (11.6%)*	*15 (5.3%)*	*13 (7.5%)*	*13 (7.5%)*

*Significant difference ($P < 0.05$) between women with and without dysmenorrhea.
†Women who did not answer the chronic pain question (6 among menstruating women and 8 among non-menstruating women) were excluded.
‡The number of chronic pain body regions was calculated by summing pain regions including head, neck, back, shoulders, arms/hands, hips, legs/feet, knees, and others, which was categorized into none (without chronic pain), 1-2 regions, and 3 or more regions. Women who did not answer questions regarding chronic pain body regions were excluded.
§For chronic pain located in other body regions: Among menstruating women with dysmenorrhea, 1 reported finger pain and 2 reported chronic pain in other body regions; among menstruating women without dysmenorrhea, 3 reported joint pain; among non-menstruating women with dysmenorrhea, 1 reported joint pain and 2 reported chronic pain in other body regions; among non-menstruating women without dysmenorrhea, 1 reported ankle pain, 1 reported spine pain, 1 reported stomach pain, and 3 reported chronic pain in other body regions.
¶Women with chronic pain were asked to rate from 0 ("did not interfere") to 10 ("completely interfered") how the pain interfered with their general activity, mood, relationship with other people, sleep, and enjoyment of life. The degree of chronic pain interference was indicated by the mean score of the 5 items, which was categorized into none (without chronic pain), low-interference (mean score ≤4) and high-interference (mean score >4). Women who did not answer questions regarding chronic pain interference were excluded.

impairment at MIDUS 3 among those with complete data. Among menstruating women, dysmenorrhea was associated with a 77% increase (95% CI = 18%−164%) in the odds of developing chronic pain in more body regions, and a 73% increase (95% CI = 15%−159%) in the odds of developing chronic pain with more interference. No clear associations between dysmenorrhea, pain regions, and pain interference were seen among non-menstruating women.

Discussion

To our knowledge, our study is the first to examine the prospective association between dysmenorrhea and the development of chronic pain among a national sample of community-dwelling U.S. women. Among women who were still menstruating at baseline (aged 25−62), those with dysmenorrhea had a 41% greater risk of developing chronic pain during a 10-year follow-up compared to those without dysmenorrhea. Dysmenorrhea was also prospectively associated with developing more widespread and disabling pain. We did not find evidence of an association between dysmenorrhea and chronic pain (including incidence, body regions, and interference) among women who reported that they were not menstruating at baseline.

Our finding of a greater risk for chronic pain development associated with dysmenorrhea among menstruating women adds to a broader literature for dysmenorrhea-associated pain chronicity. According to a recent systematic review and meta-analysis of population-based studies, women with chronic pain had 2.5 times the odds of having dysmenorrhea compared to women without chronic pain, with similar effect sizes across chronic pelvic and non-pelvic pain conditions.[42] There was only one prospective study included in this review, which found a positive relationship between menstrual pain severity at baseline and the development of temporomandibular disorders 3 years later.[44] Our results similarly suggest that dysmenorrhea may be a general risk factor for chronic pain development. Both causal mechanisms such as central sensitization,[3,24,25,45,46,57,65,73] abnormal stress responses,[68] and the facilitation of pain catastrophizing,[14] and non-causal mechanisms such as predisposing baseline alterations in the corticolimbic structures and the hypothalamic-pituitary-adrenal axis,[30,43,69] may underlie the association between dysmenorrhea and chronic pain.

Table 3. Results from the Multivariable Clustered Modified Poisson Regression (Main Analyses) and Sensitivity Analyses for the Association between Dysmenorrhea and Chronic Pain Development, Stratified by Menstruating Status at Baseline

	Menstruating women (n = 523)		*Non-menstruating women (n = 351)*	
	N	*RR (95% CI)*	*N*	*RR (95% CI)*
Dysmenorrhea — yes vs no				
Main analyses†	*497*	*1.41 (1.06, 1.88)*	*312*	*0.90 (0.59, 1.37)*
Inverse probability-weighted*	497	1.44 (1.08, 1.92)	312	0.93 (0.62, 1.42)
Multiple imputation**	523	1.43 (1.08, 1.88)	351	0.97 (0.65, 1.43)
Additionally adjusted for years of birth control use and years of female hormone use	437	1.44 (1.05, 1.97)	273	0.94 (0.59, 1.49)
Additionally, adjusted for years of birth control use, years of female hormone use, the number of chronic conditions‡, age of menarche, and the number of biological children§	436	1.44 (1.04, 1.99)	273	0.90 (0.57, 1.44)
Dysmenorrhea — linear **(0-3)**§	497	1.22 (1.03, 1.45)	312	0.97 (0.80, 1.17)
Dysmenorrhea — ordinal§				
None at all	84	Ref	48	Ref
A little	189	0.92 (0.57, 1.48)	108	1.47 (0.76, 2.82)
Some	176	1.25 (0.79, 1.98)	89	1.29 (0.64, 2.57)
A lot	48	1.65 (0.97, 2.79)	67	1.06 (0.53, 2.12)
P for trend		*0.067*		*0.864*

Abbreviations: RR, relative risk; CI, confidence interval.
†Adjusted for age (continuous), race/ethnicity (non-Hispanic White, non-Hispanic Black, others), education (high school or less, less than college, bachelor's degree or above), marital status (married vs not married), BMI (continuous), history of daily smoking (yes vs no), level of physical activity (continuous), regular fish oil intake (yes vs no), childhood physical abuse by parents (continuous), childhood emotional abuse by parents (continuous), MDD (yes vs no), anxiety disorder (yes vs no), and somatic amplification.
*Weights were calculated as the inverse of the probability of participation in MIDUS 3, derived from a multinomial logistic regression with 4 outcomes that included participation in MIDUS 3 and 3 reasons for attrition from MIDUS 2 to MIDUS 3: not reachable (eg, a non-working number), unable to participate due to health concerns (physically or mentally unable to participate or deceased), and refusal to participate or SAQs not returned in MIDUS 3. Independent variables in the multinomial logistic regression model included self-rated health (poor, fair, good, very good, excellent, coded from 1 to 5), the number of chronic conditions (a count of common chronic conditions), in addition to dysmenorrhea and all covariates in the main model.
**A fully conditional, multiple imputation with 10 imputations was conducted within the analytic sample for menstruating and non-menstruating women, respectively, not including those lost to follow-up.
‡Chronic conditions included experience of the following conditions during the past 12 months: asthma, bronchitis, or emphysema; tuberculosis; other lung problems; arthritis, rheumatism, or other bone or joint diseases; sciatica, lumbago, or recurring backache; persistent skin trouble (eg, eczema); thyroid disease; hay fever; recurring stomach trouble, indigestion, or diarrhea; urinary or bladder problems; being constipated all or most of the time; gall bladder trouble; persistent foot trouble (eg, bunions, ingrown toenails); trouble with varicose veins requiring medical treatment; AIDS or HIV infection; Lupus or other autoimmune disorders; persistent trouble with gums or mouth; persistent trouble with teeth; high blood pressure; anxiety, depression, or some other emotional disorder; alcohol or drug problems; migraine headaches; chronic sleeping problems; diabetes or high blood sugar; multiple sclerosis, epilepsy, or other neurological disorders; stroke; ulcer; and hernia or rupture.
§Same model specification as the main analyses, without weighting or imputation.

Table 4. Results from the Multivariable Ordinal/Multinomial Logistic Regression for the Association between Dysmenorrhea and Chronic Pain Regions and Chronic Pain Interference, Stratified by Menstruating Status at Baseline

Dysmenorrhea: yes vs no	*Chronic pain regions (≥3 vs 1-2 vs none)*		*Chronic pain interference (high vs low vs none)*	
	N	*OR (95% CI)*	*N*	*OR (95% CI)*
Menstruating women **(n = 523)**				
Ordinal logistic regression	497	1.77 (1.18, 2.64)	496	1.73 (1.15, 2.59)
Non-menstruating women **(n = 351)**				
Ordinal logistic regression	-	-	310	0.80 (0.45, 1.43)
Multinomial logistic regression†				
No chronic pain	234	Ref	-	-
Chronic pain in 1-2 regions	44	0.77 (0.39, 1.56)	-	-
Chronic pain in ≥ 3 regions	33	1.01 (0.45, 2.28)	-	-

Abbreviations: OR, odds ratio; CI, confidence interval.
†The proportional odds assumption was violated.

Among women who stopped menstruating permanently at baseline, we did not find an association between their previous history of dysmenorrhea and chronic pain development. Age may be an important explanation for this null finding, as the prevalence of some chronic pain conditions, such as temporomandibular disorders, migraine headaches, and chronic pelvic pain, peaks during women's reproductive years and declines with age particularly after menopause.[27] It is possible that in non-menstruating women, there is an increasingly minimal influence of their previous history of dysmenorrhea on the subsequent risk of developing chronic pain conditions as they age. Second, women who stopped their menstrual periods may report their menstrual discomfort less accurately, which may result in a higher degree of non-differential exposure misclassification that underestimated the association between dysmenorrhea and chronic pain. Third, women who stopped their menstrual periods due to surgical reasons may have a shorter exposure period than naturally postmenopausal women, potentially biasing the dysmenorrhea—chronic pain association downward. We excluded women who stopped menstrual periods due to gynecological surgeries performed before the age of 40 and reran the analysis, and still did not find an association between dysmenorrhea and chronic pain (RR = 0.91, 95% CI = 0.55−1.50).

Our findings of positive associations between dysmenorrhea and the number of chronic pain regions, as well as the level of chronic pain interference among menstruating women, further complement existing literature. Dysmenorrhea has been associated with greater burdens of fibromyalgia,[15,52,58,76] a female predominant chronic pain disorder characterized by widespread musculoskeletal pain, sleep disorders, physical exhaustion, and affective dysfunction. As a recurrent visceral pain condition, dysmenorrhea may enhance somatic pain through central sensitization. Dysmenorrhea has also been consistently associated with functional interference in adolescent and young adult women, but its association with interference of non-cyclic chronic pain conditions is less studied. Our results suggest that in addition to increasing the risk of chronic pain development, dysmenorrhea may also contribute to more widespread and debilitating chronic pain conditions during a woman's reproductive years.

Several limitations of our analyses must be noted. First, we were not able to account for the possibility that women may have transitioned in and out of "chronic pain status" between MIDUS 2 and MIDUS 3, and therefore we may have misclassified those who had recovered from chronic pain at the MIDUS 3 as not developing chronic pain during the 10-year follow-up. There could be a greater degree of underestimation of chronic pain incidence among women without dysmenorrhea if they were more likely to recover from chronic pain.

Second, in our cohort dysmenorrhea was measured only in MIDUS 1 while chronic pain was measured in MIDUS 2 and MIDUS 3—thus, we studied women with and without dysmenorrhea for a 10-year period that started at 10 years after the exposure was measured. Our ancillary findings for a positive association between dysmenorrhea and chronic pain presence at MIDUS 2 among both menstruating and non-menstruating women could suggest that the risk for chronic pain development associated with dysmenorrhea attenuates among postmenopausal women as they age.

Third, our measure of dysmenorrhea was based on one question of menstrual discomfort, which has not been validated clinically. However, the standardized diagnostic criteria for dysmenorrhea have not been fully established, and menstrual discomfort is a description easily understood by the general female population. We compared women's attitudes toward the termination of their menstrual periods, and found that a higher level of menstrual discomfort was associated with more frequent report of a relief attitude toward the stop of menstruation (data not shown). The measure of chronic pain was also based on self-report, although the given description is close to the scientific definition of chronic pain and we also found positive associations between dysmenorrhea and the number of chronic pain regions and the degree of chronic pain interference. As abdominal pain and pelvic pain were not explicitly asked in the assessment of chronic pain body regions, our conclusion of a greater risk of developing more widespread chronic pain associated with dysmenorrhea among menstruating women should be more applicable to chronic non-pelvic pain. Given the common presence of dysmenorrhea in chronic abdominal and pelvic pain, we expect to see a greater magnitude of association between dysmenorrhea and the number of chronic pain body regions if these chronic pain conditions are included. We were not able to examine the intensity of chronic pain as this was not asked in the MIDUS survey.

Fourth, the relative risk estimated for menstruating women in the present study encompasses a mix of the effect of dysmenorrhea on chronic pain development among women with a wide age range (25−62, >95% between 25−50 years) at baseline, and thus the effect size cannot be extrapolated to women of a particular age group. Specifically, among women who were menstruating at baseline (n = 523), about one third of them (n = 165) later stopped menstruation by MIDUS 2. Among this subgroup of women, we found a greater association between dysmenorrhea and chronic pain development from MIDUS 2 to MIDUS 3 (RR = 1.96, 95% CI = 1.16-3.32), which together with our main findings, could suggest that there may be an increasing positive association between dysmenorrhea and chronic pain development during women's reproductive years, which peaks several years after menopause, and then tends to diminish as women age.

Conclusions

Our study confirms an elevated risk of chronic pain development among menstruating women with self-reported dysmenorrhea, which has important implications for prevention of chronic pain in women. Given the challenges in optimal management of chronic pain, early intervention for risk factors associated with pain chronicity, such as dysmenorrhea, can yield substantial public health benefit. Since adolescence is a sensitive period of neurodevelopment,[12,60] mitigating the long-term impact of dysmenorrhea on centralized pain pathways through earlier medical and behavioral interventions may lower the incidence and reduce the burden of chronic pain among women. Longitudinal studies following adolescent girls immediately after menarche are needed to further elucidate whether primary dysmenorrhea is a risk factor for chronic pain, identify chronic pain-prone phenotypes in the context of dysmenorrhea, and test whether early management of dysmenorrhea contributes to reducing the burden associated with chronic pain at the population level.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2021.03.139.

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