The association between age at menarche and chronic pain outcomes in women: the Tromsø Study, 2007 to 2016

Charlotte I. Lund[a,b,*], Bo Engdahl[c], Leiv A. Rosseland[a,b], Audun Stubhaug[b,d], Guri Grimnes[e,f], Anne-Sofie Furberg[g,h], Ólöf A. Steingrímsdóttir[a,c], Christopher S. Nielsen[c,d]

Abstract

Sex differences in chronic pain are well established with documented predominance in women. This study assessed relationships between age at menarche and chronic pain, site-specific chronic pain, pain characteristics, and chronic widespread pain (CWP). We used data from the Tromsø Study conducted in 2007 to 2008 and 2015 to 2016 (Tromsø 6 and Tromsø 7 waves) including participants aged 30 to 99 years. The associations between age at menarche and chronic pain were examined in Tromsø 6 (n = 6449), Tromsø 7 (n = 5681), and the combination of Tromsø 6 and Tromsø 7 (n = 12,130). Tromsø 7 data were used further to examine the associations between age at menarche and site-specific chronic pain, 4 pain characteristics (pain duration, pain intensity, episode duration, and episode frequency), and CWP. All analyses were adjusted for body mass index, age, and economic status of the household in childhood. Lower age at menarche was associated with an increased risk of chronic pain in all 3 samples (risk ratio for each year delay in menarche 0.98, 95% CI [0.97 to 0.99] across samples). Risk differences were −0.014, CI 95% (−0.02 to −0.005) in Tromsø 6, −0.011, CI 95% (−0.02 to −0.02) in Tromsø 7, and −0.012, CI 95% (−0.02 to −0.01) in the combined sample. Age at menarche was significantly associated with chronic pain in the neck, abdomen, and both arms, and CWP. Of the 4 pain characteristics, pain duration was statistically significant. We conclude that early menarche is an independent risk factor for pain across a broad spectrum of pain outcomes.

Keywords: Chronic pain, Sex differences in pain, Site-specific chronic pain, Pain characteristics, Chronic widespread pain, Early menarche, Exposure to estrogen

1. Introduction

Sex differences are well established in clinical pain, with women more frequently reporting specific chronic pain conditions than men.[12,35,43] Findings in epidemiological research show close to 1.3 times higher prevalence of chronic pain in women.[38]

The causes of sex differences in pain are poorly understood; however, one reason might be the different hormone exposure in the sexes throughout the lifetime. Human experimental studies on pain sensitivity in women have extensively examined responses across the menstrual cycle; thereby, they indirectly investigated the associations between exposure to ovarian hormones and pain thresholds or pain tolerance.[16,19,33,36] Most earlier studies reported the effect of menstrual phase on variation in pain sensitivity, with menstrual phase reflecting the fluctuating levels of estrogen across the cycle. However, the estrogen level was merely determined by the self-reported menstrual phase instead of the direct measurement of ovarian hormones. More recent studies have failed to replicate these findings.[32] Thus, there is no clear evidence of whether experimental pain varies across the menstrual cycle in healthy women.[19] Although menstrual cycle studies assess the immediate effects of sex hormones, this design does not assess the consequences of long-term hormonal exposure that commences in prepuberty and persists throughout the reproductive span. There is a strong

need for population-based studies to assess sex hormones during puberty and the impact of lifetime hormonal exposure on pain sensitivity and chronic pain.

Early menarche is associated with higher circulating estrogen levels during puberty, across the menstrual cycle, and the levels remain increased for several years after puberty.[6,10,46] Therefore, early menarche may serve as a proxy measure of increased estrogen exposure during developmental period. Early menarche has an established clinical relevance in oncology, serving as a risk factor of hormone-related cancers, such as breast cancer.[5,10] Four studies have assessed associations between age at menarche and site-specific pain: headache,[2] pelvic girdle syndrome in pregnancy,[4] migraine,[28] and chronic lower back and upper extremity pain.[47] In addition, one study examined the association between age at menarche and chronic widespread pain in adults,[23] and one study examined the association with chronic nonspecific pain in teenagers.[22] Although effect sizes and statistical significance varied, all 6 studies concluded that early menarche was associated with increased pain prevalence.

To the best of our knowledge, no studies have examined associations between age at menarche and a broad spectrum of pain outcomes as in this study. Associations between menarche and pain characteristics, such as pain duration and intensity and episode duration and frequency, which may reflect the severity of pain, have not been previously examined. In addition, no study has included site-specific chronic pain in all body regions because earlier studies on menarche have focused only on headache or musculoskeletal pain. Moreover, this is the first study to assess chronic widespread pain (CWP) in accordance with the revised definition from 2019.[48] This study examines whether early menarche is associated with greater prevalence of chronic pain, site-specific chronic pain, pain characteristics, and CWP in adults.

2. Methods

2.1. Study population

The Tromsø Study is a population-based health study administered in the municipality of Tromsø, Northern Norway. It consists of 7 waves conducted between 1974 and 2016, with 6 to 7 years between each wave. In this study, analyses were conducted on data from the sixth wave (Tromsø 6; 2007-2008) and the seventh wave (Tromsø 7; 2015-2016) (**Fig. 1**). Tromsø 6 included 12,984 participants (women = 6928) aged between 30 and 87 years and had an attendance rate of 68% for women and 63% for men.[9] Tromsø 7 included 21,083 participants (women = 11,074) aged between 40 and 99 years and had a 67% attendance rate for women and 62% for men. Among Tromsø 7 participants, 12,177 had participated in Tromsø 6 previously, whereas 8906 were new participants.

2.2. Research samples

Cross-sectional analyses were performed on 6 samples (**Fig. 1**). The associations between age at menarche and pain lasting for at least 3 months (see 2.3.2. for more details) were tested on 3 samples: (1) all female participants in Tromsø 6 (N = 6449), (2) all new female participants in Tromsø 7 (N = 5681), excluding those participants who were included in the Tromsø 6 sample, and (3) the combined sample (N = 12,130). The remaining 3 samples were based on responses to the Graphical Index of Pain (GRIP; see 2.3.3 for more details), which was administered only in Tromsø 7. Of the 11,074 female participants in Tromsø 7, GRIP

was completed by 10,367 who constituted the sample for analysis of site-specific chronic pain during the last 4 weeks. Of them, 5354 reported site-specific chronic pain, had complete data on pain duration and intensity and episode frequency duration, and formed the sample of pain characteristics. Additional GRIP information was used to create a sample of 9406 participants for investigating associations between age at menarche and CWP. Information about missing values and exclusion is listed in **Table 1**.

2.3. Measurements

2.3.1. Age at menarche

Participants self-reported their age at menarche in full years in response to the questionnaire item: "How old were you when you started menstruating?" Women reporting age at menarche younger than 9 years (T6, n = 14; T7 n = 4) and older than 18 years (T6 n= 15; T7 n= 19) were excluded.
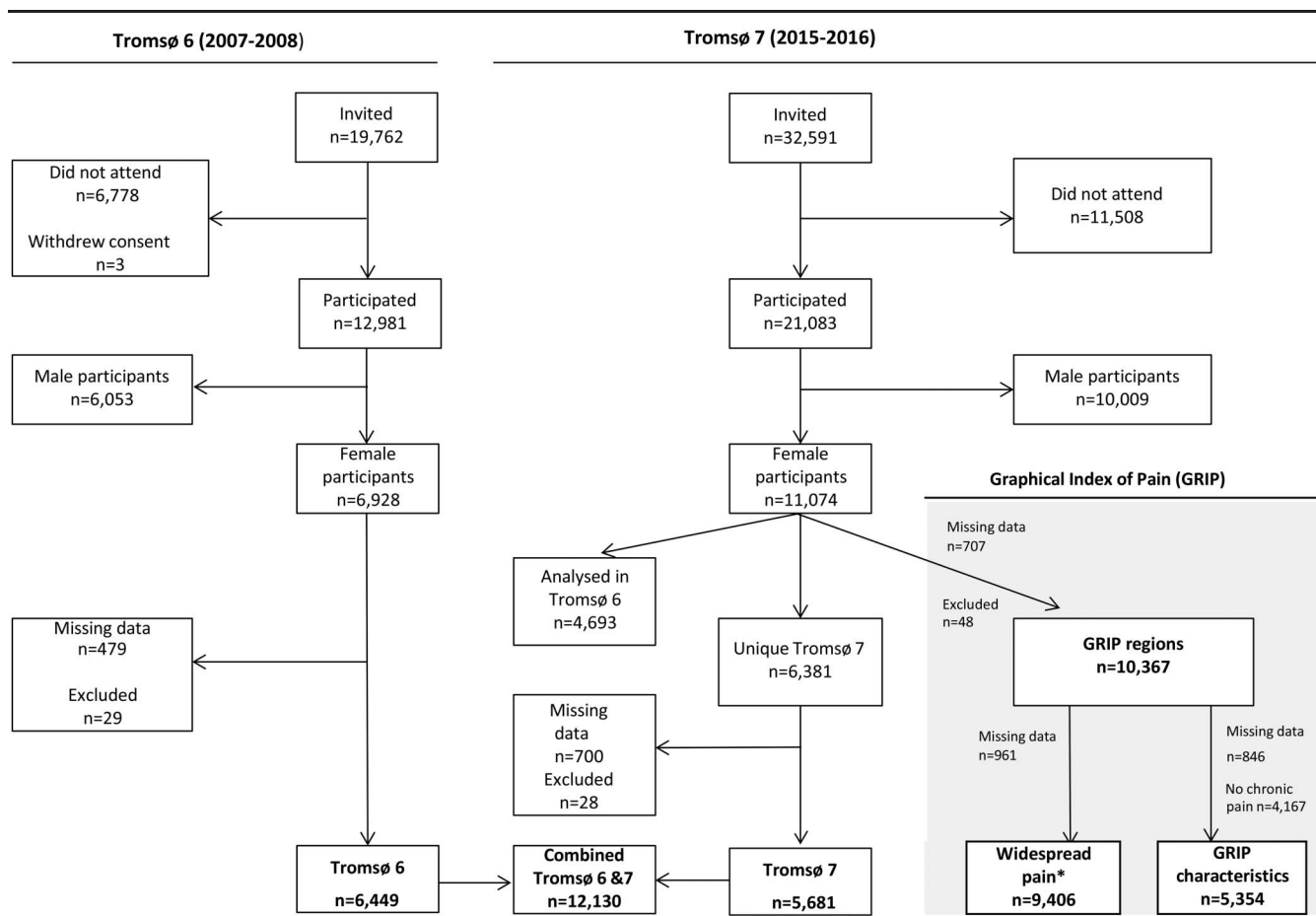
2.3.2. Chronic pain

Chronic pain was defined in line with the *International Classification of Diseases (ICD) 11*.[40] Thus, in Tromsø 6 and Tromsø 7, participants who responded "yes" to the questionnaire item: "Do you have persistent or recurrent pain that has lasted for at least 3 months,"—were defined as experiencing chronic pain.

2.3.3. Site-specific chronic pain

In Tromsø 7, additional information on pain locations and characteristics was obtained using GRIP.[37] The Graphical Index of Pain is a hierarchical body map of 2 tiers where participants mark the location of pain that has occurred during the last 4 weeks. The first tier includes 10 predefined anatomical regions: head, neck, chest, back, abdomen, genital area, left arm, right arm, left leg, and right leg. For each marked anatomic region at first tier, participants completed questions on 5 pain characteristics: pain duration, episode frequency, episode duration, pain intensity, and pain bothering. The first 4 pain characteristics are included in this study. For participants who indicated chronic pain in 2 or more anatomical regions, the region with the maximum rating on each characteristic of pain were chosen for the analysis. Chronic pain in each of the 10 body regions was defined as pain lasting for at least 3 months and with pain intensity >1 using additional information on pain characteristics (see further).

Pain duration was measured with the questionnaire item: "How long is it since you first felt the pain?," with response categories less than 4 weeks, 1 to 2 months, 3 to 5 months, 6 to 11 months, 1 to 2 years, 3 to 5 years, and more than 5 years. Episode frequency was assessed with the questionnaire item: "During the last 4 weeks: How many days have you had the pain?," and response options ranged from 0 to 28 days. With more than half of the participants reporting pain duration of 5 years or more (56.6%), the variable was recoded to a binary variable <5 years and ≥5 years. Episode frequency in the last 4 weeks was dichotomised to daily pain (28 days) and nondaily pain (1-27 days). Dichotomisation was based on the skewed distribution of the data, with 52.7% of the participants reporting daily pain according to this definition. Episode duration was measured with the questionnaire item: "About how much of the day have you usually had the pain? (only count the time when you are awake)," with response options less than 1 hour, 1 to 2 hours, 3 to 6 hours, 7 to 10 hours, longer than 10 hours, or continuously without a

Tromsø 6 (2007-2008)

Invited
n=19,762

Did not attend
n=6,778

Withdrew consent
n=3

Participated
n=12,981

Male participants
n=6,053

Female participants
n=6,928

Missing data
n=479

Excluded
n=29

Tromsø 6
n=6,449

Tromsø 7 (2015-2016)

Invited
n=32,591

Did not attend
n=11,508

Participated
n=21,083

Male participants
n=10,009

Female participants
n=11,074

Analysed in Tromsø 6
n=4,693

Unique Tromsø 7
n=6,381

Missing data
n=700
Excluded
n=28

Combined Tromsø 6 &7
n=12,130

Tromsø 7
n=5,681

Graphical Index of Pain (GRIP)

Missing data
n=707

Excluded
n=48

GRIP regions
n=10,367

Missing data
n=961

Missing data
n=846

No chronic pain n=4,167

Widespread pain*
n=9,406

GRIP characteristics
n=5,354

*Widespread pain sample, participants were assessed for chronic widespread pain. See Methods 2.3.4.

Figure 1. Flow chart of the study. Additional information on missing data is summarized in Table 1.

pause. Similarly, episode duration was dichotomised to intermittent pain and constant pain without a pause. Finally, pain intensity was measured on an 11-point numeric rating scale (NRS; 0-10) with the anchors "no pain" (0) and "the strongest pain imaginable" (10) in response to the question: "How strong has the pain usually been?"

2.3.4. Chronic widespread pain

Chronic widespread pain was defined by Wolfe and coauthors[48] as pain in 4 or 5 regions (0-5) and a total pain site score ≥7 (0-19 sites). According to this definition, they classified pain sites into 5 body regions: axial region (neck, upper back, and lower back), right/left upper region (lower arm, upper arm, and shoulder), and right/left lower region (lower leg, upper leg, hip). We used information from the second tier of GRIP to create a binary chronic widespread pain variable based on their classification. Four pain sites included in GRIP (chest, abdomen, left jaw, and right jaw) were not part of the 5 body regions[48] but contributed to the total pain site score in this study.

2.4. Covariates

Body mass index (BMI), socioeconomic status in childhood, and age have been associated with both age at menarche and chronic pain. Body mass index was calculated from the on-site

measurements of height and weight, as kg/m². To account for socioeconomic status in childhood, we used the economic status of the household in childhood ($ES_{childhood}$). It was assessed with the questionnaire item: "How was your family's financial situation during childhood?," with the response categories 1-very good, 2-good, 3-difficult, and 4-very difficult.

Using the combined sample of Tromsø 6 and Tromsø 7 waves required us to control for the effect of birth cohort on the associations between age at menarche and chronic pain. Therefore, we generated a new 5-item categorical variable "cohort" based on the questionnaire item: "What is your year of birth?" The 5 items included the following birth years: (1) 1920 to 1929, (2) 1930 to 1939, (3) 1940 to 1949, (4) 1950 to 1959, and (5) 1960 to 1977. Consecutively, we created an interaction term for age at menarche and cohort to assess the effect of birth cohort. Moreover, "cohort" variable was used as a potential confounder in multivariable regression models in the analyses of combined sample. Age at menarche differed for the earliest vs the most recent cohorts, that is, 13.9 years (SD 1.30) for cohort 1, 13.6 (1.34) for cohort 2, 13.2 (1.38) for cohort 3, 13.2 (1.40) for cohort 4, and 13.0 (1.38) for cohort 5.

2.5. Statistical analysis

Age at menarche served as the primary predictor and was treated as a continuous variable in all univariable and multivariable

Table 1

Missing and excluded values in Tromsø 6 sample, Tromsø 7 sample, and samples from Graphical Index of Pain (GRIP).

	Variables	Missing values	Excluded
Tromsø 6 sample, n = 6449	Age at menarche	180	29*
	BMI	15	
	ES$_{childhood}$	274	
	Chronic pain	21	
	Total number of individuals	479	29
Tromsø 7 sample, n = 5681	Age at menarche	132	29*
	BMI	15	
	ES$_{childhood}$	142	
	Chronic pain	382	
	Total number of individuals	700	29
GRIP regions sample, n = 10,367 GRIP first-tier regions	Age at menarche	132	48*
	BMI	36	
	ES$_{childhood}$	151	
	No response to GRIP questions	435	
	Total number of individuals	707	48
GRIP CWP sample†, n = 9406 GRIP second-tier regions	Head	41	
	Neck	259	
	Back	207	
	Left arm	129	
	Right arm	79	
	Left leg	111	
	Right leg	77	
	Abdomen	58	
	Total number of individuals	961	
GRIP characteristics‡, n = 5354	No chronic pain	n/a	4167
	Pain intensity	245	
	Episode duration	234	
	Episode frequency	585	
	Total number of individuals	846	4167

* Exclusion criterion: age at menarche younger than 9 or older than 18 years.
† Participants were assessed for chronic widespread pain. See Methods 2.3.4.
‡ Women with no chronic pain were excluded from this sample.
BMI, body mass index; CWP, chronic widespread pain; ES$_{childhood}$, economic status of the household in childhood.

analyses. For descriptive statistics, participants were categorised into early menarche (9-11 years), typical menarche (12-14 years), and late menarche (15-18 years). The categories of age at menarche were based on the existing literature,[17,39,44] and the distribution of our data was in line with the literature. Descriptive statistics were used to present frequency, mean, and SD for the 3 menarche age groups. All multivariable analyses were adjusted for BMI, age, and ES$_{childhood}$. Body mass index was treated as a continuous variable. Economic status of the household in childhood was dichotomised into good (categories 1 and 2) and difficult (categories 3 and 4). For the relationship between menarche and pain outcomes (chronic pain, site-specific chronic pain, pain characteristics, and CWP), we used univariable and multivariable logistic regressions to calculate risk measures. Guidelines for observational studies in epidemiology recommend reporting both relative and absolute risk for description of exposure and outcome relationship over odds ratio, especially if the disease is of high prevalence.[18] Thus, we calculated risk ratio (RR as percentage), risk difference (RD as percentage points pps), and odds ratio (OR, see supplementary Tables S1, S2, S3, S4, available as supplemental digital content at http://links.lww.com/PAIN/B561) to increase comparability of our results with the existing literature on menarche and pain. All effect measures are presented with 95% confidence intervals (CIs).

The validity of linear assumption was tested by comparing model fit between the original regression model and age at menarche variable with spline effects. The linear assumption was met in Tromsø 6 and the combined sample of Tromsø 6 and

Tromsø 7. Although linearity assumption was not statistically met in the Tromsø 7 data (likelihood ratio test, $P = 0.002$), the other 2 samples showed that the linearity between exposure and outcome variables was robust. Data on male individuals were excluded from the analyses, except for the inclusion of pain prevalence among male individuals for comparative purposes in **Figure 2** (see Results section).

2.6. Statistical software

All statistical analyses were performed in Stata (Stata MP15.1-64; StataCorp, College Station, TX) software.

2.7. Ethics

The Regional Committee for Medical and Health Research Ethics approved this study (8948 REK Sør-Øst). A Data Protection Impact Assessment was performed and approved by the Data Protection Officer at Oslo University Hospital. All participants gave informed consent before participation in the Tromsø Study.

3. Results

3.1. Chronic pain

The characteristics of participants in Tromsø 6, Tromsø 7, and the combined sample are summarised in **Table 2**. The mean age in the Tromsø 6 sample (56.9 years, SD = 12.7) was higher than

that in the Tromsø 7 sample (51.9 years, SD = 8.6) because a high proportion of Tromsø 7 participants (n = 4693) previously completed Tromsø 6 and, therefore they were excluded from Tromsø 7 sample (**Fig. 1**). The mean age of the combined sample was 54.6 years (SD = 11.2). The mean age at menarche was 13.3 years, 13.1 years, and 13.2 years in Tromsø 6 sample, Tromsø 7 sample, and the combined sample, respectively. The overall prevalence of chronic pain was 38.0% in Tromsø 6 sample, 43.6% in Tromsø 7 sample, and 40.7% in the combined sample.

As shown in **Figure 2**, women with early age at menarche had the highest prevalence of chronic pain, both in Tromsø 6 and Tromsø 7. In Tromsø 7, the prevalence of chronic pain among women with late menarche was similar to the prevalence among men (**Fig. 2**).

Univariable analyses showed that for each 1-year delay in menarche, the risk of chronic pain decreased by 3% in Tromsø 6 and the combined sample and by 2% in the Tromsø 7 sample (**Table 3**). When adjustment was made for potential confounders, the risk of chronic pain decreased by 2% for each 1-year delay in menarche across all samples and remained significant. The absolute risk was 1.1 to 1.4 pps lower for each year's delay. The interaction term for age at menarche and birth cohort was not statistically significant; no cohort effects were detected in the combined sample.

3.2. Site-specific chronic pain

Prevalence of chronic site-specific pain in each of the 10 body regions by the age at menarche group is listed in **Table 4**. Lower prevalence of chronic pain was observed for increasing age at menarche in all anatomical regions (**Table 4**, **Fig. 3**). The highest prevalence of site-specific chronic pain across menarche age groups was reported in the back (25.7%), neck (25.1%), and the right arm (23.6%). Meanwhile, the lowest prevalence of chronic pain was indicated in the chest (6.2%) and abdomen (9.4%) across the groups, whereas a

small percentage of women reported chronic pain in the genital area across menarche age groups.

Results from the univariable and multivariable logistic regression analyses are summarised in **Table 5**. Univariable analyses showed significant associations between age at menarche and chronic pain in all body regions except for the genitals (9 of 10 areas). The strongest associations were found in the chest and abdomen (RR = 0.93 in both areas). In multivariable analyses, the effect sizes were slightly reduced, and 4 of 10 regions remained statistically significant (**Table 5**).

3.3. Chronic pain characteristics

Among participants with chronic pain, 56.6% of women reported pain lasting longer than 5 years. The proportion of participants experiencing chronic pain every day was 52.7%, and 25.1% of participants indicated that they had constant pain without a pause. **Table 6** summarises that long pain duration and daily pain were more prevalent in the group with early age at menarche than in the other 2 groups.

Younger age at menarche was significantly associated with the longer pain duration (RR = 0.99, 95% CI [0.98 to 0.99]; RD = −0.011, 95% CI [−0.016 to −0.005]) (**Table 7**). A 1-year increase in age at menarche reduced the risk of experiencing pain longer than 5 years by 1%. After adjustment for covariates, the association with pain duration remained significant. Daily pain, constant pain without a pause, and pain intensity were not significantly related to the age at menarche in either univariable or multivariable analyses.

3.4. Chronic widespread pain

The overall prevalence of CWP was 7.4%. A 1-year increase in age at menarche decreased the risk of experiencing CWP by
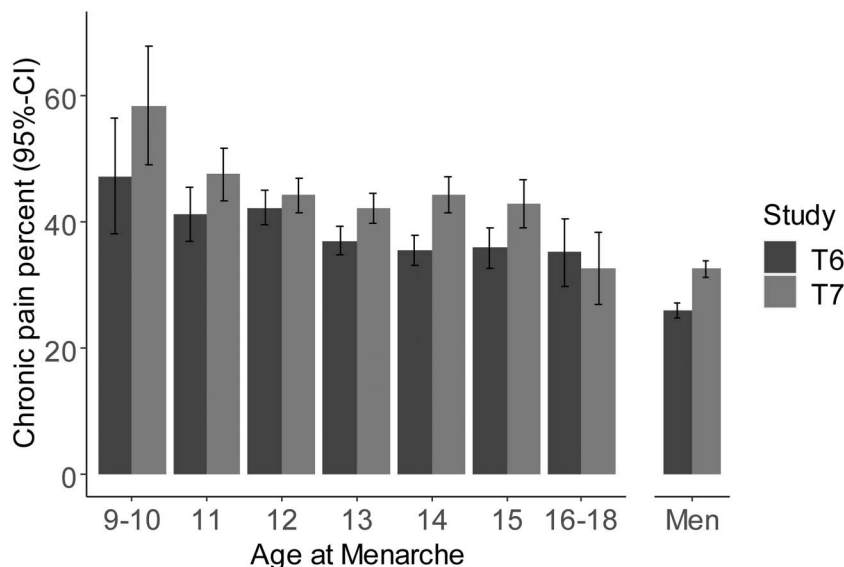
Sample size	Women (age at menarche)							Men
	9-10	11	12	13	14	15	16-18	N
N (Tromsø 6)	112	526	1259	1826	1575	850	301	5854
N (Tromsø 7)	106	542	1281	1624	1231	634	263	5480

Figure 2. Prevalence of chronic pain and sample size by age at menarche and for men in Tromsø 6 and Tromsø 7.

Table 2

Baseline characteristics of study participants by sample Tromsø 6, Tromsø 7, and the combined sample of Tromsø 6 and Tromsø 7 stratified by age at menarche.

	Age at menarche		
	Early	Typical	Late
Tromsø 6 n = 6449	n = 638 (9.9%)	n = 4660 (72.3%)	n = 1151 (17.9%)
Age mean (SD)	53.6 (11.3)	56.8 (12.6)	59.7 (13.0)
BMI mean (SD)	28.3 (5.3)	26.6 (4.63)	25.5 (4.1)
Chronic pain, n (%)	270 (42.3)	1770 (37.9)	412 (35.8)
ES$_{childhood}$ good, n (%)	455 (71.3)	3462 (74.3)	865 (75.2)
Tromsø 7 n = 5681	n = 648 (11.4%)	n = 4136 (72.8%)	n = 897 (15.8%)
Age mean (SD)	50.4 (8.5)	51.9 (8.5)	53.3 (8.9)
BMI mean (SD)	28.7 (5.9)	26.8 (4.9)	25.5 (4.4)
Chronic pain, n (%)	320 (49.4)	1799 (43.5)	358 (39.9)
ES$_{childhood}$ good, n (%)	476 (73.5)	3207 (77.5)	670 (74.7)
Combined sample n = 12,130	n = 1286 (10.6%)	n = 8796 (72.5%)	n = 2048 (16.9%)
Age mean (SD)	51.9 (10.1)	54.5 (11.2)	56.9 (11.9)
BMI mean (SD)	28.5 (5.6)	26.7 (4.8)	25.5 (4.2)
Chronic pain, n (%)	590 (45.9)	3569 (40.6)	770 (37.6)
ES$_{childhood}$ good, n (%)	931 (72.4)	6669 (75.8)	1535 (74.9)

Age at menarche used as a categorical variable in descriptive statistical analyses. Early menarche age (9-11 years), typical menarche age (12-14 years), and late menarche age (15-18 years).
BMI, body mass index; ES$_{childhood}$, economic status of the household in childhood.

10% in univariable analysis (RR = 0.90, 95% CI [0.90 to 0.91]), and the absolute risk difference was 3.8 pps (RD = −0.038, 95% CI [−0.06 to −0.02]). In multivariable analysis, the risk ratio was 7% (RR = 0.93, 95% CI [0.90 to 0.96]) and risk difference was 1.5 pps (RD = −0.015, 95% CI [−0.03 to 0.0004]). For OR, see supplementary Table S4, available as supplemental digital content at http://links.lww.com/PAIN/B561.

4. Discussion

In this study, we found strong associations between age at menarche and chronic pain outcomes in adult women. With each 1-year delay in menarche, the risk of chronic pain decreased by 2% and overall contributed to 18% relative risk

reduction over 9 years (menarche from 9 to 18 years) and absolute risk reduction by 12.6 pps. The same pattern was found for all body regions, albeit only statistically significant for the neck, abdomen, and both arms after adjusting for putative confounders. Moreover, we observed that an additional year at menarche was associated with a lower risk of experiencing chronic pain of 5 years duration or more. Associations with other pain characteristics were not statistically significant. Chronic widespread pain was significantly associated with age at menarche; each additional year of age at menarche reduced the risk of CWP by 7% when adjusted for covariates.

As summarized earlier, we found strong associations between age at menarche and chronic pain, site-specific chronic pain, and CWP. This pattern of results is consistent

Table 3

Risk ratio (RR) and risk difference (RD) for the association between age at menarche and chronic pain.

	Univariable analysis		Multivariable analysis	
	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Tromsø 6 (n = 6449) Age at menarche	0.97 (0.97 to 0.98)	−0.018 (−0.02 to −0.01)	0.98 (0.97 to 0.99)	−0.014 (−0.02 to −0.005)
Tromsø 7 (n = 5681) Age at menarche	0.98 (0.97 to 0.98)	−0.016 (−0.02 to −0.01)	0.98 (0.97 to 0.99)	−0.011 (−0.02 to −0.002)
Combined sample (n = 12,130) Age at menarche	0.97 (0.97 to 0.98)	−0.018 (−0.02 to −0.01)	0.98 (0.97 to 0.99)	−0.012 (−0.02 to −0.01)

Main results for Tromsø 6, Tromsø 7, and combined sample of Tromsø 6 and Tromsø 7.
Age at menarche used as a continuous variable in univariable and multivariable logistic regression analyses.
Multivariable analyses adjusted for body mass index (BMI), economic status of the household in childhood (ES$_{childhood}$), and age. Combined sample (n = 12,130) was additionally adjusted for cohort effects due to age differences in Tromsø 6 and Tromsø 7 waves.
See supplementary Table S1 for odds ratios (ORs, available as supplemental digital content at http://links.lww.com/PAIN/B561).

Prevalence of chronic pain by age at menarche group in 10 body regions.

Body regions	Pain prevalence (%) by age at menarche		
	Early n = 1089	Typical n = 7553	Late n = 1725
Head	11.6	10.2	8.5
Neck	28.6	24.8	24.0
Back	29.2	25.7	23.8
Chest	8.1	6.2	5.5
Abdomen	13.1	9.2	8.4
Genital area	3.5	2.7	2.8
Left arm	23.6	20.1	16.6
Right arm	26.6	23.8	20.6
Left leg	25.5	21.2	18.2
Right leg	28.8	22.9	20.9

The Graphical Index of Pain (GRIP), Tromsø 7, GRIP regions sample, n = 10,367.
Age at menarche used as a categorical variable in descriptive statistical analyses.
Early menarche age (9-11 years), typical menarche age (12-14 years), and late menarche age (15-18 years).

Figure 3. Prevalence of chronic pain across 10 body regions in women with early (age 9-11 years), typical (age 12-14 years) and late (age 15-18 years) menarche. Color scale 0 to 35 is used; darker body areas present higher prevalence of chronic pain.

with the previous literature.[2,22,24] These 3 studies[2,22,24] conducted analyses on the population-based data from the Nord-Trøndelag Health Study in Mid-Norway (HUNT studies); thus, the population is similar to the one in our study.[2,22,24] However, direct comparisons of effect sizes between our findings and previous studies are implausible. Although we performed analyses providing both odds ratios and risk ratios due to the differences between studies in prevalence of chronic pain, the odds ratios were not comparable. In addition, other discrepancies between the studies are due to the categorisation of exposure variable—age at menarche as well as differences in chosen cutoffs of menarche age, whereas we used age at menarche as a continuous variable.

The HUNT2 indicated a weak association between early menarche (younger than 12 years) and chronic widespread musculoskeletal pain in 32,673 adult women aged 20 to 92 years.[23] The Young-HUNT3 study observed a similar weak association between early menarche and nonspecific chronic pain in 3008 teenage girls aged 13 to 18; girls with early menarche had a higher prevalence of chronic pain than girls with typical and late menarche.[22] Moreover, Aegidius and colleagues investigated the prevalence of headache in the Head-HUNT study and concluded that headache was more prevalent among female individuals with early menarche compared with those with typical and late onset.[2,22,24] However, this association between age at menarche and headache was the weakest among the HUNT studies mentioned earlier. Possibly, weak associations in HUNT studies might be explained by a much higher percentage of younger participants, (age groups ranging between 20 and 30 years), thus yielding lower prevalence of pain in their sample. Younger participants from recent birth cohorts were more likely to reach menarche at an earlier age than women from previous birth cohorts.[20] The authors suggest that the results might be biased by cohort effects.[23] We did not find a significant interaction between cohort and menarche in our data set; however, the prevalence of chronic pain was higher in Tromsø 7 than in Tromsø 6. The difference may reflect older age of participants by a decade at the inception of the Tromsø 7 study. Moreover, certain pain conditions, such as osteoarthritis, are a common pain disorder in older adults and eldery people.
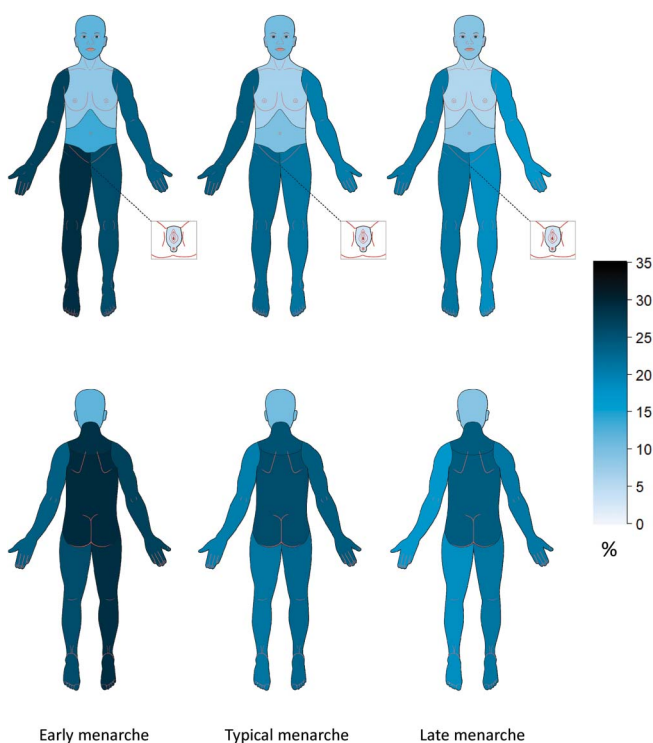
Furthermore, a study from the United States[28] reported that a delay of menarche by 1 year decreased the odds of migraine by 7%, but the associations did not remain statistically significant when adjusted for age, a family history of migraine, and BMI. The authors found no association with the non-migraine headaches.

The MORGEN study indicated a similar pattern to our findings; Wijnhoven (2006) found an association between age at menarche and the upper extremity pain but not with the lower back pain.[47] Our study had statistically significant associations in the upper extremities and back pain, though, in multivariable analyses, these associations remained significant only in both arms (upper extremities).

Bjelland et al.[4] found an association between pelvic girdle syndrome (PGS) in pregnancy and early menarche, suggesting a link between hormonal factors and PGS. Their hypothesis was more focused on biomechanical alterations, whereby high levels of estrogen increased pelvic joint mobility, and consequently, pain developed in the pelvic area. However, the association between early menarche and PGS implies that development of PGS could be due to a long exposure to estrogen before pregnancy. Thus, our findings support this inference that prepregnancy hormonal factors may unfavorably affect body systems instead of hormonal exposure during pregnancy.[4]

We did not find statistically significant associations between age at menarche and pain characteristics, except pain duration. We dichotomised pain characteristic variables resulting in categories of pain duration in more than 5 years, daily pain, and constant pain without a pause. Dichotomisation of variables presents a limitation, which could have affected the results of the study. Second, the individual pain characteristics might be inadequate to characterise the severity of chronic pain. Third, the

Table 5

Risk ratio (RR) and risk difference (RD) post hoc analyses for the association between age at menarche and chronic pain in 10 body regions.

Body regions	Univariable analysis		Multivariable analysis	
	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Head	0.94 (0.91 to 0.96)	−0.02 (−0.03 to −0.003)	0.98 (0.94 to 1.01)	−0.003 (−0.01 to 0.004)
Neck	0.96 (0.95 to 0.97)	−0.02 (−0.03 to −0.01)	0.98 (0.96 to 0.99)	−0.01(−0.02 to 0.0003)
Back	0.97 (0.95 to 0.98)	−0.01(−0.02 to −0.004)	0.99 (0.97 to 1.01)	−0.004 (−0.01 to 0.004)
Chest	0.93 (0.89 to 0.96)	−0.01 (−0.03 to 0.001)	0.96 (0.91 to 1.01)	−0.005 (−0.01 to 0.004)
Abdomen	0.93 (0.91 to 0.96)	−0.02 (−0.03 to −0.004)	0.96 (0.92 to 0.99)	−0.007 (−0.02 to 0.002)
Genital area	0.98 (0.90 to 1.06)	−0.001(−0.004 to 0.003)	1.03 (0.94 to 1.12)	0.001 (−0.001 to 0.002)
Left arm	0.95 (0.94 to 0.97)	−0.02 (−0.03 to −0.01)	0.97 (0.95 to 0.98)	−0.01 (−0.02 to −0.002)
Right arm	0.96 (0.95 to 0.97)	−0.02(−0.03 to −0.01)	0.97 (0.95 to 0.99)	−0.01 (−0.02 to −0.002)
Left leg	0.96 (0.95 to 0.97)	−0.02(−0.03 to −0.01)	0.99 (0.96 to 1.01)	−0.004 (−0.01 to 0.004)
Right leg	0.96 (0.95 to 0.97)	−0.02(−0.03 to −0.01)	0.98 (0.96 to 1.00)	−0.005 (−0.01 to 0.003)

The Graphical Index of Pain (GRIP), Tromsø 7, GRIP regions sample, n = 10,367.
Age at menarche as a continuous variable in univariable and multivariable logistic regression analyses.
Multivariable analyses adjusted for body mass index (BMI), economic status of the household in childhood (ES$_{childhood}$), and age. See supplementary Table S2 for odds ratios (OR), available as supplemental digital content at http://links.lww.com/PAIN/B561.

distribution of pain characteristics might be specific to different pain syndrome, for instance, tension headache or migraine. Moreover, it may be possible that pain characteristics are more suitable to describe acute pain than chronic pain because the severity of pain may fluctuate more in participants with chronic pain.[15]

To the best of our knowledge, classification for normal age at menarche has been addressed in a small number of articles, and mostly information was shared on behalf of women's health organisations.[1,17] Commonly, girls start their first menstruation at 9 years, and 95% to 98% of girls have had menarche before 15 years.[17] Those girls with earlier menarche at age younger than 9 years qualify for a precocious puberty, whereas today experiencing menarche after the age of 15 years is considered delayed puberty or the sign of primary amenorrhea.[17] In our study, we chose to include participants who reported menarche after the age of 15 years because it was more common for women from our earlier birth cohorts to have late menarche.

We hypothesised that higher prevalence of chronic pain is related to early menarche, and it is based on the theory that girls with early age at menarche have higher levels of estrogen, which might be associated to an increased risk of developing chronic pain.[27] Vihko and Apter,[45] in their longitudinal study in girls 7 to 17 years, found that girls with early menarche showed higher levels of circulating estradiol. Even within 5 years follow-up, higher levels of estradiol persisted in girls with early menarche.[5,10] There is a growing body of evidence suggesting interactions between sex hormones and the immune system.[29,34] For instance, research suggests female predominance in autoimmune diseases with direct effects of inflammation on disease pathology.[29,34] We found strong associations between menarche age and CWP. Research shows implicative evidence of the role of innate immune response in patients with chronic multisite musculoskeletal pain, increased levels of cytokines in fibromyalgia, and irritable bowel syndrome.[14,25,42] One might also view age at menarche as a marker for the organisational effects of sex hormones on pain processing. It has been assumed that organisational effects of sex hormones on the nervous system took place only during perinatal life and that puberty reflected the activational effects of the hormones (for reviews, see Refs. 8 and 21). However, preclinical studies have shown evidence of peripubertal remodelling of subcortical and cortical areas, which may, for instance, generate sex differences in volume and

number of brain region–specific cells in adult life.[3,41] There is also support for additional puberty-specific organisational effects on the nervous system in humans (for reviews, see Refs. 24, 31).

A major strength in this study was the large sample size with a high participation rate. It provided sufficient statistical power to assess the underlying association between age at menarche and pain, including chronic pain, site-specific chronic pain, pain characteristics, and CWP, adjusted for several possible confounders. Moreover, associations with chronic pain were assessed using 2 separate data sets (Tromsø 6 and Tromsø 7), thereby allowing for replication of findings. However, these findings are limited by the possibility of unmeasured confounding of birth weight, a known predictor of age at menarche.[13] A probable explanation is that age at menarche could be a mediator for the association between birth weight and chronic pain. Analyses were adjusted for participants' BMI in adulthood because we had no measurements on birth weight or BMI in childhood.[20] However, research indicates that BMI tends to remain stable over the lifetime.[11] Observational data are subject to recall bias due to self-report. Previous studies showed that self-reported age at menarche in adulthood was highly correlated with the true age at menarche.[7,26,30]

Table 6

Pain characteristics stratified by age at menarche group.

Pain characteristics	Age at menarche*		
	Early n = 609	Typical n = 3891	Late n = 854
	%	%	%
Pain duration ≥ 5 years†	60.6	56.0	56.6
Daily pain‡	54.8	52.3	53.2
Constant pain without pause§	27.1	24.3	27.1
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Pain intensity‖	5.2 (2.1)	5.1 (2.1)	5.2 (2.2)

The Graphical Index of Pain (GRIP), Tromsø 7, GRIP characteristics sample (n = 5354).
* Early (age 9-11 years), typical (age 12-14 years), and late (age 15-18 years).
† Pain duration is a dichotomous variable, 3 months to 5 years and ≥5 years.
‡ Episode frequency is a dichotomous variable, daily pain and nondaily pain.
§ Episode duration is a dichotomous variable, intermittent pain and constant pain without a pause.
‖ Pain intensity, NRS; 0 to 10, individuals who experienced no chronic pain (0) removed from this sample.

Table 7

Risk ratio (RR) and risk difference (RD) for the association between age at menarche and pain characteristics.*

Pain characteristics	Univariable analysis		Multivariable analysis	
	RR (95% CI)	RD (95% CI)	RR (95% CI)	RD (95% CI)
Pain ≥ 5 years	0.99 (0.98 to 0.99)	−0.01 (−0.02 to −0.01)	0.99 (0.98 to 0.99)	−0.01 (−0.02 to −0.01)
Daily pain	1.00 (0.98 to 1.01)	−0.002(−0.01 to 0.01)	1.00 (0.98 to 1.01)	−0.003 (−0.01 to 0.01)
Constant pain without pause	1.00 (0.96 to 1.03)	−0.001(−0.01 to 0.01)	0.99 (0.96 to 1.03)	−0.002 (−0.01 to 0.01)
		Beta coefficient		Beta coefficient
Pain intensity*		−0.001 (−0.04 to 0.04)		0.03 (−0.01 to 0.07)

The Graphical Index of Pain (GRIP), Tromsø 7, GRIP characteristics sample (n = 5354).
Age at menarche as a continuous variable in univariable and multivariable logistic regression analyses.
Multivariable analyses adjusted for body mass index (BMI), economic status of the household in childhood (ES$_{childhood}$), and age.
See supplementary Table S3 for odds ratios (OR), available as supplemental digital content at http://links.lww.com/PAIN/B561.
* Pain intensity analysed with linear regression (beta coefficients presented).

5. Conclusion

We conclude that age at menarche is an independent risk factor for chronic pain, site-specific chronic pain, and CWP and whereby contribute to the explanation of sex differences in pain. The associations between age at menarche and pain characteristics remain inconclusive.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B561.

References

[1] Adams Hillard PJ. Menstruation in adolescents: what's normal, what's not. Ann N Y Acad Sci 2008;1135:29–35.

[2] Aegidius K, Zwart JA, Hagen K, Dyb G, Holmen T, Stovner L. Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. Eur J Neurol 2011;18:321–8.

[3] Ahmed EI, Zehr JL, Schulz KM, Lorenz BH, DonCarlos LL, Sisk CL. Pubertal hormones modulate the addition of new cells to sexually dimorphic brain regions. Nat Neurosci 2008;11:995–7.

[4] Bjelland EK, Eberhard-Gran M, Nielsen CS, Eskild A. Age at menarche and pelvic girdle syndrome in pregnancy: a population study of 74 973 women. BJOG 2011;118:1646–52.

[5] Cancer CGoHFiB. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141–51.

[6] Clancy KB, Klein LD, Ziomkiewicz A, Nenko I, Jasienska G, Bribiescas RG. Relationships between biomarkers of inflammation, ovarian steroids, and age at menarche in a rural Polish sample. Am J Hum Biol 2013;25:389–98.

[7] Cooper R, Blell M, Hardy R, Black S, Pollard TM, Wadsworth ME, Pearce MS, Kuh D. Validity of age at menarche self-reported in adulthood. J Epidemiol Community Health 2006;60:993–7.

[8] Craft RM. Modulation of pain by estrogens. PAIN 2007;132(suppl 1):S3–12.

[9] Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njølstad I. The sixth survey of the Tromsø study (Tromsø 6) in 2007–08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. Scand J Public Health 2013;41:65–80.

[10] Emaus A, Espetvedt S, Veierød MB, Ballard-Barbash R, Furberg AS, Ellison PT, Jasienska G, Hjartåker A, Thune I. 17-beta-estradiol in relation to age at menarche and adult obesity in premenopausal women. Hum Reprod 2008;23:919–27.

[11] Evensen E, Wilsgaard T, Furberg A-S, Skeie G. Tracking of overweight and obesity from early childhood to adolescence in a population-based cohort–the Tromsø study, fit futures. BMC Pediatr 2016;16:1–11.

[12] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447–85.

[13] Finstad SE, Emaus A, Potischman N, Barrett E, Furberg A-S, Ellison PT, Jasienska G, Thune I. Influence of birth weight and adult body composition on 17β-estradiol levels in young women. Cancer Causes Control 2009;20:233–42.

[14] Generaal E, Vogelzangs N, Macfarlane GJ, Geenen R, Smit JH, Dekker J, Penninx BW. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. PAIN 2014;155:1605–12.

[15] Glette M, Stiles TC, Borchgrevink PC, Landmark T. The natural course of chronic pain in a general population: stability and change in an eight–wave longitudinal study over four years (the HUNT pain study). J Pain 2020;21:689–99.

[16] Hassan S, Muere A, Einstein G. Ovarian hormones and chronic pain: a comprehensive review. PAIN 2014;155:2448–60.

[17] Hillard PJA. Menstruation in adolescents: what do we know? And what do we do with the information? J Pediatr Adolesc Gynecol 2014;27:309–19.

[18] Holmberg MJ, Andersen LW. Estimating risk ratios and risk differences: alternatives to odds ratios. JAMA 2020;324:1098–9.

[19] Iacovides S, Avidon I, Baker F. Does pain vary across the menstrual cycle? A review. Eur J Pain 2015;19:1389–405.

[20] Iversen JM, Indredavik MS, Evensen KA, Romundstad PR, Rygg M. Self-reported chronic pain in young adults with a low birth weight. Clin J Pain 2017;33:348–55.

[21] Juraska JM, Sisk CL, DonCarlos LL. Sexual differentiation of the adolescent rodent brain: hormonal influences and developmental mechanisms. Horm Behav 2013;64:203–10.

[22] Kløven B, Hoftun GB, Romundstad PR, Rygg M. Relationship between pubertal timing and chronic nonspecific pain in adolescent girls: the Young-HUNT3 study (2006-2008). PAIN 2017;158:1554–60.

[23] Kvalheim S, Sandvik L, Winsvold B, Hagen K, Zwart JA. Early menarche and chronic widespread musculoskeletal complaints-results from the HUNT study. PAIN 2016;20:458–64.

[24] Ladouceur CD, Peper JS, Crone EA, Dahl RE. White matter development in adolescence: the influence of puberty and implications for affective disorders. Dev Cogn Neurosci 2012;2:36–54.

[25] Lee JY, Kim N, Park JH, Nam RH, Lee SM, Song C-H, Kim G, Na HY, Choi YJ, Kim JJ. Expression of neurotrophic factors, tight junction proteins, and cytokines according to the irritable bowel syndrome subtype and sex. J Neurogastroenterol Motil 2020;26:106.

[26] Lundblad MW, Jacobsen BK. The reproducibility of self-reported age at menarche: the Tromsø Study. BMC Womens Health 2017;17: 1–7.

[27] Macmahon B, Trichopoulos D, Brown J, Andersen AP, Cole P, Dewaard F, Kauraniemi T, Polychronopoulou A, Ravnihar B, Stormby N, Westlund K. Age at menarche, urine estrogens and breast cancer risk. Int J Cancer 1982;30:427–31.

[28] Maleki N, Kurth T, Field AE. Age at menarche and risk of developing migraine or non-migraine headaches by young adulthood: a prospective cohort study. Cephalalgia 2017;37:1257–63.

[29] Markle JG, Fish EN. SeXX matters in immunity. Trends Immunol 2014;35: 97–104.

[30] Must A, Phillips S, Naumova E, Blum M, Harris S, Dawson-Hughes B, Rand W. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? Am J Epidemiol 2002;155:672–9.

[31] Peper JS, Hulshoff Pol HE, Crone EA, van Honk J. Sex steroids and brain structure in pubertal boys and girls: a mini-review of neuroimaging studies. Neuroscience 2011;191:28–37.

[32] Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10 years of research on sex/gender and experimental pain perception–part 1: are there really differences between women and men? PAIN 2012;153:602–18.

[33] Riley JL III, Robinson ME, Wise EA, Price D. A meta-analytic review of pain perception across the menstrual cycle. PAIN 1999;81:225–35.

[34] Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. J Neurosci Res 2017;95:500–8.

[35] Ruau D, Liu LY, Clark JD, Angst MS, Butte AJ. Sex differences in reported pain across 11,000 patients captured in electronic medical records. J Pain 2012;13:228–34.

[36] Sherman JJ, LeResche L. Does experimental pain response vary across the menstrual cycle? A methodological review. Am J Physiol Regul Integr Comp Physiol 2006;291:R245–56.

[37] Steingrímsdóttir ÓA, Engdahl B, Hansson P, Stubhaug A, Nielsen CS. The Graphical Index of Pain: a new web-based method for high-throughput screening of pain. PAIN 2020;161:2255–62.

[38] Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. PAIN 2017;158:2092–107.

[39] Tayebi N, Yazdznpanahi Z, Yektatalab S, Akbarzadeh M, Zare N. Pattern of menarche age (normal, early and late) and its relationship with some demographic characteristics in girls and their parents. Int J Adolesc Med Health 2018;30:263.

[40] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). PAIN 2019;160:19–27.

[41] Trova S, Bovetti S, Bonzano S, De Marchis S, Peretto P. Sex steroids and the shaping of the peripubertal brain: the sexual-dimorphic set-up of adult neurogenesis. Int J Mol Sci 2021;22:7984.

[42] Uçeyler N, Häuser W, Sommer C. Systematic review with meta-analysis: cytokines in fibromyalgia syndrome. BMC Musculoskelet Disord 2011; 12:245–15.

[43] Unruh AM. Gender variations in clinical pain experience. PAIN 1996;65: 123–67.

[44] Varimo T, Huttunen H, Miettinen PJ, Kariola L, Hietamäki J, Tarkkanen A, Hero M, Raivio T. Precocious puberty or premature thelarche: analysis of a large patient series in a single tertiary center with special emphasis on 6- to 8-year-old girls. Front Endocrinol (Lausanne) 2017;8:213.

[45] Vihko R, Apter D. Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. J Steroid Biochem 1984;20:231–6.

[46] Vihko RK, Apter DL. The epidemiology and endocrinology of the menarche in relation to breast cancer. Cancer Surv 1986;5:561–71.

[47] Wijnhoven HA, De Vet HC, Smit HA, Picavet HSJ. Hormonal and reproductive factors are associated with chronic low back pain and chronic upper extremity pain in women–the MORGEN study. Spine 2006;31:1496–502.

[48] Wolfe F, Butler SH, Fitzcharles M, Häuser W, Katz RL, Mease PJ, Rasker JJ, Russell AS, Russell IJ, Walitt B. Revised chronic widespread pain criteria: development from and integration with fibromyalgia criteria. Scand J Pain 2020;20:77–86.