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

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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 pain and upper extremity pain.4,11 In addition, one study examined the association between age at menarche and chronic widespread pain in adults.35 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
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 as pain in 4 or 5 regions (0-5) and a total pain site score of 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 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\text{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
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,\(^1\) 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 ESchildhood. 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.\(^1\) 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 Table 1

| Variables | Missing values | Excluded |
|-----------|----------------|----------|
| Age at menarche | 180 | 29* |
| BMI | 15 | 15 |
| ESchildhood | 274 | 274 |
| Chronic pain | 21 | 21 |
| Total number of individuals | 479 | 479 |
| Age at menarche | 132 | 132 |
| BMI | 15 | 15 |
| ESchildhood | 142 | 142 |
| Chronic pain | 382 | 382 |
| Total number of individuals | 700 | 700 |
| Age at menarche | 132 | 132 |
| BMI | 36 | 36 |
| ESchildhood | 151 | 151 |
| No response to GRIP questions | 435 | 435 |
| Total number of individuals | 707 | 707 |
| Head | 41 | 41 |
| Neck | 259 | 259 |
| Back | 207 | 207 |
| Left arm | 119 | 119 |
| Right arm | 79 | 79 |
| Left leg | 111 | 111 |
| Right leg | 77 | 77 |
| Abdomen | 58 | 58 |
| Total number of individuals | 961 | 961 |

* 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; ESchildhood, economic status of the household in childhood.
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...
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 0.004]). 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 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.

|                      | Early | Typical | Late        |
|----------------------|-------|---------|-------------|
|                      | n     | n (%)   | n           |
| Tromsø 6             |       |         |             |
| n = 6449             |       |         |             |
| Age mean (SD)        | 53.6  | 11.3    | 56.8 (12.6) |
| BMI mean (SD)        | 28.3  | 5.3     | 26.6 (4.63) |
| Chronic pain, n (%)  | 270   | 42.3    | 1770 (37.9) |
| ESchildhood good, n (%) | 455 | 71.3    | 3462 (74.3) |
| Tromsø 7             |       |         |             |
| n = 5681             |       |         |             |
| Age mean (SD)        | 50.4  | 8.5     | 51.9 (8.5)  |
| BMI mean (SD)        | 28.7  | 5.9     | 26.8 (4.9)  |
| Chronic pain, n (%)  | 320   | 49.4    | 1799 (43.5) |
| ESchildhood good, n (%) | 476 | 73.5    | 3207 (77.5) |
| Combined sample      |       |         |             |
| n = 12,130           |       |         |             |
| Age mean (SD)        | 51.9  | 10.1    | 54.5 (11.2) |
| BMI mean (SD)        | 28.5  | 5.6     | 26.7 (4.8)  |
| Chronic pain, n (%)  | 590   | 45.9    | 3569 (40.6) |
| ESchildhood good, n (%) | 931 | 72.4    | 6669 (75.8) |

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; ESchildhood, economic status of the household in childhood.

### 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 analysis adjusted for body mass index (BMI), economic status of the household in childhood (ESchildhood), 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).
with the previous literature. These 3 studies 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. 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. 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. However, 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 menarche. 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. The authors suggest that the results might be biased by cohort effects. However, 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 elderly people.

Furthermore, a study from the United States 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. 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).

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.

Furthermore, a study from the United States 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.

Table 4
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 (8-11 years), typical menarche age (12-14 years), and late menarche age (15-18 years).
and Apter,45 in their longitudinal study in girls 7 to 17 years, found that amenorrhea. In our study, we chose to include participants where today experiencing menarche after the age of 15 at age younger than 9 years qualify for a precocious puberty, whereas at menarche.5,10 There is a growing body of evidence girls with early menarche showed higher levels of circulating estradiol.32,33 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 activation effects of the hormones (for reviews, see Refs. 6 and 21). However, preclinical studies have shown evidence of perinatal 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.9,41 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.10,17 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 those 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 Vilko and Apter,16 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 activation effects of the hormones (for reviews, see Refs. 6 and 21). However, preclinical studies have shown evidence of perinatal 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.9,41 There is also support for additional puberty-specific organisational effects on the nervous system in humans (for reviews, see Refs. 24, 31).

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### Table 5

| 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 (−0.00 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 −0.02) |
| 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 −0.02) |
| Left leg         | 0.96 (0.95 to 0.97)  | −0.02 (−0.03 to −0.01) | 0.96 (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) | 0.96 (0.96 to 1.00)   | −0.005 (−0.01 to 0.003) |

The Graphical Index of Pain (GRIP), Tromsø 7, GRIP characteristics sample, n = 10,367. Multivariable analyses adjusted for body mass index (BMI), economic status of the household in childhood (EStchildhood), and age. See supplementary Table S2 for odds ratios (OR), available as supplemental digital content at http://links.lww.com/PAIN/8561.

### Table 6

| 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 | Mean (SD) | Mean (SD) | Mean (SD) |
|---------------|-----------|-----------|-----------|
|               | 5.2 (2.1) | 6.1 (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 6 months to 5 years.
‡ Episode frequency is a dichotomous variable, daily pain and non-daily pain.
§ Pain intensity, NRS, 0 to 10, individuals who experienced no chronic pain (0) removed from this sample.
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.

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Access to data: The Tromso Study has an open access database for qualified researchers (PhD) who are affiliated with a research institution. Guidelines for data access applications can be found at http://uit.no/research/tromsostudy. An overview of available institution. Guidelines for data access applications can be found at http://links.lww.com/PAIN/B561.

Appendix A. Supplemental digital content

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

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) |
| Pain intensity*      | −0.01 (−0.04 to 0.04) | 0.03 (−0.01 to 0.07) |

The Graphical Index of Pain (GRIP) in the Tromsø 7, GRIP characteristics sample (n = 5354).

* Pain intensity analysed with linear regression (beta coefficients presented).

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