Association between dysmenorrhea and chronic pain: A systematic review and meta-analysis of population-based studies

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**Condensation:** Dysmenorrhea was positively associated with the presence of chronic pelvic pain and chronic non-pelvic pain based on a systematic synthesis of population-based studies.

**Short title:** Dysmenorrhea and chronic pain

**AJOG at a glance**

*Why was this study conducted?*

- Past research has suggested that dysmenorrhea is associated with enhanced pain sensitivity, and structural and functional changes in the brain related to pain chronicity.
- The overall association between dysmenorrhea and the presence and severity of chronic pain, as well as potential heterogeneity of the association by chronic pelvic pain versus chronic non-pelvic pain are unknown.
- The association between primary dysmenorrhea and chronic pain is unknown.

*What are the key findings?*

- Dysmenorrhea was positively associated with the presence and severity of chronic pelvic pain and chronic non-pelvic pain.

*What does this add to what is known?*

- Dysmenorrhea may be a general risk factor for chronic pain.
- Studies focusing on primary dysmenorrhea and chronic pain are urgently needed.

**Keywords:** chronic non-pelvic pain, chronic pelvic pain, dysmenorrhea, endometriosis, menstrual pain, meta-analysis, pelvic pain, primary dysmenorrhea, systematic review
ABSTRACT

OBJECTIVE: To synthesize the epidemiological findings for the associations between dysmenorrhea, including primary dysmenorrhea and endometriosis-associated dysmenorrhea, and any chronic pain conditions, including chronic pelvic pain, and chronic non-pelvic pain.


STUDY ELIGIBILITY CRITERIA: Observational population-based studies in which the relationship between dysmenorrhea and the presence or severity of chronic pain was examined.

STUDY APPRAISAL AND SYNTHESIS METHODS: Each study was double-coded and evaluated for bias based on the modified Newcastle and Ottawa Scale. Random-effect meta-analyses were conducted to quantify the associations between dysmenorrhea and the presence of chronic pelvic and non-pelvic pain.

RESULTS: Out of 9,452 records, 32 studies were included, with 14 reporting associations between dysmenorrhea and chronic pelvic pain, and 20 for dysmenorrhea and chronic non-pelvic pain. Primary dysmenorrhea and endometriosis-associated dysmenorrhea were examined in 7 studies, respectively. Over 30% of the studies were categorized as poor quality, 56% as moderate, and 12.5% as high. Dysmenorrhea was positively associated with both the presence and severity of chronic pelvic and non-pelvic pain conditions. Based on 6,689 women from 8 studies, those with chronic pelvic pain had 2.43 (95% confidence interval = 1.98, 2.99, $I^2 = 42\%$) times the odds of having dysmenorrhea compared to those without. Based on 3,750 women from 11 studies, those with chronic non-pelvic pain had 2.62 (95% confidence interval = 1.84, 3.72, $I^2 = 72\%$) times the odds of having dysmenorrhea compared to those without. Overall, dysmenorrhea was associated with 2.50 (95% confidence interval = 2.02, 3.10) times the odds of chronic pain,
which did not differ by chronic pelvic vs chronic non-pelvic pain, community vs clinical
populations, or different geographical regions.

**CONCLUSIONS:** Dysmenorrhea may be a general risk factor for chronic pain, although
whether primary dysmenorrhea increases the risk for chronic pain is unclear. Given that
adolescence is a sensitive period for neurodevelopment, elucidating the role of primary
dysmenorrhea in pain chronicity in future longitudinal studies is important for preventing both
chronic pelvic and non-pelvic pain.
Introduction

Dysmenorrhea, or menstrual pain, is the most common gynecological complaint among women of reproductive age, which is clinically divided into primary dysmenorrhea (PD, menstrual pain without any discernable macroscopic pelvic pathology), and secondary dysmenorrhea (due to identifiable pelvic pathological conditions such as endometriosis, adenomyosis, and pelvic inflammatory disease).\(^1\) In addition to directly reducing the quality of life in women,\(^2\) dysmenorrhea has also been associated with higher risk for developing chronic pain.

Research in experimental settings has demonstrated enhanced pain sensitivity in women with dysmenorrhea across the menstrual cycles, both in areas of referred pain and remote body regions.\(^1,3,4\) Neuro-imaging studies have associated dysmenorrhea with changes in cerebral metabolism,\(^5\) grey matter,\(^6\) white matter,\(^7\) stimulus-evoked functional magnetic resonance imaging (fMRI) signals,\(^8\) functional connectivity (resting-state fMRI images),\(^9\) brain complexity,\(^10\) and spectrum features and brain asymmetry.\(^10\) Some of those structural and functional changes are suggested to occur in people with chronic pain. Dysmenorrhea has also been associated with gene polymorphisms for nerve growth factor (NGF)\(^11\) and brain-derived neurotrophic factor (BDNF),\(^12\) the two known factors associated with pain sensitivity and psychiatric disorders, as well as with allodynia in women with chronic pelvic pain.\(^13\)

However, there remain several key knowledge gaps in the relationship between dysmenorrhea and chronic pain. First, despite the suggested association between dysmenorrhea and pain sensitivity, chronic pain features and mechanisms, whether dysmenorrhea is associated with the presence of chronic pain is unknown, which is essential for determining whether dysmenorrhea directly contributes to chronic pain development. Despite correlations suggested between dysmenorrhea and chronic pelvic pain (CPP),\(^14,15\) it remains a question as to whether
dysmenorrhea is a risk factor for CPP. Meanwhile, there have been fewer studies on
dysmenorrhea and the presence of chronic non-pelvic pain (CNPP), and the effects of
dysmenorrhea on different CNPP conditions are not clear. Therefore, a systematic synthesis of
population-based studies on the associations between dysmenorrhea and CPP and CNPP is an
important step for providing preliminary evidence and illuminating future directions. Second, it
is also unknown whether dysmenorrhea is associated with greater severity of CPP and CNPP,
which is important for developing interventions to mitigate chronic pain suffering. Third, since
PD is seldomly separated from dysmenorrhea in previous studies, it remains unknown whether
PD facilitates chronic pain development and influences its severity. It has been increasingly
recognized that adolescence is a sensitive, if not critical, period for neurodevelopment, when
contextual factors play an important role in shaping the developmental trajectories of several key
brain areas related to cognition and emotions, such as the prefrontal cortex and subcortical
areas. Since PD usually starts during adolescence, and given its common prevalence in
women, it is important to know whether PD is a risk factor for chronic pain, which may provide
an opportunity for early intervention.

Therefore, this systematic review and meta-analysis was aimed at synthesizing the current
population-based findings on the associations between dysmenorrhea and the presence and
severity of both CPP and CNPP. PD, endometriosis-associated dysmenorrhea, and
undifferentiated dysmenorrhea were summarized separately with respect to chronic pain
outcomes. The overall objective of the study was to aggregate and evaluate the epidemiologic
evidence for the association between dysmenorrhea and chronic pain in women, including both
CPP and CNPP conditions.
Methods

Search strategy and study selection

PubMed, Embase, and CINAHL were searched since inception until December 2019, using the key concept of “dysmenorrhea” and a specification for epidemiologic/population studies with no language restriction to obtain a comprehensive literature including the maximum possible number of studies related to dysmenorrhea—chronic pain relationship. The detailed searching strategy is summarized in Appendix A. Chronic pain was determined by one of the following criteria after reviewing each record: 1) “chronic pain” described in the text, 2) definition of the pain conditions in the text that was judged to be chronic by the first author (e.g., frequent headaches, chronic migraines, studies where frequency of pain was described as “always” or “persistent” by researchers), 3) clinically recognized chronic pain conditions such as fibromyalgia, arthritis, vestibulodynia (vulvodynia/vulvar pain), temporomandibular disorders, complex regional pain syndrome and post-mastectomy pain syndrome. Studies were required to meet the following criteria to be eligible for this review: 1) population-based observational study (cross-sectional, case control, or cohort study), 2) dysmenorrhea data reported, including PD, endometriosis-associated dysmenorrhea, and undifferentiated dysmenorrhea, 3) chronic pain data reported, including the presence and/or the severity of chronic pain, 4) comparison of dysmenorrhea in women with and without chronic pain, or in women with different severity of chronic pain. The title and abstract of each record, as well as the full-text if needed, were reviewed to determine eligibility. Conference abstracts and non-English articles were reviewed and summarized, although they were not evaluated for bias and therefore not included in the full qualitative review and meta-analyses. From the eligible studies, duplicate publications or subgroup analyses for the same study were not found.
Data extraction

A coding manual was developed to extract information from each study (Appendix B). Variables extracted from each paper include: publication information (author, journal, country, publication year), whether dysmenorrhea – chronic pain association was a pre-specified research question, the target population of the study (the general female population or a clinical population), the definition and measurement of dysmenorrhea, whether the severity of dysmenorrhea (e.g., intensity) was captured, and if so, how the severity was captured, the type of chronic pain studied, whether the presence and severity of chronic pain were examined, how chronic pain was measured, the study design (cross-sectional, case-control, or cohort study), whether the temporal relationship between dysmenorrhea and chronic pain was ascertained (dysmenorrhea occurred before chronic pain), the sample size, where the subjects were recruited, the response rate, the differences between the responding and non-responding subjects, how the confounders were selected and measured, the statistical methods used for quantifying the association between dysmenorrhea and chronic pain, and the effect sizes (from both unadjusted and adjusted analyses) for the association. When more than 2 types of chronic pain conditions were compared with the control group, data were extracted for the comparison between each chronic pain condition and the control group. Two coders independently extracted all the variables from each paper, and any discrepancy was reviewed and resolved by the first author. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Rochester.\(^{18,19}\)

Qualitative synthesis of studies
After data extraction, a bias evaluation was performed by the first author based on a modified version of the Newcastle and Ottawa Scale (NOS), which was specifically developed for this review (Appendix C). The maximum score for cross-sectional, case-control, and cohort studies were 8, 9, 9 respectively, with a higher score indicating a lower degree of bias and therefore higher quality. Studies were summarized into four non-exclusive categories: the association between dysmenorrhea and the presence of CPP, the association between dysmenorrhea and the severity of CPP, the association between dysmenorrhea and the presence of CNPP, and the association between dysmenorrhea and the severity of CNPP. For each study, key information including authors, publication year, country of the study, study design, the comparison groups, age range of the study population, the type of chronic pain studied, the sample size, the type of dysmenorrhea studied (PD, endometriosis-associated dysmenorrhea, or undifferentiated dysmenorrhea), the severity of dysmenorrhea (e.g., intensity), the temporal relationship between dysmenorrhea and chronic pain, the unadjusted and adjusted analysis results, and the NOS score were summarized.

Quantitative synthesis of studies for dysmenorrhea—chronic pain presence

To quantitatively synthesize the strength of the association between dysmenorrhea and the presence of chronic pain, meta-analyses were conducted to estimate the relative odds of dysmenorrhea associated with the presence of CPP and CNPP. First, the unadjusted bivariate associations between dysmenorrhea and CPP/CNPP were synthesized, and aggregated to test whether there was a significant difference for the associations between dysmenorrhea and CPP, and between dysmenorrhea and CNPP. If no difference was detected, further sensitivity and moderator analyses were conducted based on the pooled CPP and CNPP studies. Second, a
sensitivity analysis was conducted excluding poor quality studies (NOS < 4). Third, results from adjusted analyses for the association between dysmenorrhea and CPP/CNPP presence were synthesized. Fourth, we conducted moderator analyses to examine the effect of study population (community vs the clinical population), region of the study (Europe, North America, others), type of dysmenorrhea (PD, endometriosis-associated dysmenorrhea, undifferentiated dysmenorrhea), and study design (cross-sectional, case-control, cohort) on the association between dysmenorrhea and chronic pain presence.

The meta-analyses were conducted in Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark), using the inverse variance method and a random effects model. Heterogeneity was assessed by $I^2$ statistics, with $I^2 < 25\%$ representing small, $25\% - 50\%$ representing moderate, $50\% - 75\%$ representing high, and $I^2 > 75\%$ representing substantial heterogeneity. Publication bias was examined using the funnel plot. Due to the inadequate report and the large heterogeneity in the reported outcomes, meta-analyses for the association between dysmenorrhea and CPP/CNPP severity were not conducted.

Results

The initial search returned 4,012 records from PubMed, 6,643 records from Embase, and 1,104 records from CINAHL. After merging the databases, a total of 9,452 unique records were identified and 38 studies meeting the inclusion criteria were included, consisting of 26 cross-sectional, 9 case-control, and 3 cohort studies. In the identified studies, 3 were non-English articles (1 in German, 1 in Icelandic, and 1 in Turkish) and 3 were conference abstracts only which did not undergo full-text review. Therefore, comprehensive qualitative review was conducted for 32 studies. The study selection process is presented in Figure 1, which
is consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.\textsuperscript{60}

![PRISMA diagram for study selection]

Figure 1. PRISMA diagram for study selection

The characteristics and findings of the 32 in-depth reviewed studies are summarized in Table 1. Studies were published from 1989 to 2019, with 12 from North America, 11 from Europe, 4 from South America, 4 from Asia, and 1 from Australia. The sample size ranged from 21 to 2,485. Among the 2 studies that compared the characteristics between respondents and non-respondents, there were no systematic differences in demographics.\textsuperscript{25, 35} Fourteen studies examined CPP\textsuperscript{22, 23, 25, 27, 36, 44-47, 49, 52, 53, 61, 62} and 20 examined CNPP.\textsuperscript{28, 35, 37-44, 48-52, 54, 55, 57-59} Dysmenorrhea was clearly defined in 6 studies,\textsuperscript{24, 26, 42, 44, 46, 48} and well-classified based on predetermined criteria in 4 studies.\textsuperscript{24, 44, 45, 50} It was specified as the presence of any menstrual pain.\textsuperscript{42}
recurrent menstrual pain of severe intensity that limits school/work activity, menstrual pain lasting throughout the entire menstrual cycle with significant impairment of daily life activity, menstrual pain intensity greater than 7 on the numerical rating scale (NRS); or operationalized continuously by pain intensity using the numerical or ordinal rating scale (0 - 10), by pain interference with daily life, by overall severity measured ordinally, or by the derived score from the Menstrual Symptom Questionnaire (MSQ). PD was examined in 7 studies, but only clinically ascertained in 2 of them. Endometriosis-associated dysmenorrhea was examined in 7 studies, with endometriosis laparoscopically confirmed in 3 and biopsy-proven in 3. The dysmenorrhea—chronic pain association was a pre-specified research question in 21 studies (7 for CPP, 15 for CNPP). The bias evaluation for each study is summarized in Appendix D. The NOS score ranged from 1 to 8, with 31.25% of the articles categorized as poor quality (NOS 0 - 3), 56.25% as moderate quality (NOS 4 - 6), and 12.25% as high quality (NOS 7 - 9). The major methodological limitations are issues with sample selection (13/32), inadequate dysmenorrhea assessment (15/32), inadequate confounding control (24/32), and the general lack of longitudinal studies (only 1 in our current review) that examined the different incidence of chronic pain in women with and without dysmenorrhea at baseline.

Eight studies (NOS 2 - 7, mean = 4.5, median = 4) reported findings on the association between dysmenorrhea (7 for undifferentiated dysmenorrhea and 1 for PD) and CPP presence, including interstitial cystitis/bladder pain syndrome (IC/BPS), chronic vulvar pain, provoked vestibulodynia (PVD), and irritable bowel syndrome (IBS). Women with CPP had higher prevalence of dysmenorrhea in all 8 studies. Dysmenorrhea gradient effect was only examined in 1 study in which more severe dysmenorrhea (moderate/severe vs mild vs no
dysmenorrhea) was correlated with greater prevalence of CPP among the general female population.\textsuperscript{25} Seven studies (NOS 1 - 6, mean = 3.4, median = 4.0) reported associations between dysmenorrhea and CPP severity, among which 4 examined the correlation between dysmenorrhea intensity and CPP intensity.\textsuperscript{22, 23, 29, 47} 1 compared the frequency and intensity of dysmenorrhea among women with CPP only, with CPP and IBS, with CPP and genitourinary symptoms, and with CPP, IBS and genitourinary symptoms,\textsuperscript{25} 1 compared dysmenorrhea frequency between women with CPP and women with both CPP and IBS,\textsuperscript{26} and 1 compared the severity of dysmenorrhea and the presence of persistent dyspareunia, low back pain, pain at ovulation, rectal pain, dysuria, and pelvic pain at other times among women with endometriosis.\textsuperscript{44} Of the 7 studies, 1 was focused on PD which did not find a correlation between PD intensity and CPP intensity;\textsuperscript{22} 3 were focused on dysmenorrhea in women with endometriosis and all found significant associations between dysmenorrhea severity and CPP severity;\textsuperscript{23, 44, 47} and 2\textsuperscript{25, 62} of the remaining 3 studies on undifferentiated dysmenorrhea reported significant positive associations with CPP severity.

Fifteen studies (NOS 2 - 8, mean = 4.8, median = 5.0) reported associations between dysmenorrhea and the presence of CNPP conditions, including headaches (frequent headaches,\textsuperscript{35} chronic migraines,\textsuperscript{43, 55} menstrual-related headaches\textsuperscript{42}), temporomandibular disorders (TMD),\textsuperscript{41} fibromyalgia,\textsuperscript{38, 48, 50, 51, 54} arthritis,\textsuperscript{48, 50, 51} complex regional pain syndrome type 1 (CRPS 1),\textsuperscript{52} post-mastectomy pain syndrome (PMPS),\textsuperscript{40} and CNPP in general (most musculoskeletal pain).\textsuperscript{49} PD was examined in 4 studies,\textsuperscript{43, 44, 48, 55} and endometriosis-associated dysmenorrhea in 2.\textsuperscript{43, 55} Dysmenorrhea was more prevalent in women with CNPP conditions compared to controls, except for an absence of association in 4 studies between arthritis and teenage dysmenorrhea,\textsuperscript{50} between arthritis and menstrual pain score,\textsuperscript{51} between regional pain and dysmenorrhea in women
with systemic lupus erythematosus,\textsuperscript{38} and between migraine and severe PD,\textsuperscript{43} respectively. Dysmenorrhea gradient effect was examined in 3 studies in which more severe dysmenorrhea (moderate/severe vs mild vs no dysmenorrhea) was correlated with higher prevalence of frequent headaches among the general female population,\textsuperscript{35} migraines among women with endometriosis but not among women with PD,\textsuperscript{43} and persistent low back pain among women without gynecological complaints.\textsuperscript{44} Five studies (NOS 1 - 7, mean = 3.6, median = 3.0) reported associations between dysmenorrhea and CNPP severity, including chronic non-organic upper abdominal pain,\textsuperscript{57} migraines,\textsuperscript{28, 37} and fibromyalgia,\textsuperscript{39, 58} with 1 study on PD\textsuperscript{58} and 2 on endometriosis-associated dysmenorrhea.\textsuperscript{37, 58} Dysmenorrhea was associated with unchanged or worse chronic non-organic upper abdominal pain, greater episodes and intensity of migraines, and greater severity of fibromyalgia (more tender point count, flares, pain intensity and drug consumption).

Results from the 6 abstracts reviewed were not combined into the in-depth review. Five studied dysmenorrhea—CPP associations (4 on CPP presence and 1 on CPP severity\textsuperscript{32}), with dysmenorrhea (all undifferentiated) associated with greater odds for the presence of CPP,\textsuperscript{30} IBS,\textsuperscript{31} dyspareunia\textsuperscript{33, 34} and greater severity of IC/BPS.\textsuperscript{32} One study reported greater odds for mastalgia associated with dysmenorrhea,\textsuperscript{34} and the remaining study reported a significantly higher proportion of dysmenorrhea in menstruating adolescents with chronic pain (87.1%) compared to those without chronic pain (61.8%).\textsuperscript{56}
### TABLE 1.

Studies included in the systematic review (n = 32)

<table>
<thead>
<tr>
<th>Study (author, year, country)</th>
<th>Design</th>
<th>Contrast</th>
<th>Age</th>
<th>Chronic pain</th>
<th>Sample size</th>
<th>Type of dysmenorrhea</th>
<th>Severity of dysmenorrhea</th>
<th>Temporality</th>
<th>Unadjusted results</th>
<th>Adjusted results</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collett et al, 1998 (UK)⁴⁹</td>
<td>Case-control</td>
<td>Women with CPP, and surgical female patients with no pain</td>
<td>16–50</td>
<td>CPP</td>
<td>CPP 30, Control 30</td>
<td>Undifferentiated</td>
<td>Not measured</td>
<td>Not specified</td>
<td>15/20 of the menstruating cases, and 9/28 of the menstruating controls had the exposure</td>
<td>None</td>
<td>5</td>
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<tr>
<td>Zondervan et al, 2001 (UK)²⁵</td>
<td>Cross-sectional</td>
<td>18–49 CPP (overall CPP, CPP only, CPP+IBS, CPP+genitourinary symptoms, CPP+IBS+genitourinary symptoms)</td>
<td>1855</td>
<td>Undifferentiated</td>
<td>Intensity measured using VAS</td>
<td>Dysmenorrhea in previous 3 months</td>
<td>The prevalence of dysmenorrhea in those without CPP and with CPP was 817/1404 (58.2%), 364/451 (80.7%), respectively; Moderate or severe dysmenorrhea prevalence was 63.0% (507/805), 72.3% (261/361), respectively; dysmenorrhea intensity (VAS)</td>
<td>None</td>
<td>4</td>
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<tr>
<td>Study (Year, Country)</td>
<td>Study Design</td>
<td>Population</td>
<td>Age Range</td>
<td>Diagnosis</td>
<td>Sample Size</td>
<td>Pain Duration</td>
<td>Pain Characteristics</td>
<td>Pain Duration</td>
<td>Odds Ratio (95% CI)</td>
<td>Adjusted For</td>
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<td>Tchoudo et al, 2001 (Sweden)</td>
<td>Cross-sectional</td>
<td>Community-dwelling women with and without vulvar pain</td>
<td>15-44</td>
<td>Vulvar pain (majority more than 6 months)</td>
<td>996</td>
<td>Undifferentiated</td>
<td>Not measured</td>
<td>Not specified</td>
<td>The prevalence of dysmenorrhea was 54.4% (43/79) in the vulvar pain group, and 36.4% (334/917) in the non-vulvar pain group, p = 0.004.</td>
<td>None</td>
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<td>da Silva et al, 2011 (Brazil)</td>
<td>Cross-sectional</td>
<td>Community-dwelling women with and without CPP</td>
<td>&gt;14</td>
<td>CPP</td>
<td>841</td>
<td>Undifferentiated</td>
<td>Absence, mild, moderate or intense. Only moderate and intense dysmenorrhea was classified as having dysmenorrhea.</td>
<td>Not specified</td>
<td>The prevalence of dysmenorrhea was 38.8% (38/98) and 21.5% (160/754) in women with and without CPP, p &lt; 0.01.</td>
<td>Adjusting for dyspareunia, abdominal surgery, depression, anxiety, current sexual activity, low back pain, constipation, urinary symptoms, and lower education level, OR for dysmenorrhea was 2.6 (1.6-4.2).</td>
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<tr>
<td>CHUNG et al, 2014 (China)</td>
<td>Case-control</td>
<td>Women with and without IC/BPS determined from the IC/BPS database</td>
<td>18-45</td>
<td>IC/BPS</td>
<td>1164, case-control 1:3 matched</td>
<td>Undifferentiated</td>
<td>Not measured</td>
<td>Not specified</td>
<td>87/291 (29.9%) of the cases, and 163/873 (18.7%) of the controls had Adjusting for age, medical comorbidities including diabetes, hypertension,</td>
<td>7</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Age (years)</td>
<td>CPP Description</td>
<td>Sample Size</td>
<td>Pain Intensity</td>
<td>Outcome Measure</td>
<td>Analysis Adjustments</td>
<td>Odds Ratio (95% CI)</td>
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<tr>
<td>Coelho et al, 2014 (Brazil)</td>
<td>Cross-sectional</td>
<td>Community-dwelling women with and without CPP</td>
<td>14–60</td>
<td>1434</td>
<td>Undifferentiated</td>
<td>Not measured</td>
<td>The prevalence of dysmenorrhea in women with and without CPP was 106/248 (42.7%) and 242/1186 (19.8%), p &lt; 0.0001. Adjusting for uterine surgery, perineal surgery, IBS, irregular menstrual flow, premenopause, dysperunia, smoking, self-report of health, OR for dysmenorrhea – CPP was 1.77 (1.19, 2.62).</td>
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<tr>
<td>Bao et al, 2014</td>
<td>Cross-sectional</td>
<td>Women</td>
<td>18-49</td>
<td>129</td>
<td>Undifferentiated</td>
<td>Intensity</td>
<td>The prevalence of dysmenorrhea was 291:873 (1.86 (1.37-2.52)).</td>
<td>\begin{itemize} \item coronary heart disease \item obesity \item hyperlipidemia \item CPP, IBS \item fibromyalgia \item chronic fatigue syndrome \item depression \item panic disorder \item migraine, Sjögren syndrome \item allergy, endometriosis, and asthma \item OR for dysmenorrhea – IC/BPS was 1.59 (1.13, 2.23). \end{itemize}</td>
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<tr>
<td>Year</td>
<td>Study Type</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Intensity Measure</td>
<td>Intensity Comparison</td>
<td>Results</td>
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<tr>
<td>2019</td>
<td>Sectional</td>
<td>vestibulodynia (PVD) who had or not had provoked vestibulodynia (PVD)</td>
<td>vestibulodynia (PVD) who had or not had provoked vestibulodynia (PVD)</td>
<td>NRS</td>
<td>greater than 7 classified as having dysmenorrhea.</td>
<td>Prevalence of dysmenorrhea in menstruating women with and without PVD was 62% (23/37) and 56% (44/79), respectively, OR = 1.31 (0.59, 2.91); dysmenorrhea intensity scores (NRS) were 6.2 (3.3) and 5.9 (3.2), respectively, p = 0.52.</td>
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<td>2019</td>
<td>Cross-sectional</td>
<td>Community-dwelling adolescent girls with and without IBS.</td>
<td>Community-dwelling adolescent girls with and without IBS.</td>
<td>Not measured</td>
<td>Not specified</td>
<td>The prevalence of IBS in those with and without PD was 19.9% (32/161) and 8.1% (6/74), respectively.</td>
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<td>1999</td>
<td>Cross-sectional</td>
<td>Between dysmenorrhea intensity and CPP intensity in women with endometriosis.</td>
<td>Between dysmenorrhea intensity and CPP intensity in women with endometriosis.</td>
<td>Not specified</td>
<td>VAS</td>
<td>The correlation between dysmenorrhea intensity and CPP intensity was significant, p = 0.002.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Contrast 2: Dysmenorrhea and the severity of CPP (7)**
<table>
<thead>
<tr>
<th>Study Authors and Year (Location)</th>
<th>Study Type</th>
<th>Objective</th>
<th>Sample Size</th>
<th>Age Range</th>
<th>Clinical Diagnosis</th>
<th>Intensity</th>
<th>Dysmenorrhea in Previous 3 Months</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurel et al, 1999 (Turkey)²</td>
<td>Cross-sectional</td>
<td>Between PD intensity and CPP intensity in women with various gynecological problems.</td>
<td>235</td>
<td>18–56</td>
<td>Unclear, but the majority of women had CPP (80.4%).</td>
<td>Not sure</td>
<td>Not specified</td>
<td>The correlation for PD and CPP r = 0.027 (not significant).</td>
</tr>
<tr>
<td>Zondervan et al, 2001 (UK)²⁵</td>
<td>Cross-sectional</td>
<td>Different comorbidities in women with CPP.</td>
<td>483</td>
<td>18–49</td>
<td>CPP (overall CPP, CPP only, CPP+IBS, CPP+genitourinary symptoms, CPP+IBS+genitourinary symptoms)</td>
<td>Undifferentiated</td>
<td>Intensity measured using VAS</td>
<td>The prevalence of dysmenorrhea in those with CPP only, with CPP+IBS, with CPP+genitourinary symptoms, and with CPP+IBS+genitourinary symptoms, was 193/239 (80.8%), 88/111 (79.3%), 28/37 (75.7%), and 53/60 (88.3%) respectively; Moderate or severe dysmenorrhea prevalence was 63.9% (122/191), 78.4% (69/88),</td>
</tr>
</tbody>
</table>

² Reference for PD and CPP intensity in women with various gynecological problems:
²⁵ Reference for different comorbidities in women with CPP.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Sample Size</th>
<th>Pain Measurement</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lessa, et al 2013 (Brazil)</td>
<td>Cross-sectional</td>
<td>Woman with CPP+IBS, and women with only CPP</td>
<td>242</td>
<td>Undifferentiated</td>
<td>Not measured</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IBS in addition to existing CPP</td>
<td></td>
<td></td>
<td>Dysmenorrhea was prevalent in 41/48 (85.4%) of women with both IBS and CPP, and 149/206 (72.2%) of women with only CPP (not significant).</td>
</tr>
<tr>
<td>Yosef et al, 2016 (Canada)</td>
<td>Cross-sectional</td>
<td>Between dysmenorrhea intensity and CPP intensity among women with CPP.</td>
<td>656</td>
<td>Undifferentiated</td>
<td>Intensity measured using NRS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50, mean = 34.5</td>
<td></td>
<td></td>
<td>Dysmenorrhea intensity was 7.33, 7.79, and 7.82 in the mild, moderate, and severe CPP pain groups.</td>
</tr>
<tr>
<td>Markham et al, 2019 (Australia)</td>
<td>Cross-sectional</td>
<td>Dysmenorrhea severity and symptoms in women with Endometriosis-associated pain.</td>
<td>529</td>
<td>Endometriosis</td>
<td>Never, slight, moderate, severe, and incapacitating.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.9 (16-69)</td>
<td></td>
<td></td>
<td>Always dyspareunia: 0 (0/0) for never, 13% (3/24) for the slight, 33%</td>
</tr>
</tbody>
</table>
endometriosis.

(51/153) for the moderate, 39% (79/204) for the severe, and 46% (51/112) for the incapacitating groups, p < 0.01 for linear trend; Always low back pain: 0 (0/0), 19% (5/26), 43% (68/158), 60% (132/220), 63% (78/123), p < 0.001; Always pain at ovulation: 0 (0/0), 19% (5/26), 25% (40/158), 38% (84/219), 44% (54/122), p < 0.001; Always rectal pain: 0 (0/0), 4% (1/26), 8% (12/158), 14% (31/220), 21% (25/121), p < 0.001; Always dysuria: 0 (0/0), 0 (0/26), 3% (4/156), 4% (8/217), 4% (5/123), ns;
### Contrast 3: Dysmenorrhea and the presence of chronic non-pelvic pain (15)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Dysmenorrhea</th>
<th>Pain Duration</th>
<th>Pain Intensity</th>
<th>Pain Location</th>
<th>Other Pain</th>
<th>Method</th>
<th>Other Measures</th>
<th>Adjusting for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yunus et al, 1989 (USA)</td>
<td>Case-control</td>
<td>Women with primary fibromyalgia syndrome (PFS), women with rheumatoid arthritis (RA), and healthy female controls</td>
<td>PFS, RA</td>
<td>Not measured</td>
<td>Dysmenorrhea before the age of 25</td>
<td>The prevalence of PD was 33/73 (45%), 5/41 (12%), and 8/46 (17%) among menstruating women with PFS, RA, and healthy controls (p&lt;0.005 for PFS vs RA or HCs)</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromaa et al, 1993 (Finland)</td>
<td>Cross-sectional</td>
<td>Community-dwelling women with and without</td>
<td>Frequent headaches including migraines (at least once a month)</td>
<td>Undifferentiated</td>
<td>Prior to first pregnancy</td>
<td>The prevalence of frequent headaches was 26.6% (62/233) in menstruating women with PD</td>
<td>Adjusting for SES, depression and stress, mild menstrual pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Dysmenorrhea</th>
<th>Pain Duration</th>
<th>Pain Intensity</th>
<th>Pain Location</th>
<th>Other Pain</th>
<th>Method</th>
<th>Other Measures</th>
<th>Adjusting for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cozzolino et al, 2019 (Italy)</td>
<td>Cross-sectional</td>
<td>Between dysmenorrhea intensity and CPP intensity in women with endometriosis</td>
<td>CPP in women with endometriosis</td>
<td>Endometriosis</td>
<td>Intensity measured using VAS</td>
<td>Not specified</td>
<td>Spearman correlation coefficient for dysmenorrhea and CPP intensity = 0.21 (P&lt;0.001)</td>
<td>Adjusting for age, dyschezia, and dysuria, dyspareunia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes

Always pelvic pain at other times: 0 (0/0), 4% (1/26), 10% (16/157), 20% (42/213), 26% (31/120), p < 0.001.
<table>
<thead>
<tr>
<th>Case-control Study</th>
<th>Outcome</th>
<th>Participants</th>
<th>Location</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collett et al, 1998 (UK)</td>
<td>Chronic non-pelvic pain (mainly musculoskeletal pain)</td>
<td>Women with chronic non-pelvic pain, and surgical female patients with no pain</td>
<td>UK</td>
<td>16–50</td>
</tr>
<tr>
<td>Poyhia et al, 2001 (Canada)</td>
<td>Dysmenorrhea in both teenage years and in adult life</td>
<td>Women with fibromyalgia (FM), women with inflammatory arthritis (IR), and nonpainful healthy female controls</td>
<td>Canada</td>
<td>Around 50</td>
</tr>
</tbody>
</table>

Frequent headaches (month) not specified.

The prevalence of dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of adult dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of menstrual pain (OR = 1.8, 1.2-2.8) were associated with frequent headaches.

The prevalence of dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of adult dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of menstrual pain (OR = 1.8, 1.2-2.8) were associated with frequent headaches.

The prevalence of dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of adult dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of menstrual pain (OR = 1.8, 1.2-2.8) were associated with frequent headaches.

The prevalence of dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of adult dysmenorrhea of severe intensity in FM, arthritis, and HCs, was 26/51 (51%), 12/44 (27%), and 16/52 (31%) (p<0.05); the prevalence of menstrual pain (OR = 1.8, 1.2-2.8) were associated with frequent headaches.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Design</th>
<th>Population</th>
<th>Menstrual Pain Score Subtracted from the Menstrual Symptom Questionnaire (MSQ)</th>
<th>Menstrual Pain Score (from factor analysis of the MSQ) in the Group of FM, RA and HCs</th>
<th>Prevalence of Dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso et al, 2004 (USA)</td>
<td>Case-control</td>
<td>Women with FM, rheumatoid arthritis (RA), and healthy female controls</td>
<td>FM, RA</td>
<td>Menstrual pain score was significantly different from the Menstrual Symptom Questionnaire (MSQ).</td>
<td>Menstrual pain scores were 2.1, 1.7, and 1.1 (FM significantly different from HCs).</td>
<td>25/51 (49%), 9/44 (20%) and 3/52 (6%) (p&lt;0.001).</td>
</tr>
<tr>
<td>Valencia-Flores et al, 2004 (Mexico)</td>
<td>Cross-sectional</td>
<td>Women diagnosed with systemic lupus erythematosus</td>
<td>FM, regional pain</td>
<td>Not measured</td>
<td>The prevalence of dysmenorrhea was 44.4% (8/18) in the FM group, 16.0% (17/106) in the regional pain group, and 16.9% (11/65) in the non-pain group, p = 0.008</td>
<td>None</td>
</tr>
<tr>
<td>Shaver et al, 2006 (USA)</td>
<td>Case-control</td>
<td>Community-dwelling women with and without FM</td>
<td>FM</td>
<td>Not measured</td>
<td>The prevalence of dysmenorrhea was 37.4% (165/442) in the FM group, and 11.3% ( Adjusting for age, BMI, employed, married, education, income, race and</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Population</td>
<td>Age Range</td>
<td>Condition(s)</td>
<td>Outcomes</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tietjen et al, 2007 (USA)</td>
<td>Case-control</td>
<td>Community-dwelling women with and without migraine</td>
<td>37.6 (18-67)</td>
<td>Migraine</td>
<td>PD case 127, Endometriosis case 36, HCs 104</td>
<td>A global score of interference of menstrual periods with 7 activities of daily living</td>
</tr>
<tr>
<td>van den Berg et al, 2009 (Netherlands)</td>
<td>Case-control</td>
<td>Women with complex regional pain syndrome type 1 (CRPS-1), and healthy female controls</td>
<td>18–82</td>
<td>Complex regional pain syndrome type 1 (CRPS-1)</td>
<td>CPRS-1 34, HCs 147</td>
<td>Not measured</td>
</tr>
<tr>
<td>Lim et al, 2010 (USA)</td>
<td>Cohort</td>
<td>Community-dwelling women</td>
<td>18-34</td>
<td>Temporomandibular Disorders</td>
<td>266</td>
<td>Score from Symptom Report</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Population</td>
<td>Sample Size</td>
<td>Assessment</td>
<td>Pain Measurement</td>
<td>Results</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>de Menezes Couceiro et al, 2014 (Brazil)</td>
<td>Cross-sectional</td>
<td>Women treated surgically for breast cancer who developed post-mastectomy pain syndrome (PMPS) vs those not</td>
<td>54 (12, 18-75)</td>
<td>post-mastectomy pain syndrome (PMPS)</td>
<td>250</td>
<td>Undifferentiated</td>
</tr>
<tr>
<td>Østensjø et al, 2017 (Norway)</td>
<td>Cross-sectional</td>
<td>Community-dwelling adolescent girls with and without Painful Temporomandibular Disorders</td>
<td>13-19</td>
<td>Painful temporomandibular disorders (TMD-P)</td>
<td>286</td>
<td>Undifferentiated</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Group Description</td>
<td>Mean Age (Range)</td>
<td>Sample Size</td>
<td>Menstrual Category</td>
<td>Other Variables</td>
</tr>
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</tr>
<tr>
<td>Carman et al, 2018 (Turkey)</td>
<td>Cross-sectional</td>
<td>Community-dwelling adolescent girls with and without menstrual-related headache</td>
<td>15.89 (14-19)</td>
<td>2,485</td>
<td>Undifferentiated</td>
<td>Not measured, Not specified</td>
</tr>
<tr>
<td>Miller et al, 2018 (USA)</td>
<td>Cross-sectional</td>
<td>Between dysmenorrhea and migraine in women with and without endometriosis</td>
<td>17.4 (12-21)</td>
<td>95</td>
<td>PD, endometriosis</td>
<td>None-mild, moderate, severe</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Population Description</td>
<td>Dysmenorrhea Severity</td>
<td>Symptoms Description</td>
<td>PD</td>
<td>Not Specified</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Markham et al, 2019 (Australia)</td>
<td>Cross-sectional</td>
<td>Dysmenorrhea severity and symptoms in generally healthy women.</td>
<td>34.9 (16-69)</td>
<td>Various pain symptoms with a persistent nature.</td>
<td>208</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

For endometriosis-associated dysmenorrhea, the prevalence was 4.9% (10/205), 27.8% (57/205) and 67.3% (138/205) in the migraine group, and 7.7% (7/91), 33.0% (30/91) and 59.3% (54/91) in the non-migraine group.
Contrast 4: Dysmenorrhea and the severity of chronic non-pelvic pain (5)

<table>
<thead>
<tr>
<th>Söth et al, 1989 (Denmark)</th>
<th>Cohort</th>
<th>Female outpatients of chronic non-organic upper abdominal pain</th>
<th>21–55</th>
<th>The course of chronic non-organic upper abdominal pain over 5–7 years: unfavorable vs favorable</th>
<th>Undifferentiated</th>
<th>Not measured</th>
<th>Not specified</th>
<th>6/11 of women with unfavorable chronic non-organic upper abdominal pain outcomes had dysmenorrhea</th>
<th>None</th>
</tr>
</thead>
</table>

(1/2), p < 0.01;
Always pain at ovulation: 0
(0/22), 8%
(8/97), 9%
(7/75), 8%
(1/12), 50%
(1/2), ns;
Always rectal pain: 0 (0/22), 0 (0/95), 0 (0/74), 0 (0/12), 0 (0/1), ns;
Always dysuria: 0 (0/22), 0 (0/95), 0 (0/75), 0 (0/11), 0 (0/2), ns;
Always pelvic pain at other times: 0 (0/21), 2%
(2/95), 0 (0/74), 0 (0/10), 50%
(1/2), ns.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Research Question</th>
<th>Participants</th>
<th>Intensity Measure</th>
<th>Statistic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrero et al, 2004 (Italy)</td>
<td>Cross-sectional</td>
<td>Between dysmenorrhea intensity and migraine intensity among women with endometriosis</td>
<td>34.0 (4.4)</td>
<td>Migraine intensity</td>
<td>43</td>
<td>Endometriosis intensity measured using NRS. In women with migraine and endometriosis (43), the spearman correlation coefficient between dysmenorrhea and migraines intensity was 0.035, p=0.824</td>
</tr>
<tr>
<td>Rios et al, 2014 (USA)</td>
<td>Cross-sectional</td>
<td>Between dysmenorrhea and tender point count in women with FM</td>
<td>50.2 (9.9)</td>
<td>Tender point count</td>
<td>137</td>
<td>Undifferentiated Tender point count was 16.9 (2.7) in the dysmenorrhea group and 12.5 (5.4) in the non-dysmenorrhea group, p = 0.000.</td>
</tr>
<tr>
<td>Spierings et al, 2015 (USA)</td>
<td>Cross-sectional</td>
<td>Women with episode migraine and chronic migraine among female headache patients</td>
<td>18–49</td>
<td>Chronic migraine compared to episode migraine</td>
<td>96</td>
<td>Undifferentiated The prevalence of dysmenorrhea among women with episode migraine and chronic migraine was 13/45 (28.9%) and 26/51</td>
</tr>
<tr>
<td>Cohort</td>
<td>The correlation between PD and FM severity, and endometriosis-associated dysmenorrhea and FM severity, among women with FM</td>
<td>PD+FM 31, Endometriosis+FM 25, FM only 33</td>
<td>PD, Endometriosis</td>
<td>Not measured</td>
<td>Within 5 years</td>
<td>PD and endometriosis respectively associated with FM outcomes: correlations between the number of painful menstrual cycles and the number of monthly flares ($r = 0.7654, r = 0.7335$); with pain intensity ($r = 0.8484, r = 0.6564$); with mean monthly number of drug consumption ($r = 0.8939, r = 0.5712$).</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
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<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Costantini et al, 2017 (Italy)</td>
<td>18–45 FM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
The quantitative synthesis of the associations between dysmenorrhea and the presence of chronic pain conditions is presented in Figure 2. Eight studies including 6,689 women, of overall moderate quality, were suitable for meta-analysis for dysmenorrhea—CPP presence. With moderate heterogeneity ($I^2 = 42\%$), women with CPP had 2.43 (95% CI = 1.98, 2.99) times the odds of having dysmenorrhea compared to women without CPP (when excluding 2 poor studies, OR = 2.46, 95% CI = 1.91, 3.17, $I^2 = 56\%$). Eleven studies including 3,750 women, of overall moderate quality, were suitable for meta-analysis for dysmenorrhea—CNPP presence. With large heterogeneity ($I^2 = 72\%$), women with CNPP had 2.62 (95% CI = 1.84, 3.72) times the odds of having dysmenorrhea compared to women without CNPP (when excluding 2 poor studies, OR = 2.74, 95% CI = 1.83, 4.11, $I^2 = 75\%$). There was no significant difference in the magnitude of the association by CPP vs CNPP ($\chi^2 = 0.13$, df = 1, $p = 0.72$). Overall, women with chronic pain had 2.50 (95% CI = 2.03, 3.10, $I^2 = 66\%$) times the odds of having dysmenorrhea compared to women without chronic pain. Pooling adjusted results, the odds of dysmenorrhea associated with the presence of chronic pain was 2.12 (95% CI = 1.61, 2.77, $I^2 = 65\%$). Visual examination of the funnel plot suggests some publication bias for studies on dysmenorrhea—CNPP associations, which is mainly driven by the large effect estimates for endometriosis-associated dysmenorrhea and migraine in 1 study, and for adult dysmenorrhea and fibromyalgia in the other.

Pooling all studies together, there was no significant difference in the magnitude of association between the community populations (OR = 2.63, 95% CI = 2.01, 3.45) and the clinical populations (OR = 2.27, 95% CI = 1.58, 3.27) ($p = 0.52$); and between studies conducted in North America (OR = 2.67, 95% CI = 1.71, 4.19), Europe (OR = 2.32, 95% CI = 1.64, 3.30), and other places (OR = 2.42, 95% CI = 1.96, 2.98) ($p = 0.89$). Despite only 4 studies on PD, 2 on
endometriosis-associated dysmenorrhea, the ORs for PD, endometriosis-associated dysmenorrhea, and undifferentiated dysmenorrhea were 2.17 (95% CI, 1.32, 3.56), 7.52 (95% CI, 0.34, 167.20), and 2.43 (95% CI, 1.96, 3.03), respectively. The pooled effect size was larger for case-control studies (OR = 3.29, 95% CI = 2.18, 4.96) compared to cross-sectional studies (OR = 2.09, 95% CI = 1.71, 2.57) (p = 0.05).

**Figure 2.** Relative odds of dysmenorrhea associated with the presence of chronic pain

**Comment**

**Main findings**

Our review is the first to systematically synthesize the population-based findings of the associations between dysmenorrhea and the presence and severity of both CPP and CNPP. It is also the first quantitative synthesis of the strength of the association between dysmenorrhea and
the presence of CPP and CNPP. Our findings suggest a positive association between
dysmenorrhea and chronic pain, including chronic pain beyond the pelvic region. Altogether,
women with chronic pain had 2.50 times the odds (95% CI = 2.02, 3.10) of having dysmenorrhea
compared to women without chronic pain, and the magnitude of the association was similar for
CPP and CNPP, which further implies that the mechanism underlying the associations between
dysmenorrhea and different types of chronic pain may be similar. However, given the
methodological limitations of the included articles, whether PD is a risk factor for either CPP or
CNPP remains unknown.

**Strengths and limitations**

This study has the following strengths. First, we took a systematic approach to select published
population-based studies on the association between dysmenorrhea and chronic pain,
incorporating both the presence of chronic pain as the primary outcome, and the severity of
chronic pain as the secondary outcome, which provides a more direct clue as to whether
dysmenorrhea is associated with the occurrence and trajectory of chronic pain. Second, we
separated CPP and CNPP, thus creating an opportunity to explore potential heterogeneity in the
existence and strength of the association with dysmenorrhea. Our results provide some
preliminary evidence that dysmenorrhea may be a general risk factor for chronic pain within and
beyond the pelvic region. Third, we further aggregated the findings by PD, endometriosis-
associated dysmenorrhea, and undifferentiated dysmenorrhea. Although endometriosis is an
identified cause of CPP, and often co-exists with other chronic pain conditions,\(^{65,66}\) whether PD
increases the risk for chronic pain is unknown. However, the limited number of studies on PD
included in this review prohibited more conclusions to be drawn beyond a tentative positive
relationship between PD and fibromyalgia. Fourth, each study (except 6 studies with only
abstract review) was thoroughly examined and evaluated based on bias evaluation criteria, which
illustrates the current methodology limitations in the investigations for the association between
dysmenorrhea and chronic pain, and informs future research directions.

However, there are several key limitations regarding the conduct of this systematic review
and meta-analysis. First, despite our effort in capturing comprehensive literature by using
dysmenorrhea and study types in our searching strategy, the judgment of chronic pain is made by
the authors based on several criteria, which may result in potential missed articles. Nevertheless,
the combination of “chronic pain” and pain description in the text and clinical judgment should
capture the majority of eligible studies. Second, we did not include the 3 non-English articles in
our complete review but briefly described their results. Since all these 3 studies were focused on
CPP, and all reported significant associations with dysmenorrhea, including them will not change
our results for the dysmenorrhea—CPP association. Third, we were not able to conduct meta-
analyses using adjusted results from each article. However, the combined OR from the 7 adjusted
studies (2.01, 95% CI = 1.61, 2.77) were not considerably different from the unadjusted OR from
the 18 studies (2.50, 95% CI = 2.02, 3.10). Fourth, in studies with more than 2 chronic pain
conditions studied, the healthy controls were counted twice for calculating the OR for each
comparison. Therefore, a total of 3,750 unique individuals contributed to a meta-analytic sample
of 4,267 for calculating the pooled OR for dysmenorrhea—CNPP presence, which slightly
inflated the precision (about 7% decrease in the standard error) but is less likely to bias our
estimates. Fifth, due to the inadequate report and large variation in the reported effect measures,
we did not perform further meta-analyses for synthesizing linear or non-linear relationships
between dysmenorrhea severity and chronic pain severity. Based on the qualitative review,
however, there is an overall positive association between the two, especially for CNPP conditions. Sixth, we did not register the protocol in advance for this systematic review and meta-analysis. Protocol registration is recommended in order to decrease the likelihood of selective reporting. Nevertheless, we did develop a protocol and did not conduct any analyses that have not been reported here.

**Interpretation of the findings**

The positive relationship between dysmenorrhea and the presence of CPP and CNPP should be considered in the context of the inadequate quality of the included studies. First of all, only 1 study examined the occurrence of chronic pain (TMD) in a prospective nature. However, the quality of the study is moderate, with participant characteristics unknown and dysmenorrhea undefined. Second, only half of the 8 studies for the association between dysmenorrhea and CPP presence specified the dysmenorrhea—CPP association as an a priori research question, which prevents an accurate estimate of the association. Third, the definition, measurement, and classification of dysmenorrhea are far from consistent across studies, which weakens the credibility of the detected association and limits cross-study comparison. Fourth, the inadequate control of confounding (for unadjusted analyses), or the improper control of confounding (when dysmenorrhea was controlled in the model to answer other questions) both distorted the true association between dysmenorrhea and chronic pain. It is likely that the association has been overestimated based on the reviewed studies, which is consistent with the reduced OR for dysmenorrhea—chronic pain presence from the adjusted synthesis (from unadjusted to adjusted pooling, OR turned from 2.50 to 2.12). Fifth, only 8 of the 22 included studies conducted random
sampling in the study design,\textsuperscript{25, 27, 35, 41, 42, 46, 53, 61} which may weaken the generalization of the
study findings to the target populations.

A positive association between dysmenorrhea and CPP presence was seen in all 8 studies (7
significant) included in the meta-analyses. We included CPP, IBS, IC/BPS and vulvar pain as
CPP conditions which may have different degrees of association with dysmenorrhea. That may
partly explain for the moderate heterogeneity for the combined effect size. In addition, women
recruited from gynecologic practices compared to women recruited from the community and
non-gynecologic practices may exhibit smaller association between dysmenorrhea and CPP.
Among the included studies, the lowest magnitude of the association (OR = 1.31) was seen
between dysmenorrhea and PVD among women with various pelvic pain conditions,\textsuperscript{45, 53} and the
largest was seen in the study of the smallest sample size comparing women with CPP in a pelvic
pain clinic and women without pain conditions selected from general practitioner surgeries (OR
= 6.33).\textsuperscript{49} Only 1 study examined PD and reported a positive association with IBS.\textsuperscript{46} However,
PD was poorly ascertained, and cases of PD were likely to be undifferentiated dysmenorrhea.
Therefore, despite a consistent increased odds of CPP associated with dysmenorrhea, whether
PD directly increases the risk for CPP remains unknown.

There was larger heterogeneity for the association between dysmenorrhea and CNPP, which
is expected given the various pain conditions examined. In our subgroup analysis (results not
shown here), the combined effect size for musculoskeletal chronic pain (OR = 2.49, 95\% CI =
1.42, 4.34) was slightly smaller than that of head/facial/jaw (OR = 2.85, 95\% CI = 1.48, 5.52) or
surgery-related chronic pain (OR = 2.80, 95\% CI = 1.73, 4.52), which may be explained by
different pain etiopathology. One case-control study\textsuperscript{55} and 1 cross-sectional study\textsuperscript{43} both
compared migraine prevalence associated with dysmenorrhea, stratified by the presence of
endometriosis. The effect estimates were greater in the first study which may be due to different sample selection and age groups, and in both studies, there was a greater association between dysmenorrhea and migraine in women with endometriosis. Four studies with a total sample size of 952 examined dysmenorrhea and fibromyalgia, and all of them showed a significant association (pooled OR = 4.36, 95% CI = 2.72, 7.01; when excluding teenage dysmenorrhea OR = 5.05, 95% CI = 3.23, 7.88). As only 1 of the studies was focused on PD, whether PD is a risk factor for the development of fibromyalgia is less clear. In 1 study, only dysmenorrhea in adult life but not teenage years was associated with the presence of inflammatory arthritis. A possible explanation is that dysmenorrhea in teenage years is more likely to represent PD while dysmenorrhea during adult life is more likely to suggest secondary dysmenorrhea. A null association between PD and arthritis might be conceivable given the peak prevalence of arthritis in later life and a general remitting trajectory of PD, which is consistent with the other study in this review that found no association between PD and rheumatoid arthritis. One study found a positive correlation between dysmenorrhea severity and the presence of persistent low back pain in women with no gynecological complaints. However, given the low quality of the study (NOS = 2), whether PD is associated with the development of chronic low back pain remains to be studied. Considering the results for CRPS 1 and PMPS, dysmenorrhea might be correlated with an increased risk for surgery or trauma-related chronic pain syndromes, which needs further research. Taken together, dysmenorrhea is associated with higher odds of CNPP conditions, with potentially larger effects for endometriosis-associated dysmenorrhea, and more tentative associations for PD.

There was a consistent positive association between dysmenorrhea and CPP severity in women with endometriosis, while the results were mixed for PD and undifferentiated...
dysmenorrhea. Although the association between stage of endometriosis and CPP severity is controversial, our review based on a total sample of 1,007 women suggested a positive correlation between dysmenorrhea severity and CPP severity in women with endometriosis. Among the 3 studies on undifferentiated dysmenorrhea, women with CPP and IBS did not have greater prevalence of dysmenorrhea compared to women with CPP only, but may have more severe dysmenorrhea. In the same study, women with CPP and genitourinary symptoms had the greatest severity of dysmenorrhea, even compared to women with CPP, IBS, and genitourinary symptoms, which may imply some complex interaction between distinct visceral pain mechanisms. The single study for PD is of poor quality, and no conclusions can be made for the association between PD severity and CPP severity. The studies on CNPP severity suggested a positive relationship between the severity of dysmenorrhea and the severity of migraine and fibromyalgia. PD severity was positively associated with fibromyalgia severity in 1 study of good quality. Taken together, the severity of endometriosis-associated dysmenorrhea is correlated with the severity of CPP, migraine and fibromyalgia. Despite a positive correlation with fibromyalgia severity, whether PD severity is related to other chronic pain severity is largely unknown.

The potential mechanisms underlying dysmenorrhea—chronic pain associations can include peripheral sensitization, central sensitization, and abnormal stress responses. At the peripheral level, over-release of prostanoids and possibly eicosanoids from the endometrium during menstruation may increase peripheral nerve hypersensitivity, which through mechanisms of cross-system convergence, viscero-visceral and viscero-somatic interaction, may increase the risk for CPP. Central sensitization is an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity. The afferent visceral barrage brought about by
recurrent menstrual pain can contribute to spinal hyperexcitability,\textsuperscript{71, 72} and is also associated with long-lasting functional and structural changes in the brain regions responsible for pain processing and stress regulation.\textsuperscript{7, 73-77} Under persistent or recurrent pain, abnormal stress responses occur due to the overload to the hypothalamus-pituitary-adrenal (HPA) axis that negatively shape the corticolimbic system in the central nervous system, contributing to the transition from acute to chronic pain.\textsuperscript{78} It has been suggested that women with dysmenorrhea have suppressed HPA functioning and lower cortisol levels, which can reduce pain inhibition.\textsuperscript{79, 80} However, it is possible that predisposing factors (e.g., baseline alterations in the corticolimbic structures and HPA functioning) contribute to both dysmenorrhea and chronic pain.\textsuperscript{1, 79, 81} It is likely that multiples mechanisms exist to explain the association between dysmenorrhea and chronic pain. It is also possible that dysmenorrhea may be a risk factor for CPP/CNPP only in women with certain characteristics. In the included articles, we did not find any subgroup analyses based on subject characteristics. Future studies may explore potential phenotypes of adolescent girls with dysmenorrhea who are more likely to develop CPP/CNPP conditions in later life.

Based on the current systematic review, we are not able to draw an overall conclusion on whether PD is a risk factor for CPP or CNPP, mainly due to the small number of relevant studies. Payne et al (2017)’s paper provides an in-depth review of the experimental pain studies related to PD, suggesting increased pain reactivity in areas outside of referred pain in women with PD. This pattern is more consistent during menstruation and less clear for the non-menstrual-cycle phases, which may be due to significant methodological issues.\textsuperscript{82} Two recently published studies focusing on pain sensitivity and central pain processing in women with PD reported inconsistent findings. Payne et al’s study (2019) compared the excitatory and inhibitory measures of pain
processing in 32 girls with PD and 34 healthy controls, and found lower heat pain tolerance in women with PD across the menstrual cycle, but no group differences in cold pain tolerance, temporal summation, or conditioned pain modulation. Böttcher et al’s study (2019), based on 19 women with PD and 20 healthy controls, found only higher chronic pain intensity and interference in women with PD, but no differences between groups in visceral sensitivity, or neural responses indicated by MRI scanning. Currently, a general conclusion of PD contributing to central sensitization has not been fully achieved.

Conclusions and implications

This systematic synthesis of the association between dysmenorrhea and chronic pain demonstrates a positive relationship between the presence of dysmenorrhea and the presence of CPP and CNPP, as well as a positive correlation between the severity of dysmenorrhea and the severity of CPP, migraine and fibromyalgia. However, whether PD is a risk factor for chronic pain is far from clear, despite its potential association with fibromyalgia. Prospective studies following adolescent girls right after menarche are urgently needed to disentangle the subgroups or features that are associated with the mechanisms for pain chronicity, the onset of CPP, as well as the development of different CNPP conditions. Such studies can provide an opportunity to both unpack the complex process of pain development and evolvement in the pelvic region, and elucidate the general mechanisms for pain chronicity. Even without a clear answer to the cause-and-effect relationship between PD and chronic pain, raising the awareness of dysmenorrhea in the medical community, timely referral to gynecological care, and systematic assessment of dysmenorrhea in women may not only ensure timely diagnosis and treatment of debilitating
gynecological conditions such as endometriosis, but also create an opportunity for proper
monitoring and early intervention among high-risk adolescents.

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80. BOURKE JH, LANGFORD RM, WHITE PD. The common link between functional somatic syndromes may be central sensitisation. J Psychosom Res 2015;78:228-36.

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Figure 1. PRISMA diagram for study selection

- PubMed: 4,012 results
- Embase: 6,643 results
- CINAHL: 1,104 results

11,759 records

Exclude 2,307 duplicate records after merging the database

9,452 unique records

Excluded records: 9,414
  - Review of title/abstract
    - Not relevant: 2,912
    - Not human study: 72
    - Treatment only/clinical trials: 3,826
    - Review article: 645
    - Either dysmenorrhea/menstrual pain or chronic pain not involved: 1,686
    - Chronic pain not one of the outcomes: 67
    - Chronic pain not clearly defined: 34
    - No comparison groups: 172

- 6 abstracts
- 32 qualified full-text articles

- 3 non-English full-text articles
- 3 conference abstracts

- Cross-sectional studies: 21
- Case-control studies: 8
- Cohort studies: 3
Figure 2. Relative odds of dysmenorrhea associated with the presence of chronic pain
Appendix A.
Searching strategy for the association between dysmenorrhea and chronic pain

PubMed
dysmenorrhea OR Dysmenorrh* OR primary dysmenorrhea OR primary dysmenorrh* OR menstrual pain OR painful mens*or menstrual cramp* AND (case control OR observational OR cohort OR cross section OR epidemiolog* OR population based OR case crossover OR surv* OR screen* OR incidence OR prevalence OR longitudinal OR follow-up)

Date Searched: 12/23/2019
Filter: None
Result: 4012

Embase
('dysmenorrhea'/exp OR 'dysmenorrhea' OR 'dysmenorrhoea' OR 'primary dysmenorrhea' OR 'primary dysmenorrhoea') AND ('case control study'/exp OR 'case control study' OR 'case-control studies' OR 'case-control study' OR 'control study, case' OR 'matched case control' OR 'matched case control studies' OR 'matched case control study' OR 'case report/exp OR 'case report' OR 'observational study'/exp OR 'non experimental studies' OR 'non experimental study' OR 'nonexperimental studies' OR 'nonexperimental study' OR 'observation studies' OR 'observation study' OR 'observational studies' OR 'observational studies as topic' OR 'observational study' OR 'observational study as topic' OR cohort OR 'cross-sectional study'/exp OR 'cross-sectional design' OR 'cross-sectional research' OR 'cross-sectional studies' OR 'cross-sectional study' OR 'epidemiology'/exp OR 'clinical epidemiology' OR 'cohort effect' OR 'confounding factors (epidemiology)' OR 'controlled before after studies' OR 'controlled before and after studies' OR 'controlled before before and after study' OR 'controlled before-after studies' OR 'effect modifier, epidemiologic' OR 'effect modifiers (epidemiology)' OR 'effect modifiers (psychology)' OR 'environmental epidemiology' OR 'epidemiologic factors' OR 'epidemiologic methods' OR 'epidemiologic research' OR 'epidemiologic research design' OR 'epidemiologic studies' OR 'epidemiologic study characteristics' OR 'epidemiologic study characteristics as topic' OR 'epidemiologic survey' OR 'epidemiological research' OR 'epidemiology' OR 'epidemiology model' OR 'epidemiometry' OR 'healthy worker effect' OR 'historically controlled study' OR 'interrupted time series analysis' OR 'precipitating factors' OR 'sampling studies' OR 'population based' OR 'case crossover' OR 'questionnaire/exp OR 'questionnaire' OR 'questionnaires' OR 'surveys and questionnaires' OR 'technique, delphi' OR 'health survey/exp OR 'health care surveillance, registration and quality control' OR 'health survey' OR 'health surveys' OR 'population surveillance' OR 'public health surveillance' OR 'survey, health' OR 'screening/exp OR 'multiple screening' OR 'prescreening' OR 'project, screening' OR 'screening' OR 'screening method' OR 'screening procedure' OR 'screening program' OR 'screening programme' OR 'screening project' OR 'incidence/exp OR 'incidence' OR 'incidence rate' OR 'rate, incidence' OR 'prevalence/exp OR 'prevalence' OR 'prevalence study' OR 'longitudinal OR
'follow up/exp OR 'follow up' OR 'follow up study' OR 'follow-up studies' OR 'followup' OR 'lost to follow up' OR 'lost to follow-up')

Date Searched: December 23, 2019
Result: 6,643

CINAHL

(MH "Dysmenorrhea") OR "dysmenorrhea" OR "dysmennorh" OR "primary dysmenorrhea" OR "primary dysmenorrhea*" OR menstrual n5 pain OR pain* n5 mens* AND (MH "Case Control Studies+") OR "case control" OR (MH "Observational Methods+") OR (MH "Nonexperimental Studies+") OR (MH "Nonparticipant Observation") OR (MH "Participant Observation") OR "observational" OR (MH "Prospective Studies+") OR (MH "Concurrent Prospective Studies") OR (MH "Nonconcurrent Prospective Studies") OR "cohort" OR (MH "Cross Sectional Studies") OR "cross section" OR (MH "Epidemiology+") OR "epidemiolog*" OR (MH "Population-Based Case Control") OR "population based" OR (MH "Crossover Design") OR "case cross over" OR (MH "Surveys+") OR "survey" OR (MH "Questionnaires+") OR "questionnaire" OR "screen*" OR (MH "Incidence") OR "incidence" OR (MH "Prevalence") OR "prevalence" OR "longitudinal" OR "follow-up"

Date Searched: 12/23/2019
Result: 1,104
Appendix B.

The association between dysmenorrhea and chronic pain – coding manual

• Coder
• Article
  o First author
  o Country where the study was conducted
  o Year of publication
  o Journal
• Research question
  o Dysmenorrhea – chronic pain is a pre-specified research question/hypothesis
  o Dysmenorrhea – chronic pain is not a pre-specified research question/hypothesis
• Target population
  o Community population? Clinical population?
  o Age range of the sample when chronic pain was ascertained (if the age range is not specified, extract the information about the mean/median of age)
• Generalizability
  o The response rate
  o Comparison between the respondents and the non-respondents
• Exposure
  o Dysmenorrhea without endometriosis
  o Dysmenorrhea with endometriosis
  o Dysmenorrhea without specifying endometriosis
• Outcome
  o Chronic pain condition
  o Presence: yes/no (this is the primary outcome)
  o Pain severity measures: list all (these are secondary outcomes)
• Study design
  o Cross-sectional: Studies in which the exposure status and disease status of an individual are measured at one point in time. Here, cross-sectional studies are those in which the dysmenorrhea and chronic pain measures were collected at the same time. (The time for the measure of endometriosis is not important because it is a variable for dividing subgroups)
  o Case-control: Studies that involve comparing the frequency of past exposure between cases who develop the disease and controls who do not. Here, case-control studies are those in which the participants were recruited based on whether they had chronic pain or not (cases and matched controls), and their dysmenorrhea exposure were measured. (The time for the measure of endometriosis is not important because it is a variable for dividing subgroups)
  o Cohort: Studies that compare the incidence of disease over time in groups that differ on their exposure. Here, cohort studies are those in which either a group of women without chronic pain were recruited and measured for dysmenorrhea measured, and followed up for a period of time to measure chronic pain status, or
women with dysmenorrhea and women without dysmenorrhea were recruited and followed up for a period of time to measure chronic pain status. (The time for the measure of endometriosis is not important because it is a variable for dividing subgroups)

- Sample size for dysmenorrhea – chronic pain relationship (if separate analysis were done for dysmenorrhea with and without endometriosis, specify both sample sizes)
- Case/exposed (comparison group: in cross-sectional and case-control studies, the cases are women with chronic pain; in cohort studies, the exposed are women with dysmenorrhea)
  - Recruited from?
  - Number
- Reference group (in cross-sectional and case-control studies, the reference group are women without chronic pain; in cohort studies, the reference group are women without dysmenorrhea)
  - Recruited from?
  - Number
- Measure of dysmenorrhea
  - Tool: Survey? Clinical diagnosis? Disease code from administrative databases?
  - Captured time window for dysmenorrhea measure (e.g., current, past-year, life-time prevalence)
  - Measured in the same way in the comparison and reference group?
  - Whether the severity of dysmenorrhea (e.g., intensity) was captured, and if so, how was the severity captured?
- Measure of chronic pain
  - Whether the onset of chronic pain is captured: yes/no
  - Tool: Survey? Clinical diagnosis? Disease code from administrative databases?
  - Captured time window for chronic pain measure (e.g., current diagnosis, life-time prevalence)
  - Measured in the same way in the comparison and reference group?
- Measure of endometriosis (if relevant)
  - Tool: Laparoscopy (with/without histology)? Survey?
  - Measured in the same way in the comparison and reference group?
- Confounding
  - List all the covariates adjusted in the main analysis for the association between dysmenorrhea and chronic pain
  - Rationale for the selected confounding
    - A priori
    - Data-based
    - Both
    - Not specified
- Statistical analysis
  - Main analysis
  - Measure of exposure – outcome association
• Result
  o Effect estimate
  o 95% confidence interval (with or without p value)
Appendix C.
Newcastle-Ottawa Scale for case-control studies

MAX TOTAL – 9 POINTS

SELECTION – max 4

1) Is the Case Definition Adequate?
   - Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records) – 1
   - Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record – 0
   - No description – 0

2) Representativeness of the Cases
   - All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample) – 1
   - Not satisfying requirements above or not stated. – 0

3) Selection of Controls: This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present
   - Community controls – 1
   - Hospital controls, within same community as cases – 0
   - No description – 0

4) Definition of Controls
   - If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. – 1
   - No mention of history of outcome – 0

COMPARABILITY – max 2

1) Comparability of Cases and Controls on the Basis of the Design or Analysis
   - Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment – score 0/1/2
**EXPOSURE – max 3**

1) Ascertainment of exposure
   - Secure record (eg surgical records) or structured interview where blind to case/control status – 1
   - Interview not blinded to case/control status – 0
   - Written self-report or medical record only – 0
   - No description – 0

2) Same method of ascertainment for cases and controls – 0/1

3) Non-Response Rate
   - Same rate for both groups – 1
   - Non respondents described – 0
   - Rate different and no designation – 0

---

**Newcastle-Ottawa Scale for cohort studies**

**MAX TOTAL – 9 POINTS**

**SELECTION – max 4**

1) Representativeness of the Exposed Cohort
   - Truly or somewhat representative of the target population in the community – 1
   - Selected group of users e.g., nurses, volunteers – 0
   - No description of the derivation of the cohort – 0

2) Selection of the Non-Exposed Cohort
   - Drawn from the same community as the exposed cohort – 1
   - Drawn from a different source – 0
   - No description of the derivation of the non-exposed cohort – 0

3) Ascertainment of Exposure
   - Secure records or structured interview – 1
   - Written self-report – 0
   - No description – 0

4) Demonstration that outcome of interest was not present at start of study – 0/1

**COMPARABILITY – max 2**

1) Comparability of Cohorts on the Basis of the Design or Analysis
• Study controls for key confounding factors – 0/1/2

OUTCOME – max 3

1) Assessment of outcome
   • Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.) or Record linkage (e.g. identified through ICD codes on database records) – 1
   • Self-report – 0
   • No description – 0

2) Was Follow-Up Long Enough for Outcomes to Occur
   • An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants) – 0/1

3) Adequacy of Follow-Up of Cohorts
   • Complete follow-up - all subjects accounted for or subjects lost to follow up unlikely to introduce bias - small number >= 75% - 1
   • Follow-up rate < 75% - 0
   • No description – 0

Adapted Newcastle-Ottawa Score for Cross-sectional studies

MAX TOTAL – 8 POINTS

SELECTION – max 4

1) Representativeness of the sample
   • Truly representative of the average in the target population (random sample). – 1
   • Somewhat representative of the average in the target population (non-random sampling). – 1
   • Selected groups of users – 0
   • No description of the sampling strategy – 0

2) Sample size
   • Justified and satisfactory – 1
   • Not justified – 0

3) Non-respondents
• Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. – 1
• The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. – 0
• No description of the response rate or the characteristics of the responders and the non-responders. – 0

4) Ascertainment of the exposure (risk factor)

• Validated measure, secure records, or structured interview (clinical diagnosis) – 1
• Self-report – 0
• No description – 0

COMPARABILITY – max 2

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled

• The study controls for the most important factor (select one). – 1
• The study control for any additional factor. – 2

OUTCOME – max 2

1) Assessment of outcomes

• Validated assessment of chronic pain (clinical diagnosis or self-report based on validated questionnaires) – 1
• Self-report – 0
• Not described - 0

2) Statistical analysis

• The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). – 1
• The statistical test is not appropriate, not described or incomplete. – 0
### Table 1. Bias evaluation of cross-sectional studies (n = 21)

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Table 3. Bias evaluation of cohort studies (n = 3)

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