Title page

Musculoskeletal pain in adults born preterm: Evidence from two birth cohort studies

Running head/short title: *Musculoskeletal pain in adults born preterm*

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Significance: Young adults born preterm do not have increased rates of musculoskeletal pain. Our findings rather suggest that these rates may be slightly lower than among those born at term.

Abstract

Background: Individuals born preterm are at risk for later developmental problems and long-term morbidities. There is conflicting evidence regarding musculoskeletal pain in young adulthood. We investigated the prevalence of self-reported musculoskeletal pain in young adults born across the range of preterm birth compared with a term-born reference group.

Methods: From two Finnish birth cohorts, 184 individuals born early preterm (<34 weeks), 350 late preterm (34 to <37 weeks), and 641 at term completed a self-report questionnaire of musculoskeletal pain at mean age 24.1 (SD1.4) years. Group differences were examined by logistic regression models adjusting for sex, age and cohort (Model 1), potential early life confounders (Model 2), and lifestyle factors related to physical (Model 3) and mental health (Model 4).

Results: The late preterm group had lower odds for reporting neck pain (0.73; 95% confidence interval (CI): 0.56-0.96), which was further reduced when adjusting for early life confounders and lifestyle factors (Model 4). Odds for reporting peripheral pain was 0.69 (95% CI: 0.48-0.99, Model 4) in the early preterm group. The odds for reporting any pain, shoulder, low back or widespread pain did not differ significantly between groups, although odds for reporting widespread pain was 0.77 (95% CI: 0.58-1.03, Model 4) in the late preterm group.

Conclusions: We did not find evidence of increased prevalence of musculoskeletal pain in adults born early or late preterm. In contrast, our results suggest that adults born preterm have a slightly lower risk for reporting musculoskeletal pain, also when we adjusted for lifestyle factors.

Introduction

Musculoskeletal conditions, especially low back and neck pain, constitute one of the leading causes of disability globally, accounting for 12% of years lived with disability in 2015 (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016). Although localized musculoskeletal pain does exist, pain in any body region is frequently associated with pain in other regions. This may also give rise to functional limitations (Kamaleri et al. 2008). Musculoskeletal pain and symptoms are frequent in the general population, with a prevalence ranging from 70% for adults with a recall period of one week (Kamaleri et al. 2008), increasing up to 95% during a lifetime (Baldwin et al. 2017). The pathophysiology is not clear and some speculate whether early life conditions may influence development of pain (Beggs et al. 2012, Walker 2017).

Worldwide, 11.1% of children are born preterm, *i.e.* prior to 37 weeks of gestation (Blencowe et al. 2012). Most of these neonates survive, but there is an increased risk of later developmental problems and long-term morbidities (Aarnoudse-Moens et al. 2009, Raju et al. 2017). In particular those born very preterm (before week 32 of gestation) undergo multiple invasive pain procedures including intubation, intravenous or intra-arterial cannula and, in high-resource settings, most preterm infants undergo frequent blood sampling (Grunau 2013). Such early pain exposure has raised concern about long-term hypersensitivity to pain.

Previous studies on pain sensitivity and self-reported pain in individuals born preterm are inconsistent. Some experimental studies have demonstrated increased sensitivity to tender points (Buskila et al. 2003), heat (Hermann et al. 2006) and cold (Vederhus et al. 2012) in children and adolescents born very preterm/at very low birth weight (VLBW: <1500g) or at extremely low birth weight (ELBW: <1000g), whereas others have not (Walker et al. 2009).

In ELBW children and adolescents, as well as in ELBW and VLBW adults, there are self- and parent-reports of lesser (Grunau, Whitfield and Petrie 1994a), equal (Cooke 2004, Vederhus et al. 2012, Buskila et al. 2003, Walker et al. 2009, Baumgardt et al. 2012, Husby et al. 2016, Batsvik et al. 2015, Grunau, Whitfield and Petrie 1998, Saigal et al. 2006, Lund et al. 2012) and higher (Saigal et al. 1996, Iversen et al. 2017, Grunau et al. 1994b, Husby et al. 2016) levels of pain and somatic complaints. Also in children born 32-35 weeks of gestation, the risk for somatic complaints was reported to be almost twice as high when compared with term-born children (Potijk et al. 2012). Larger studies examining musculoskeletal pain in adolescents and adults across the whole range of preterm birth have not been able to demonstrate consistent associations with chronic or non-chronic pain (Iversen et al. 2015, Mallen et al. 2006, Littlejohn et al. 2012). One study has even reported lower risk of low back pain in 12-22 year old males with low birth weight (LBW: <2500g) (Hestbaek et al. 2003).

The prevalence and experience of musculoskeletal pain may undergo age-related changes (Baldwin et al. 2017, GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016). Previous studies on pain in preterm individuals have mainly been conducted in children (Grunau et al. 1994a, Grunau et al. 1994b, Saigal et al. 1996, Grunau et al. 1998, Hermann et al. 2006, Potijk et al. 2012, Valeri et al. 2016, Walker et al. 2009) and adolescents (Buskila et al. 2003, Batsvik et al. 2015, Saigal et al. 1996, Hohmeister et al. 2010, Vederhus et al. 2012, Iversen et al. 2015) or in mixed populations comprising both adolescents and adults (Mallen et al. 2006, Hestbaek et al. 2003). As studies in adulthood yield mixed findings (Littlejohn et al. 2012, Husby et al. 2016, Iversen et al. 2017, Cooke 2004, Baumgardt et al. 2012, Saigal et al. 2006), it still remains unclear whether individuals born preterm and at term differ in self-reports of pain in young adulthood. Accordingly, we aimed to investigate the prevalence of self-reported musculoskeletal pain in two birth cohorts of young adults born across the whole range of prematurity and a reference group born at term.

Participants and Methods

Study design

The study participants were recruited from two separate birth cohorts in Finland; the Preterm Birth and Early-Life Programming of Adult Health and Disease (ESTER) Preterm Birth Study (Sipola-Leppänen et al. 2015) and the Arvo Ylppö Longitudinal Study (AYLS) (Heinonen et al. 2008) (Figure 1).

The ESTER Preterm Birth cohort comprised 1980 individuals born in the two northernmost provinces of Finland between 1985 and 1989, and aimed to explore effects of early (<34 weeks of gestational age: GA) and late (34 to <37 weeks of GA) preterm birth on health and well-being in young adult life. Young adults born preterm (<37 weeks of GA) were traced through Northern Finland Birth Cohort 1986 (NFBC, births 1985-1986) or Finnish Medical Birth Registry (FMBR, births 1987-1989 in the same geographical area) and a term-born reference group was randomly selected from the same source population.

The original AYLS cohort comprised 2193 individuals born between March 14 1985 and March 15 1986 in the province of Uusimaa in Southern Finland. They comprised 1535 infants born alive and admitted to neonatal wards of the birth hospitals or transferred to the Neonatal Intensive Care Unit of the Children’s Hospital, University of Helsinki and Helsinki University Hospital within ten days of birth, and 658 infants without evidence of neonatal illness and born after every second admitted infant in one of the three largest maternity hospitals in the area.

In young adult age, individuals from both studies were invited to a clinical examination, including a self-report pain questionnaire. Both studies were approved by the Coordinating Ethics Committee at Helsinki and Uusimaa Hospital District, and all participants gave written informed consent according to the Helsinki Declaration.

Participants

Of the 1980 invited individuals in the ESTER Preterm Birth cohort, 779 (39.3%) took part in a clinical examination between 2009 and 2011 (Figure 1); 152 were born early preterm, 266 late preterm and 361 at term. Length of gestation was confirmed from medical records in 149 early preterm, 248 late preterm and 356 term-born participants. Of these, 143 born early preterm, 240 born late preterm and 345 term-born participants answered the pain questionnaire.

Of the 2193 individuals in the AYLS cohort, 1913 were invited and 1136 (51.8% of original cohort) took part in a clinical examination between 2009 and 2012. As in previous ESTER-AYLS publications (Matinolli et al. 2016, Bjorkqvist et al. 2018), we included as term controls only individuals from the group not admitted to neonatal ward (see Study design above), because the admitted group represents a range of prenatal and neonatal adversities not representative of those born at term. Length of gestation was confirmed from medical records for 489 individuals who gave their permission; 46 were born early preterm, 129 late preterm and 314 were born at term. Of these, 41 born early preterm, 110 born late preterm and 296 term-born participants answered the pain questionnaire.

In total, we report results on 1175 participants; 184 born early preterm, 350 late preterm and 641 at term (reference group). Detailed non-participation analyses have been published (Sipola-Leppänen et al. 2015, Matinolli et al. 2016).

Musculoskeletal pain

The participants completed a self-report questionnaire of musculoskeletal pain during the last six months, in which they were asked if they had had any aches or pains during the last six months in the following areas of the body: Head, neck, shoulders, low back, elbows, wrists, knees, and ankle–foot area. As headache may not be primarily musculoskeletal, this area was not included in our analyses. The response alternatives were: 1) No, 2) Yes, but I have not consulted a physician, physiotherapist, nurse, or other health professional because of the pain and 3) Yes, and I have consulted a physician, physiotherapist, nurse, or other health professional because of the pain. For our main analyses, we compared the response alternative "No" (1) with the two "Yes" alternatives (2 and 3). In supplementary analyses, we also compared participants who had sought health care (3) with those who had no pain or had not sought health care for the pain (1 and 2). Pain locations were categorized in four separate body regions as previously described by Auvinen et al. (Auvinen et al. 2009): 1) Neck, 2) Shoulder, 3) Low back, and 4) Peripheral areas (elbow, wrist, knee, or ankle–foot). We defined widespread pain as three or more pain sites including both upper and lower parts of the body as well as axial pain (neck and/or low back), as this is close to the definition of chronic widespread pain (Wolfe et al. 2010), except we did not have information on duration of pain.

Covariates

Maternal smoking during pregnancy (yes/no) was based on a questionnaire completed during pregnancy for ESTER participants from NFBC (Tikanmäki et al. 2017b), and on medical records for ESTER participants from FMBR and for AYLS participants. Diagnosis of gestational diabetes and hypertension (gestational/chronic or preeclampsia) were reviewed from hospital records and confirmed according to current criteria for all participants (Matinolli et al. 2016). We calculated the birth weight standard deviation (SD) score by gestational age and sex according to Finnish birth weight standards (Pihkala et al. 1989). We used educational attainment of the higher educated parent, reported by the participant at the clinical examination to indicate the childhood socioeconomic status (dummy coded, with separate category for missing data). Current body mass index (BMI) was calculated from the height and weight measured during the clinical visit and current smoking (daily smoking, yes/no) as self-reported by questionnaire. Physical activity level was calculated in metabolic equivalent (MET) hours per week on the basis of a questionnaire on light (assuming a value of 3 METs), moderate to vigorous (5 METs), and commuting from home to work or study and back (4 METs) physical activity (Tikanmäki et al. 2016). Depressive symptoms were measured by the Beck Depression Inventory – second edition (BDI-II) (Beck, Steer and Brown 1996), with scores 0-13 indicative of no depression, scores 14-19 indicative of mild depression and scores >19 indicative of moderate/severe depression (dummy coded, with separate category for missing data). Information about neurosensory impairment, severe physical or cognitive disability, fracture history and whether the participant was pregnant was obtained through self-report at the clinical examination.

Statistical analyses

Statistical analyses were performed with IBM SPSS for Windows 23.0. Two-tailed p-values <0.05 were considered statistically significant. Background/descriptive characteristics were compared by using one-way ANOVA for continuous data, and linear-by-linear association for categorical data. Logistic regression models were used to compare differences between the groups and covariates selected as in previous publications from the source cohorts (Matinolli et al. 2016, Sipola-Leppänen et al. 2015, Tikanmäki et al. 2016) (Figure S1). We first estimated the crude effect of preterm birth, adjusting for sex, age and cohort (Model 1). To assess the total effect, we adjusted for variables in Model 1 in addition to potential early life confounders; parental educational level as a proxy of childhood socioeconomic position, maternal smoking during pregnancy, gestational diabetes, maternal hypertension and birth weight SD score as indicators of fetal conditions during pregnancy (Model 2). Specifically, birth weight SD score, which indicates birth weight in relation to gestational age and is a commonly used indicator of fetal growth, was included as another marker of pregnancy conditions predisposing to preterm birth. Additionally, as potential mediators, we adjusted for lifestyle factors related to physical health; BMI, self-reported physical activity level and daily smoking (Model 3), and mental health; depressive symptoms (Model 4) at the time of the study. We also ran the analyses by replacing current BMI with lean body mass, without and with fat percentage, available for 1140 (97%) participants assessed by segmental multifrequency bioelectrical impendance (InBody 3.0, Biospace Co., Seoul, Korea) (Sipola-Leppänen et al. 2015). We performed a subgroup analysis comparing individuals born VLBW (<1500g; n=67) with the term-born reference group. We also performed logistic regression analyses after exclusion of individuals with self-reported neurosensory impairment, severe physical or cognitive disability (n=17), individuals with fractures within the same year as the clinical examination (n=13), and pregnant women (n=26), due to their possible effect on musculoskeletal pain.

Results

Background characteristics

Table 1 shows the background characteristics of the study groups.

Prevalence of musculoskeletal pain

Table 2 shows the prevalence of musculoskeletal pain in different areas of the body and Figure 2 shows the proportion of participants with no, one or more pain sites in the three study groups. Any pain was reported in 82.3-85.8% and widespread pain in 39.1-45.1% of all participants.

Table 3 shows the odds ratio for reporting any pain, pain in the four body regions and widespread pain. The late preterm group had lower odds for reporting neck pain (OR: 0.73; 95% CI: 0.56-0.96), which was unchanged when adjusting for potential early life confounders (Model 2), and further reduced when adjusting for BMI, physical activity level and daily smoking (Model 3), and depressive symptoms (Model 4). The odds for reporting peripheral pain was 0.73; 95% CI: 0.52-1.02 in the early preterm group, and significantly reduced after adjustment for early life confounders and lifestyle factors (0.69; 95% CI: 0.48-0.99, Model 4). The odds for reporting any pain, shoulder, low back or widespread pain did not differ significantly between groups, although the late preterm group had a tendency of reporting less widespread pain (0.80; 95% CI: 0.61-1.05), which remained when we adjusted for early life confounders and lifestyle factors.

Seeking health care for musculoskeletal pain

Table S1 shows the prevalence of musculoskeletal pain and health care seeking in the three groups. When we compared young adults who had sought health care with all participants who had not sought health care (with or without pain), there were no significant group differences, except the late preterm group had lower odds for seeking provider for widespread pain when adjusted for early life confounders and lifestyle factors (OR: 0.42; 95% CI: 0.18-0.98, Model 4) (Table S2).

Subgroup analyses

Table S3 shows the odds ratio for reporting any pain, pain in the four body regions and widespread pain in a subgroup of VLBW participants compared with the term-born reference group. The VLBW group had a tendency of reporting less peripheral pain (0.67; 95% CI: 0.40-1.14), the difference was significant when we adjusted for early life confounders, and lifestyle factors (0.50; 95% CI: 0.26-0.94, Model 4).

Sensitivity analyses

All results were essentially the same when we excluded individuals with neurosensory impairment, severe physical or cognitive disability (n=17), fractures during the last year (n=13) and/or pregnant women (n=26) (data not shown).

Discussion

The preterm groups reported similar prevalence of musculoskeletal pain during the last six months in most body regions as the term-born reference group. The early preterm group tended to report less peripheral pain and the late preterm group had lower odds for reporting neck pain. Results were relatively unchanged when we adjusted for covariates and in sensitivity analyses when we excluded individuals with neurosensory impairment, severe physical or cognitive disability, fractures during the last year and pregnant women.

The pain questionnaire used in this study is similar to the Standardized Nordic Questionnaire (SNQ) (Kuorinka et al. 1987), which has been used in several studies of musculoskeletal pain worldwide. The original SNQ has nine anatomical regions, including upper back and hip, that were not recorded in our study. Although pain in the specified body areas may not necessarily be primarily musculoskeletal, this term has been widely applied when using these types of questionnaires (Kuorinka et al. 1987, Kamaleri et al. 2008, Auvinen et al. 2009). Furthermore, as other types of pain, such as neuropathic pain, are quite rare in the general population (Torrance et al. 2006), it is likely that most pain recorded in the specified body areas in our study is musculoskeletal. As we did not ask for duration of pain, the questionnaire used in our study provides six months prevalence of pain and may thus include both acute and chronic pain. We defined widespread pain according to the literature as three or more pain sites including upper and lower body parts as well as axial pain (Wolfe et al. 2010). Our definition may be regarded as a proxy for chronic widespread pain, as pain in several body regions is likely to be lasting. Furthermore, in the general population, there is a strong association between number of musculoskeletal pain sites and functional problems (Kamaleri et al. 2008).

Studies on self-reported pain in children, adolescents and adults born preterm include smaller clinical cohort studies and larger population-based studies. The findings are conflicting. This may be due to different definitions and methods used as well as ages and populations studied. It has been speculated that early pain and stressful events may alter pain modulating systems (Grunau 2013), although studies are not consistent on the role of neonatal intensive care unit

(NICU) experiences (Iversen et al. 2017, Vederhus et al. 2012). Even though ELBW infants are more prone to have a prolonged stay in the NICU than most of the participants in our study, importantly studies of ELBW children (Grunau et al. 1998), adolescents (Vederhus et al. 2012) and adults (Saigal et al. 2006) have not found differences in pain ratings compared with controls. The VLBW participants in our study did not report more pain than the term-born reference group. This is consistent with findings of no differences in self-report of bodily pain by the Short Form 36 Health Survey (Ware and Gandek 1998) between adults born at VLBW and at term in UK, Norwegian and Swiss cohorts at 20 (Cooke 2004, Lund et al. 2012) and 23 years of age (Baumgardt et al. 2012). Also supportive of our findings, no consistent association was found between preterm birth and self-reported chronic pain in a large Norwegian study linking birth registry data with a population-based health survey conducted at 13-18 years (Iversen et al. 2015). Boys born preterm did report higher rates of chronic daily pain than did boys born at term, but so did also boys born post-term (Iversen et al. 2015). Furthermore, in a population-based Danish twin register study including 12-22 year olds, there was no significant association between preterm birth and lifetime prevalence of low back pain (Hestbaek et al. 2003). In contrast, this study reported a positive association between increasing birth weight and low back pain in males (Hestbaek et al. 2003).

If anything, some of our findings also suggested lower pain ratings in adults born preterm. Those born early preterm had lower odds for reporting peripheral pain, statistically significant after adjustment for lifestyle factors. This was supported by the lower odds in the subgroup analysis of VLBW participants. Adults born late preterm did have lower odds for neck pain, and their lower odds for widespread pain were close to statistical significance. However, no difference was present in relation to the other pain sites, and the findings above were not seen when we compared those who had sought health care for their pain with the other participants. Therefore we urge for caution when interpreting these findings. Yet, there would be a number of plausible explanations. Studies have demonstrated that individuals born preterm have a different personality type than term-born individuals with more conscientiousness, agreeableness and neuroticism, but less extraversion (Allin et al. 2006, Pesonen et al. 2008), which may predispose them to give more socially desirable answers and report less pain. Our findings may also be influenced by parental and surrounding attitudes towards pain or reflect true differences in the programming of sensitivity to pain.

Most participants (82-86%) in our study reported some form of musculoskeletal pain. This is in accordance with results from the Northern Finland Birth Cohort, where 85% of 18-year-olds reported musculoskeletal pain (Auvinen et al. 2009). Also, the Global Burden of Disease Study 2015 reports that low back pain, neck pain, osteoarthritis, and other musculoskeletal disorders are extremely common in nearly all populations (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016). In the large Australian cross-sectional observational 1000 Norms Project, 12-month prevalence of all musculoskeletal symptoms was 69% for adolescents (11-17 years) and 82% for adults (18-101 years), making the authors conclude that musculoskeletal symptoms are a “normal feature of the human experience” (Baldwin et al. 2017). Widespread pain was reported in 39-45% of all participants in our study. This estimate corresponds well with the prevalence of chronic pain of 44% in adolescence (13-18 years) (Iversen et al. 2015), but is higher than the 29% prevalence that has been reported for chronic widespread musculoskeletal complaints in young adulthood (20-29 years) (Hagen et al. 2011).

In the general population, musculoskeletal pain increases with age (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016, Baldwin et al. 2017) and physical inactivity (Landmark et al. 2011). As recent papers from the ESTER birth cohort demonstrated, young adults born early preterm were less fit (Tikanmäki et al. 2016) and less physically active than term-born controls (Tikanmäki et al. 2017a). This may predispose adults born preterm to more musculoskeletal pain with age. This may be part of the explanation of the (non-significant) association of preterm birth and VLBW with chronic widespread pain in 45-year-olds in the British 1958 Cohort Study (Littlejohn et al. 2012). The Norwegian population-based HUNT-3 study has demonstrated higher prevalence of chronic pain in individuals who smoke, are depressed and of lower educational attainment (Landmark et al. 2011); these could serve as mediators of possible altered pain in adults born preterm. However, our study gave no further support for this; additional adjustments for lifestyle factors like body composition, physical activity and smoking as well as depressive symptoms did not affect the odds of having musculoskeletal pain much. Neither did exclusion of individuals with neurosensory impairment, severe physical or cognitive disability, fractures during the last year and pregnant women.

A key strength of the present study is the large number of participants from two geographical cohorts. The narrow confidence intervals imply that we are able to exclude any but very small differences in pain between the groups. However, the participation rate especially in the ESTER study was low, but previous published non-participant analysis in ESTER (Matinolli et al. 2016, Sipola-Leppänen et al. 2015) and AYLS (Matinolli et al. 2016) cohorts have not raised concern of bias due to loss to follow-up. As the pain questionnaire was included as part of an extensive follow-up assessment, people with severe musculoskeletal pain might be less likely to participate. However, this would introduce bias only if the association between participation and musculoskeletal pain would be different in the preterm and term groups. This seems unlikely, but cannot be excluded.

Conclusion

We found no evidence of increased prevalence of musculoskeletal pain during the last six months in adults born early or late preterm compared with a term-born reference group. Our study had adequate power to exclude any other than small increases in musculoskeletal pain between the groups. Rather, our findings suggest slightly lower rates of musculoskeletal pain in young adults born preterm. This difference is likely to be small and needs to be confirmed in future studies.

Author Contributions

Dr. Evensen carried out the analyses and drafted the manuscript. Dr. Tikanmaki collected and cleaned ESTER data, interpreted the analyses and contributed to redrafts. Dr. Heinonen collected and cleaned AYLS data and contributed to redrafts. Dr. Matinolli collected and cleaned AYLS and ESTER data and contributed to redrafts. Dr. Sipola-Leppanen collected and cleaned ESTER data and contributed to redrafts. Dr. Lano saw the AYLS participants as children or contributed to the AYLS childhood data collection, designed the AYLS adult study and contributed to redrafts. Dr. Wolke contributed to the AYLS design and contributed to redrafts. Dr. Vaarasmaki designed and supervised the ESTER study and contributed to redrafts. Drs. Eriksson and Raikkonen designed the AYLS adult study, contributed to the ESTER study and contributed to redrafts. Dr. Andersson contributed to the AYLS adult study and contributed to redrafts. Drs. Jarvelin and Hovi contributed to the ESTER design and contributed to redrafts. Dr. Kajantie contributed to the AYLS adult study and data collection, designed the ESTER study, supervised data collection and cleaning and contributed to redrafts.

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Table 1. Descriptive characteristics of young adults born early and late preterm and at term.

Characteristics	Early preterm (n=184)		Late preterm (n=350)		Term-born (n=641)		No. missing	p-value
Male n (%)	88	(47.8)	174	(49.7)	293	(45.7)	0/0/0	0.393
ESTER cohort n (%)	143	(77.7)	240	(68.6)	345	(53.8)	0/0/0	<0.001
Maternal smoking during pregnancy n (%)	36	(20.3)	67	(19.5)	101	(15.9)	7/6/7	0.101
Gestational diabetes n (%)	4	(2.5)	15	(4.6)	16	(2.5)	21/23/9	0.537
Maternal hypertension n (%)								
Gestational or chronic	23	(12.8)	44	(13.1)	72	(11.7)		
Preeclampsia	39	(21.7)	43	(12.8)	19	(3.1)	4/15/24	<0.001
Normotensive	118	(65.6)	248	(74.0)	526	(85.3)		
Birth weight (g)	1737	(486)	2687	(532)	3594	(479)	0/0/0	<0.001
Birth weight SD score	-0.73	(1.41)	-0.59	(1.32)	0.03	(0.97)	0/0/0	<0.001
Parental educational level n (%)								
Basic or less	14	(7.6)	26	(7.5)	45	(7.1)		
Secondary	111	(60.3)	189	(54.3)	333	(52.4)	0/2/5	0.076
Lower-level tertiary	17	(9.2)	40	(11.5)	77	(12.1)		
Upper-level tertiary	42	(22.8)	93	(26.7)	181	(28.5)		
Age at clinical examination (years)	23.6	(1.6)	23.8	(1.5)	24.4	(1.3)	0/0/0	<0.001
Height (cm)	170.0	(10.1)	171.8	(9.1)	171.5	(9.4)	2/1/10	0.081
Weight (kg)	70.2	(17.1)	71.6	(15.6)	70.2	(14.5)	2/1/10	0.358
Body mass index (kg/m^2)	24.2	(5.0)	24.1	(4.3)	23.8	(4.0)	2/1/10	0.306
Physical activity (MET h/wk)	23.7	(14.5)	24.9	(14.6)	25.8	(13.9)	0/1/2	0.199
Daily smoking n (%)	48	(26.4)	90	(26.2)	165	(26.4)	2/6/16	0.973
Beck depression inventory n (%)								
No depression	142	(85.5)	281	(88.9)	525	(89.7)		
Mild depression	15	(9.0)	20	(6.3)	41	(7.0)	18/34/56	0.112
Moderate/severe depression	9	(5.4)	15	(4.7)	19	(3.2)		
Neurosensory impairment, severe physical or mental disability n (%)	11	(6.0)	2	(0.6)	4	(0.6)	0/0/0	<0.001
Fractures the last year n (%)	1	(0.5)	3	(0.9)	9	(1.4)	0/0/0	0.269
Pregnant women n (%)	6	(3.3)	7	(2.0)	13	(2.0)	0/0/5	0.416

One-way ANOVA for continuous data, Linear-by-linear association for categorical data.

ESTER: Preterm Birth and Early-Life Programming of Adult Health and Disease Preterm Birth Study
MET: Metabolic Equivalent
SD: Standard Deviation

Table 2. Prevalence of musculoskeletal pain in young adults born early and late preterm and at term.

	Early preterm (n=184)		Late preterm (n=350)		Term-born (n=641)	
Pain site	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any pain	152	(82.6)	288	(82.3)	550	(85.8)
Neck	94	(51.1)	154	(44.0)	335	(52.3)
Shoulder	111	(60.3)	208	(59.4)	405	(63.2)
Low back	106	(57.6)	186	(53.1)	365	(56.9)
Elbow	12	(6.5)	17	(4.9)	39	(6.1)
Wrist/hand	33	(17.9)	73	(20.9)	156	(24.3)
Knee	40	(21.7)	81	(23.1)	172	(26.8)
Ankle/foot	37	(20.1)	66	(18.9)	115	(17.9)
Widespread pain[a]	81	(44.0)	137	(39.1)	289	(45.1)

[a]Widespread pain was defined as ≥3 pain sites including upper and lower body parts and axial pain.

Table 3. Logistic regression models showing the odds ratio (95% confidence interval) for reporting any pain, pain in four body regions and widespread pain during the last six months in the early and late preterm groups compared with the term-born reference group.

Outcome variable	**Early preterm (n=184)**		**Late preterm (n=350)**	
and Model[a]	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Any pain[b]				
1	0.81	(0.52-1.28)	0.79	(0.55-1.14)
2	0.74	(0.46-1.20)	0.77	(0.53-1.13)
3	0.70	(0.43-1.14)	0.75	(0.51-1.11)
4	0.69	(0.42-1.12)	0.75	(0.51-1.11)
Neck pain[b]				
1	0.97	(0.69-1.36)	0.73	(0.56-0.96)
2	0.93	(0.65-1.33)	0.72	(0.55-0.96)
3	0.88	(0.61-1.26)	0.71	(0.54-0.95)
4	0.83	(0.58-1.20)	0.70	(0.52-0.93)
Shoulder pain[b]				
1	0.94	(0.66-1.34)	0.91	(0.68-1.20)
2	0.92	(0.63-1.34)	0.92	(0.69-1.23)
3	0.88	(0.60-1.29)	0.92	(0.68-1.23)
4	0.85	(0.58-1.24)	0.90	(0.67-1.22)
Low back pain[b]				
1	1.08	(0.77-1.52)	0.89	(0.68-1.17)
2	1.03	(0.71-1.47)	0.88	(0.67-1.17)
3	0.96	(0.67-1.39)	0.87	(0.65-1.15)
4	0.94	(0.65-1.36)	0.86	(0.64-1.14)
Peripheral pain[b]				
1	0.73	(0.52-1.02)	0.87	(0.67-1.14)
2	0.71	(0.50-1.03)	0.90	(0.68-1.19)
3	0.70	(0.49-1.01)	0.91	(0.69-1.21)
4	0.69	(0.48-0.99)	0.90	(0.68-1.19)
Widespread pain[b, c]				
1	0.97	(0.69-1.36)	0.80	(0.61-1.05)
2	0.91	(0.63-1.31)	0.79	(0.60-1.05)
3	0.86	(0.60-1.25)	0.79	(0.60-1.06)
4	0.82	(0.57-1.19)	0.77	(0.58-1.03)

[a]Model 1 was adjusted for sex, age and cohort. Model 2 was adjusted for the variables in model 1 and parental educational level, maternal smoking during pregnancy, gestational diabetes, maternal hypertension and birth weight standard deviation score. Model 3 was adjusted for the variables in model 2 and body mass index, self-reported physical activity level and daily smoking. Model 4 was adjusted for variables in Model 3 and self-reported depressive symptoms.

[b]After excluding individuals with neurosensory impairment, severe physical or mental disability (n=17), fractures the last year (n=13) and pregnant women (n=26), estimates were essentially the same.

[c]Widespread pain was defined as ≥3 pain sites including pain in upper and lower body parts and axial pain.

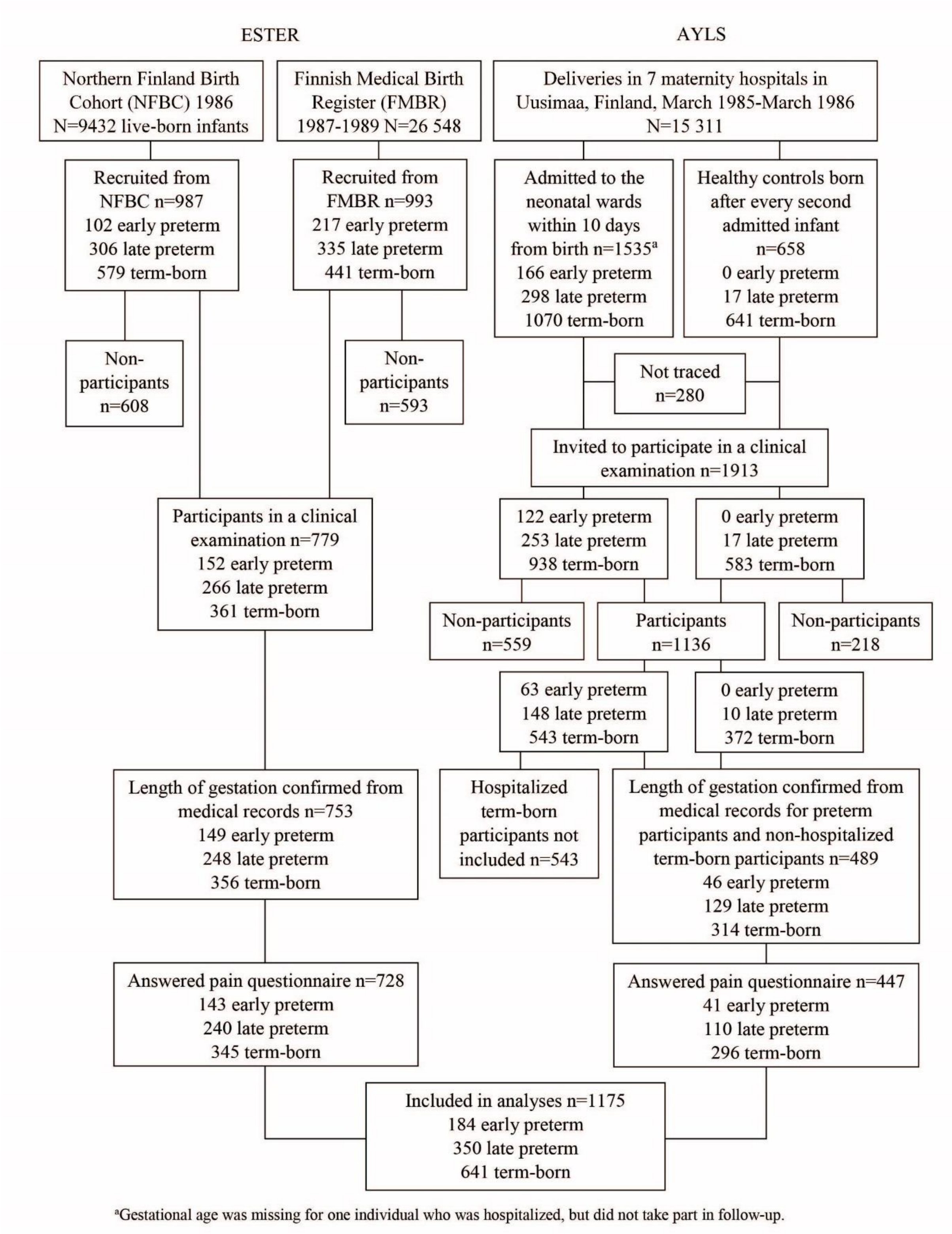

Figure 1. Flowchart of study participants in the ESTER and AYLS cohorts.

ESTER: Preterm Birth and Early-Life Programming of Adult Health and Disease Preterm Birth Study
AYLS: Arvo Ylppö Longitudinal Study

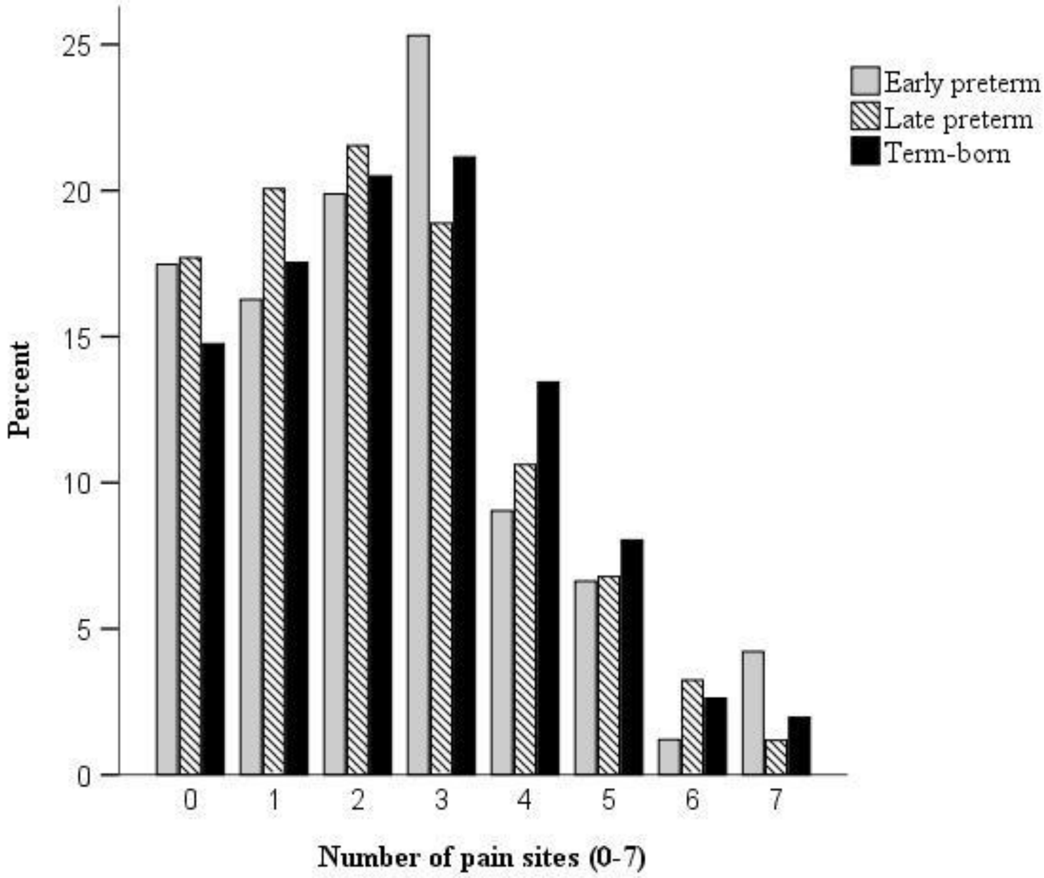

Figure 2. Proportion of young adults with no, one or more pain sites in the three study groups.

The x-axis shows the number of pain sites (0-7) and the y-axis shows the proportion of young adults in each group.

SUPPLEMENTAL MATERIAL

Table S1. Prevalence of musculoskeletal pain and health care seeking during the last six months in young adults born early and late preterm and at term.

Pain site	Early preterm (n=184) n	(%)	Late preterm (n=350) n	(%)	Term-born (n=641) n	(%)
Any pain						
No	32	(17.4)	62	(17.7)	91	(14.2)
Yes, no health provider	109	(59.2)	214	(61.1)	397	(61.9)
Yes, been to health provider	43	(23.4)	74	(21.1)	153	(23.9)
Neck						
No	90	(48.9)	196	(56.0)	306	(47.7)
Yes, no health provider	79	(42.9)	134	(38.3)	287	(44.8)
Yes, been to health provider	15	(8.2)	20	(5.7)	48	(7.5)
Shoulder						
No	73	(39.7)	142	(40.6)	236	(36.8)
Yes, no health provider	90	(48.9)	176	(50.3)	341	(53.2)
Yes, been to health provider	21	(11.4)	32	(9.1)	64	(10.0)
Low back						
No	78	(42.4)	164	(46.9)	276	(43.1)
Yes, no health provider	90	(48.9)	156	(44.6)	289	(45.1)
Yes, been to health provider	16	(8.7)	30	(8.6)	76	(11.9)
Elbow						
No	172	(93.5)	333	(95.1)	602	(93.9)
Yes, no health provider	11	(6.0)	14	(4.0)	33	(5.1)
Yes, been to health provider	1	(0.5)	3	(0.9)	6	(0.9)
Wrist/hand						
No	151	(82.1)	277	(79.1)	485	(75.7)
Yes, no health provider	27	(14.7)	65	(18.6)	138	(21.5)
Yes, been to health provider	6	(3.3)	8	(2.3)	18	(2.8)
Knee						
No	144	(78.3)	269	(76.9)	469	(73.2)
Yes, no health provider	32	(17.4)	73	(20.9)	140	(21.8)
Yes, been to health provider	8	(4.3)	8	(2.3)	32	(5.0)
Ankle/foot						
No	147	(79.9)	284	(81.1)	526	(82.1)
Yes, no health provider	26	(14.1)	51	(14.6)	89	(13.9)
Yes, been to health provider	11	(6.0)	15	(4.3)	26	(4.1)
Widespred pain[a]						
No	103	(56.0)	213	(60.9)	352	(54.9)
Yes, no health provider	70	(38.0)	129	(36.9)	256	(39.9)
Yes, been to health provider	11	(6.0)	8	(2.3)	33	(5.1)

[a]Widespread pain was defined as ≥3 pain sites including upper and lower body parts and axial pain.

Table S2. Logistic regression models showing the odds ratio (95% confidence interval) for seeking health care for pain (vs. no pain or not seeking health care for pain) during the last six months in the early and late preterm groups compared with the term-born reference group.

Outcome variable	Early preterm (n=184)		Late preterm (n=350)	
and Model[a]	OR	(95% CI)	OR	(95% CI)
Any provider[b]				
1	1.14	(0.76-1.69)	0.95	(0.69-1.32)
2	1.18	(0.77-1.79)	0.95	(0.68-1.33)
3	1.11	(0.73-1.71)	0.95	(0.68-1.34)
4	1.08	(0.70-1.66)	0.94	(0.67-1.32)
Provider for neck pain[b]				
1	1.37	(0.74-2.55)	0.88	(0.51-1.52)
2	1.58	(0.82-3.04)	0.91	(0.51-1.60)
3	1.33	(0.67-2.64)	0.92	(0.52-1.62)
4	1.23	(0.61-2.48)	0.87	(0.49-1.57)
Provider for shoulder pain[b]				
1	1.47	(0.86-2.52)	1.08	(0.68-1.71)
2	1.63	(0.92-2.89)	1.06	(0.66-1.70)
3	1.44	(0.80-2.62)	1.07	(0.66-1.74)
4	1.39	(0.76-2.54)	1.06	(0.65-1.73)
Provider for low back pain[b]				
1	0.80	(0.45-1.43)	0.77	(0.49-1.21)
2	0.82	(0.45-1.50)	0.79	(0.50-1.27)
3	0.68	(0.36-1.29)	0.75	(0.47-1.21)
4	0.61	(0.32-1.17)	0.71	(0.44-1.16)
Provider for peripheral pain[b]				
1	1.40	(0.83-2.37)	0.89	(0.56-1.43)
2	1.47	(0.84-2.56)	0.90	(0.55-1.45)
3	1.39	(0.79-2.45)	0.90	(0.55-1.46)
4	1.32	(0.74-2.34)	0.87	(0.53-1.42)
Provider for widespread pain[b,c]				
1	1.43	(0.70-2.95)	0.50	(0.23-1.11)
2	1.72	(0.81-3.64)	0.53	(0.23-1.18)
3	1.31	(0.58-2.93)	0.51	(0.23-1.15)
4	1.10	(0.48-2.55)	0.42	(0.18-0.98)

[a]Model 1 was adjusted for sex, age, and cohort. Model 2 was adjusted for the variables in model 1 and parental educational level, maternal smoking during pregnancy, gestational diabetes and hypertension and birth weight standard deviation score. Model 3 was adjusted for the variables in model 2 and body mass index, self-reported physical activity level and daily smoking. Model 4 was adjusted for variables in Model 3 and self-reported depressive symptoms.

[b]After excluding individuals with neurosensory impairment, severe physical or mental disability (n=17), fractures the last year (n=13) and pregnant women (n=26), estimates were essentially the same in the late preterm group, and reduced in the early preterm group.

[c]Widespread pain was defined as ≥3 pain sites including upper and lower body parts and axial pain.

Table S3. Logistic regression models showing the odds ratio (95% confidence interval) for reporting any pain, pain in four body regions and widespread pain during the last six months in a subgroup of young adults born with very low birth weight compared with the term-born reference group.

Outcome variable and Model[a]	VLBW (n=67) OR	(95% CI)
Any pain[b]		
1	0.92	(0.44-1.89)
2	0.85	(0.37-1.97)
3	0.79	(0.34-1.85)
4	0.75	(0.32-1.76)
Neck pain[b]		
1	1.19	(0.71-2.00)
2	1.36	(0.75-2.46)
3	1.26	(0.69-2.30)
4	1.16	(0.63-2.15)
Shoulder pain[b]		
1	0.99	(0.57-1.71)
2	1.04	(0.55-1.99)
3	0.91	(0.47-1.76)
4	0.86	(0.45-1.67)
Low back pain[b]		
1	1.23	(0.73-2.08)
2	1.20	(0.65-2.21)
3	1.08	(0.58-2.01)
4	1.06	(0.57-1.98)
Peripheral pain[b]		
1	0.67	(0.40-1.14)
2	0.58	(0.31-1.06)
3	0.53	(0.29-1.00)
4	0.50	(0.26-0.94)
Widespread pain[b,c]		
1	0.99	(0.59-1.66)
2	1.04	(0.57-1.89)
3	0.95	(0.52-1.76)
4	0.89	(0.48-1.66)

[a]Model 1 was adjusted for sex, age and cohort. Model 2 was adjusted for the variables in model 1 and parental educational level, maternal smoking during pregnancy, gestational diabetes, maternal hypertension and birth weight standard deviation score. Model 3 was adjusted for the variables in model 2 and body mass index, self-reported physical activity level and daily smoking. Model 4 was adjusted for variables in Model 3 and self-reported depressive symptoms.

[b]After excluding individuals with neurosensory impairment, severe physical or mental disability (n=11), fractures the last year (n=10) and pregnant women (n=15), estimates were essentially the same.

[c]Widespread pain was defined as ≥3 pain sites including upper and lower body parts and axial pain.

VLBW: Very Low birth Weight

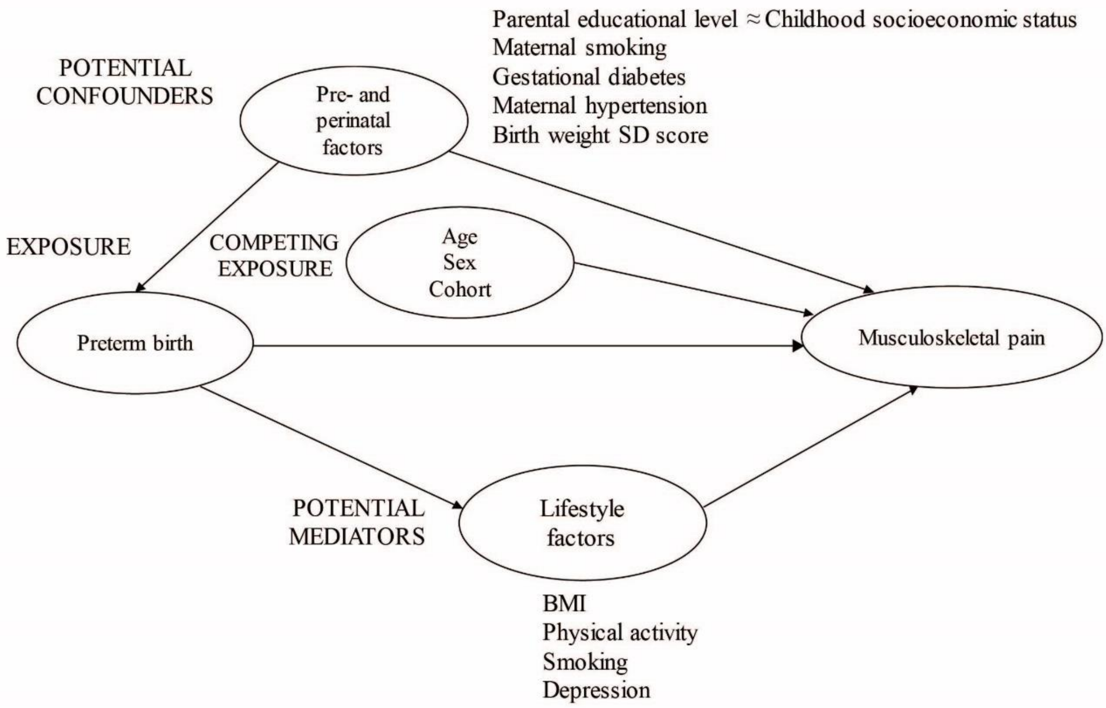

Figure S1. Causal diagram of the association between preterm birth and musculoskeletal pain with potential confounders and mediators.