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Multisite pain in adolescents and the association with ACE

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Preface

The Master's thesis in Medicine is a part of MED-3950 and is written during the 10th semester of our course of study. The thesis gives us students a chance to research a subject of interest within medicine.

I have always found psychiatry and pain conditions interesting. Peoples experience of musculoskeletal pain without a clear somatic cause seems to be an increasing public health problem, and as a future clinician I am eager to find explanations and possible treatments. I find it important to evaluate the causes and possible treatments of pain. If there turns out to be factors in childhood that can explain how some people experience more pain than others, early intervention and treatment could be crucial to prevent different pain conditions in the adult population.

This study is based on The Norwegian Arctic Adolescents Health Study; a school-based survey responded by 4881 10th grade students in North Norway, conducted in 2003–2005. The purpose of this study is to investigate a possible association between multisite musculoskeletal pain and the extent of different ACE. The results can hopefully shed some light on the psychological aspect of pain perception and maybe make clinicians more prone to ask about difficulty during childhood when dealing with complex pain conditions.

Working on this thesis I have learned a lot about how research within pain and psychiatry works, and how seldom causal direction of association can be drawn as most research depends on self-reports. I have also learned a lot about statistics and different statistical analysis. I would like to thank my thesis supervisor, Christian Eckhoff, for all the support and help with doing and understanding statistical analysis. Also, a big thanks for giving such rapid email-answers and always being available for questions.

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1 Abstract

Title: Multisite pain in adolescents and the association with ACE

Background: Both children and adolescents often express musculoskeletal pain without a clear somatic cause. The prevalence of musculoskeletal pain has been shown to be increasing. Additionally, there has been described a sharp rise in prevalence of so-called adverse childhood experiences (ACE), and studies have shown that musculoskeletal pain may be related to different ACE. The aim of this study was to evaluate possible associations between multisite musculoskeletal pain and ACE.

Method: The Norwegian Arctic Adolescent Health Study (NAAHS) was conducted among 10th graders (15–16-year old's) in the two northernmost counties in Norway during 2003-2005. Univariate analyses were carried out using descriptive statistics; Chi-square tests and one-way ANOVA. Hierarchical, linear multiple regression was used for the multivariable analysis examining the relationship between multisite musculoskeletal pain and adverse life events.

Results: We found a high prevalence of both musculoskeletal pain and adverse life events among the adolescents and the prevalence of both factors were especially high for females. We found a linear relationship between the increasing prevalence of adverse life events and increasing number of musculoskeletal pain sites, especially for females. In the multivariable analysis adverse life events was not significantly associated with musculoskeletal pain, and psychosocial factors had a mediating effect on the relationship.

Conclusion: Our study suggests an important association between the extent of ACE and the experience of multisite musculoskeletal pain in adolescents. Our findings emphasize the importance of early intervention and treatment when it comes to ACE.

2 Introduction

Musculoskeletal pain is a common and frequently disabling condition. Up to one third of adolescents report musculoskeletal pain monthly or more, and there is emerging evidence that adolescent who report musculoskeletal pain are at increased risk of having chronic pain as adults (1). This is important considering the fact that adults with persistent pain endure the bulk of individual and societal burden of painful conditions (1), with low back pain being the single leading cause of all disabilities globally (2).

Physical complaints are associated with poor mental health, and anxiety/depressive disorders have been found in about 30% of patients presenting physical complaints in primary health care and 38% in psychiatric clinics (3). Mental health problems often have their debut during adolescence, and it has been found that it affects up to 10–20% of children and adolescent worldwide (4). The debut of mental health problems may have a connection with adverse life events taking place during childhood and adolescence, so called adverse childhood experiences (ACE)(5). In this thesis, we wanted to explore the association between adverse life events in childhood and adolescence and multisite musculoskeletal pain in adolescence.

2.1 Musculoskeletal pain in adolescents

Both children and adolescents commonly express physical complaints without a clear somatic cause (3). The prevalence of musculoskeletal pain in adolescents has had an increasing trend in the last two decades, with females being more troubled than males (3;6). There has also been described a sharp increase in rates of musculoskeletal pain from childhood to adolescents (1). Data from the WHO Global Burden of Disease study shows that low back pain is responsible for the 2nd, and neck pain the 8th, most years lived with disability for 15–29 year old's of any health condition (1). Thus, they are both higher ranked than well-recognized adolescent health problems such as asthma, alcoholism, and road injury.

Cohort studies have revealed that 25–37.3% of children and adolescent report chronic pain and that this impacts their psychological, physical and social functioning (6). There has also been described prevalence rates across different chronic pain sites which shows that musculoskeletal pain is the most common pain experience in late childhood and adolescence (6). One school-based study found that musculoskeletal pain accounted for 64% of all pain

that were reported by young people (6). In a Turkish cross-sectional study on musculoskeletal pain and related factors in adolescents, they found that 82.5% of the adolescents aged 15 to 19 years reported pain in the upper and lower extremities (7). In another study, Andreicci et al. found that over >40% of the study population experienced musculoskeletal pain (8). In a national cross sectional study conducted in Finland, Hekala et al. found that the prevalence of neck, shoulder and back pain increased rapidly from 1985 to 2001 (9).

In later years, multisite pain and associating factors have been emphasized. Kamaleri et al. goes as far as questioning if localized pain sites even exist, arguing that musculoskeletal pain usually coexists with pain in other body regions and that the functional consequences are highly dependent on how widespread pain is (10). In The Norwegian Arctic Adolescent Health Study (NAAHS), Eckhoff and Kvernmo found a high prevalence of multisite pain and associating factors among adolescents, especially for females (3). Similarly, Hoftun et al. found a high prevalence of chronic non-specific pain, mainly multisite pain, among adolescents in The Young HUNT-study (11). In agreement with Eckhoff and Kvernmo, Hoftun et al. also found a higher prevalence of multisite pain among young females compared to males.

The observed rise in prevalence of musculoskeletal pain conditions in adolescence suggests a necessity to investigate conditions in both this life stage and in childhood to identify the initial onset of musculoskeletal pain conditions, because understanding factors surrounding the initial onset offers the best chance of developing treatments and is also fundamental to any efforts at primary intervention. There is reason to believe that early intervention and prevention may offer hope to prevent development of musculoskeletal pain later in life.

2.2 Adverse childhood experiences (ACE)

Adverse childhood experiences (ACE) refer to sources of stress that children may suffer early in life, and according to WHO include multiple types of abuse; neglect; violence between parents or caregivers; other kinds of serious household dysfunction such as alcohol and substance abuse; and peer, community and collective violence (12). ACE was once considered a social or mental health problem, but the impact in ACE on pediatric development and long-term adult health outcomes has since been recognized as a major public health problem. As stated by Dr. Robert Block, the American Academy of Pediatrics

(AAP) past president, "Children's exposure to adverse childhood experiences is the greatest unaddressed public health threat of our time" (13). Severe and misdiagnosed trauma can be misdiagnosed as depression, anxiety, or ADHD later in life and lead to malpractice.

One of the biggest studies of ACE was conducted from 1995 to 1997 in Southern California at Kaiser Permanente's Health Appraisal Clinic, where more than 17 000 members completed a survey as part of the study. The survey reviewed ACE and current health status (5). They found that two third of the participants reporting at least one ACE, with one in five reporting three or more ACE. The analysis showed a graded-dose relationship among adults. Those with the highest levels of childhood traumas were five times more likely to become an alcoholic, nine times more likely to abuse illegal drugs, three times more likely to have clinical depression, 17 times more likely to attempt suicide, two times more likely to develop heart disease, and two times more likely to be obese (14). Later studies have shown similar associations with ACE. In a systematic review, Petruccelli et al. identified 96 articles studying health outcomes associated with ACE (15). These articles demonstrated quite a breadth of outcomes correlated with ACE, including most major causes of death in US adults, and many psychosocial outcomes related to mental illness and poor health outcomes. The diversity of their findings suggests what a large effect ACE may have on every child and adult who experience them. The findings stress the major impact ACE have on public health and persons quality of life and emphasizes the need for early intervention and treatment.

2.3 Association between adverse childhood experiences (ACE) and multisite pain

Several studies have shown an association between ACE and the occurrence of musculoskeletal pain later in life. Imbierowicz and Egle found that patients with fibromyalgia had more frequent and/or more severe adversities during childhood (16), and McBeth and colleagues found that persons with chronic widespread pain reported more hospitalizations, operations, parental loss, and abuse in childhood (17). Other studies have demonstrated that painful infant experiences and childhood maltreatment, which are both included in WHO's description of ACE, were associated with adult fibromyalgia syndrome and that abuse in childhood was associated with a 97% increased risk of painful somatic syndromes in adulthood (18). Jones et al. found, by using the data from the 1958 British Birth Cohort

study, that both physical and social adversity prior to the age seven years was associated with an increase in the risk of chronic widespread pain nearly 40 years subsequently (19). Generaal et al. also found that adverse life events in childhood predicted onset of musculoskeletal pain, and in addition that an increased number of recent adverse life events was significantly associated with a higher hazard of chronic pain onset (20). Andreucci et al. found that adolescent at age 13 years who experienced psychological symptoms were at higher odds for musculoskeletal pain at age 17 years in their prospective cohort study (8). In the NAAHS study, Eckhoff and Kvernmo found a strong dose-response association between widespread musculoskeletal pain and psychosocial factors (3). They also found an association between negative life events and multisite musculoskeletal pain (3).

A few studies have investigated how ACE can lead to musculoskeletal pain. For example, Alvarez et al. found that rats submitted to limited bedding stress as neonates displayed muscle pain as adults, and that these rats exhibited increased numbers of expression of nociceptors (21). Waller et al. found association between early life stressors and future pain sensitivity (22). Specifically, they found that more problematic behavior at age two was associated with less pressure pain sensitivity at 22 years. Early life stress from poorer family functioning increased the odds for having high cold pain sensitivity at 22 years, and for those reporting moderate/high pain experience at 22 years; poor family functioning further increased the odds of higher cold pain sensitivity. This shows that early life stress may lead to future pain sensitivity and risk of pain (22). Ozdemir et al. found a more direct explanation. They found that body posture was related to musculoskeletal pain which again was correlated with physical activities, school desk comfort, and school grades (7).

The association between the extent of musculoskeletal pain and different kinds of ACE has been less studied. Results from the World Mental Health Surveys shows that the number of pain problems reported increases the prevalence of depressive illness accordingly, and that this relationship is observed in general population samples in countries world-wide (23). Rates of depressive illness and anxiety disorders were elevated both among persons with a single pain problem, and persons reporting multisite pain conditions, but the association was substantially stronger for persons with multisite pain. Compared to persons with one pain condition, those with multisite pains had almost double the likelihood of having both mood and anxiety disorders (23).

All these findings indicate that there is an association between adverse childhood experiences and the presence of musculoskeletal pain in adolescence. However, there is a lack of studies examining the association between the extent of different kinds of ACE and multisite pain in adolescents.

2.4 Study objective

The overall objective of this study is to evaluate the association between the extent of different kinds of adverse childhood experiences and the extent of multisite musculoskeletal pain in adolescents, using the data collected in The Norwegian Arctic Adolescent Health Study. First, we aimed to explore the prevalence of multisite musculoskeletal pain and several adverse life events in adolescents. Second, we aimed to explore the association between multisite musculoskeletal pain and adverse life events in adolescents controlling for psychosocial factors. Third, we aimed to explore potential gender differences.

3 Materials and methods

3.1 Study Design

The Norwegian Arctic Adolescent Health Study (NAAHS) was conducted among 10th graders (15–16-year-olds) in all junior high schools in the three northernmost counties in Norway, in 2003-2005. The questionnaires were administered in classroom settings and were monitored by project staff and completed during two school hours. Students who were not present in class during the questionnaire administration completed the questionnaire later. The students and their parents were given written information about the study, and the students provided written consent. The data collection was conducted and funded by a joint collaboration between the Centre for Sami Health Research at the University of Tromsø and the Norwegian Institute of Public Health. The Regional Medical Ethical Committee, the Norwegian Data Inspectorate, and the school authorities approved the study.

3.2 **Sample**

A total number of 4,881 of 5,877 (RR: 83%) invited students accepted to participate, of whom 50.1% were female and 49.9% were male. In total, 10% (450 of 4449) of the sample were indigenous Sami. In the Non-Sami group 64 adolescents reported having other nationalities, thus consisting mainly of majority Norwegians.

3.3 **Variables**

3.3.1 **Physical factors**

Musculoskeletal pain was measured by "yes/no" answers to the question: "During the last 12 months have you several times been troubled by pain in the head, neck/shoulder, arms/legs/knees, abdominal or back?" Abdominal pain was excluded based on not necessarily originating from the abdominal muscles, and the potential bias of menstrual pain in females. The four pain sites included were handled as a discrete variable ranging from 0-4 pain sites. Pain-related functional impairment: Participants were asked if the pain had resulted in reduced activity during leisure time (yes/no). In the analyses for pain-related functional impairment, those reporting functional impairment just due to abdominal pain were excluded (N=26).

Sedentary activity was measured by the question: "After school hours: How many hours per school day (Monday to Friday) do you spend in front of TV, video, and/or PC?"; up to one hour (1), 1-2 (2), 3-5 (3), or >5 hours (9) (24).

Physical activity was measured by the question: "How many hours per week do you spend on physical activity, to an extent that make you sweat and/or out of breath"; 0, 1–2, 3–4, 5–7, 8–10, or >11 hours per week. Physical activity was recoded into four groups, 0 (0), 1–4 (1), 5–7 (2) and ≥8 (3) hours per week.

Physical injury: The participants were asked if they had experienced a serious illness or injury during the last year (yes/no), and were asked to describe their illness/injury. There were few reports of illness/injury of serious nature and the number of chronic illnesses reported was too

low for statistical analysis. The number of physical injuries, mostly extremity injuries and some concussions, were 42.6% (N=136) of the total responses.

3.3.2 Adverse life events

Adverse life events (α=0.55) were measured by 12 dichotomized questions on different categories of difficult life experiences: "Have you in the last 12 months had anyone of the following problems," "conflict or fights with your parents," "parental mental health problems," "parental financial problems," "parental drug problems" or "peer problems?" Responses were measured on a four-point Likert scale from "no, never" (0), "yes, sometimes" (1), "several times" (2), to "very often" (3). Furthermore, respondents were asked, "have you in the last 12 months experienced trouble being bullied at school/ on the way to school?" with the following options: "never" (0), "sometimes" (1), "about once a week" (2), and "several times a week" (3). Also, "Have you in the last 12 months been exposed to violence?" with the following options of "never" (0), "yes, only by adolescents" (1), "yes, only by adults" (2), and "yes, by both adolescents and adults" (3). Lastly, respondents were asked, "have you in the last 12 months experienced the following:" "parental unemployment or social care," "serious illness or injury to yourself," "serious disease or injury to someone close to you," "death to someone close to you" or "sexual assault?" The total amount of adverse life events and the individual events will be examined. We also divided the adverse life events into two different categorizes – parental adverse events and individual adverse events. Parental adverse events included parental unemployment or social care, conflict or fights with your parents, parental mental health problems, parental financial problems and parental drug problem. Individual adverse events included serious illness or injury to yourself, sexual assault, bullied and exposed to violence.

3.3.3 Other psychosocial factors

Self-efficacy (α=0.77) was measured by a five-item version of the General perceived self-efficacy scale (25). Responses were scored on a four-point Likert scale from "completely wrong" (1) to "completely right" (4). Parental involvement was measured by a four-item version of the Parental Involvement Scale (α=0.78) (3;26). Parental support (α=0.88) was measured by five statements on family attachment, being valued and taken seriously, and receiving help when needed (3). Peer support (α=0.84) was measured by four statements on peer attachment and support, being valued, and receiving help when needed (3). Parental

involvement, parental and peer support were scored on a four-point Likert scale from "completely agree" (0) to "completely disagree" (4).

School-related stress ($α=0.66$) was measured by the following four experiences: work pressure, pressure to succeed, concentration difficulties, and understanding the teacher (3). Responses were scored on a three-point scale from "no" (1) to "yes, often" (3).

Anxiety/depression symptoms measured by the Hopkins Symptom Checklist 10-item version (HSCL-10) (27). The HSCL-10 ($α=0.87$) measures symptoms in the previous week. Psychometrics has been validated among subjects aged 16–24 years (28). The HSCL-10 was handled continuously in the multivariable analyses.

3.3.4   Sociodemographic factors

Socioeconomic status: Information about the participants parent's occupation was obtained and classified according to the International Standard Classification of Occupation, ISCO-88 (29), and later reclassified into five categories based on the parent with the highest rated occupation. Parental work reported "unknown" was recoded into the missing group. Family income: Adolescents reported their family's economic situation compared to other families on a four-point scale from "not well off" to "very well off."

Sami ethnicity was defined by participants having one or more of the following factors: Sami parentage or Sami language competence in parents, grandparents and the participants, or Sami self-labeling (30). The majority labeled themselves as Sami (n=261). The Sami ethnicity group was representative of the self-labeling group.

3.3.5   Data analysis

Pearson correlations was used to control for multicollinearity between explanatory and controlling factors by applying Cohen's criteria. Univariate analyses were carried out using descriptive statistics, Chi-square tests and one-way ANOVA. Chi-square test examines proportions between different groups and was chosen to describe group differences of musculoskeletal pain sites and adverse life events in percentage. One-way ANOVA can test for differences in the means of groups and was chosen to investigate if variations of the

independent variable (adverse life events, parental adverse events, individual adverse events, school related stress, parental support, peer support and self-efficacy) had a measurable effect on the dependent variable (number of musculoskeletal pain sites). Multiple linear regression is used due to a continuous dependent variable. We used hierarchical, linear multiple regression to examine the association between adverse life events and musculoskeletal pain controlling for sociodemographic factors (step 2), physical factors (step 3), and psychosocial factors (step 4/final model). The statistical significance level was set to .05 and analyzes were conducted on SPSS version 28.

4 Results

4.1 Prevalence of musculoskeletal pain and adverse life events in adolescents

Table 1 shows the self-reported prevalence of musculoskeletal pain and adverse life events. Headache was the most common reported pain site with a total of 50.8% reporting to have experienced headaches over the last 12 months (Table 1), followed by neck and shoulder pain, back pain and lastly arms, legs and knees pain. Except for pain in the extremities there was a significant gender difference at the $p \leq 0.001$ level, with females reporting more pain than males over the last 12 months (Table 1).

Conflict or fights with parents was the most reported adverse life event with a total of 80.4% reporting to have experienced it over the last 12 months, followed by peer problems with a total of 43.5%. All adverse life event factors, except serious illness or injury to yourself (p=.426), bullying (p=.148), and parental drug problems (p=.453), were significant at the $p \leq .001$ level (Table 1). Females reported significantly more adverse life events than males, except for bullying and exposure to violence. Notably, 7.1% of females reported to have experienced sexual assault during the last 12 months compared to only 1.9% of males.

4.2 **The association between musculoskeletal pain and adverse life events in adolescents**

Table 2 shows the number of musculoskeletal pain sites by associating factors. We found a linear relationship between the increasing prevalence of adverse life events and increasing number of musculoskeletal pain sites experienced over the last 12 months. This trend was similar for both genders. Conflict or fight with parents and peer problems were the variables strongest associated with multiple musculoskeletal pain sites. There were higher reports of musculoskeletal pain among those reporting serious disease or illness to someone close to you compared to serious illness or injury to yourself. Parental unemployment or social care and parental drug problems where not significant at the p<.001 level. Death to someone close to you and parental mental health problems were significant for females and the total sample, but not for males. The remaining factors were all significant at the p<.001 level.

Table 3 shows a linear relationship between the increasing number of pain sites and the associating factors. We found an increase in adverse life events, psychosocial factors and mental health problems, and a reduction in self-efficacy. The two different categorizes of adverse life events, parental adverse events and individual adverse events, show equally clear linear relationships with increasing number of pain sites. All factors, except peer support (p=.140), were significantly associated with musculoskeletal pain at the p ≤.001 level. There was an increasing level of adverse life events in those reporting more than one pain site, particularly for those reporting four pain sites.

Table 4 shows the multivariable analysis for the total sample and stratified by gender. The first model shows that adverse life events alone explained 7.5% of the variance for musculoskeletal pain (p ≤.001). For females the percentage of explained variance was 10.3% and significant at the p ≤.001 level, whereas for males the variance was 2.4% (p=.062). There was no change when adjusting for sociodemographic factors in step two. When adjusting for physical factors, in step three, there was no change for the total sample and for females with adverse live events being significant at the p ≤.001 level. There was a minor change for males (R^2 = 0.042), indicating that physical factors can explain an additional 1.1% of the variance for musculoskeletal pain. When adjusting for the psychosocial factors in step 4, there was a change for both genders and for the total sample. Adverse life events did not remain significant throughout the final model, neither for the total sample nor for the genders.

Adverse life events remained significant for the total sample and for females throughout the third model but was not significant for males. The final model, that included several psychosocial factors, accounted for 14.5% of the explained variance for the total sample. In the final model, adverse life events, physical injury, school-related stress and anxiety/depression were the strongest factors associated with musculoskeletal pain. Anxiety/depression was also the only significant factor at the $p \leq .001$ level.

5 Discussion

The aim of this study was to explore the prevalence of multisite musculoskeletal pain and several adverse life events, the association between the extent of adverse life events and multisite musculoskeletal pain, and potential gender differences, in adolescents.

5.1 Prevalence

The prevalence of multisite pain and adverse life events among the participants in the NAAHS has previously been explored by Eckhoff and Kvernmo (3), but it was in our interest to emphasize this. We found that the prevalence of musculoskeletal pain among adolescents was high. This is in agreement with Eckhoff and Kvernmo's findings (3) and several other studies (6-8). Females reported more musculoskeletal pain than males, comparable to other studies (2;3;6).

Half of the participants reported to have experienced headache over the last 12 months. Headache is a very common condition that most people will experience several times during their lives. Tension type headache is the most common type among children and adolescents and is often triggered by stress (31). It is therefore not surprising that this type of pain is common among adolescents. The second most reported pain site was shoulder and neck pain. In other studies low back pain and neck pain were found to be the most common pain site among adolescents (2;9). In the national cross sectional surveys conducted in Finland, Hakala et al. found that the prevalence of shoulder, neck and back pain had been increasing among adolescents from 1985 to 2001 (9). Neck and shoulder pain can often be related to stress or bad posture. This was the findings of Ozdemir et al., who found that body posture was related to musculoskeletal pain (7). In their study they also found that bad posture was correlated with physical activities and school grades.

The prevalence of multisite pain was also high. This is supported by several other studies (3;10;11;32). Kamaleri et al. found that localized pain was relatively rare, and that most people experiencing pain had several pain sites (10). This is an important finding considering that most musculoskeletal pains are diagnosed and treated as localized pain. There was a higher prevalence of females reporting to have experienced pain for all four pain sites in this study. This is also comparable to the findings in several other studies (3;10;11).

The prevalence of ACE among the participants was high and in agreement with the big Adverse life events study conducted in California (5), and with the systematic review conducted by Petruccelli (15). In both these studies many different negative health outcomes are mentioned as consequences of negative adverse life events in childhood. The high prevalence of ACE among the participants in this study is therefore important, emphasizing that ACE have become a serious public health problem. In our study, we found that conflict or fight with parents and peer problems were the most reported ACE. This might not be surprising considering the age of the participants. Most adolescents, one would assume, experiences some sort of conflict with their parents or friends during this time of life. The extent of conflict or fight should have been considered.

There was a significant gender difference when it came to the reporting of different ACE. In general, females reported more ACE than males, with the exception of exposure to violence and bullying. This is in agreement with previous studies (5;15). Females reported more peer problems and conflict or fights with parents than males, while males reported more bullying and exposure to violence. This might indicate that males to a bigger extent than females tend to get into physical conflicts. When it came to sexual assault, only 1.9% of males compared to 7.1% of females, reported to have experienced this over the last 12 months. Females experience sexual assault more often than males in the general Norwegian population (33). Exact statistics on the prevalence of sexual assault are not available as many victims do not disclose abuse, but it has been estimated that between 40% and 60% of all rape victims are under the age of 18, and that two-thirds of minors who have experienced sexual abuse were 12 to 17 years old when it first occurred (34). Finkelhor and colleagues found that the lifetime experience of 17 year old's with sexual abuse and sexual assault was 26.6% for girls and 5.1% for boys, and Emerson Hospital's Youth Risk Behaviour Survey found that 11% of the female subjects compared to 3% of the male subjects reported to had unwanted sexual contact with someone (34). The participants in our study are 15–16 years old which fits quite well

with the mentioned studies. Our findings are comparable to these studies and sadly, but not surprisingly, suggest a quite high prevalence of sexual assault among female adolescents. It is, however, surprising that females in general report more ACE than males, as there are not obvious reasons why females would more often experience parental unemployment or social care, serious illness or injury to yourself, serious disease or injury to someone close to you, death to someone close to you, parental mental health problems, parental financial problems, or parental drug problems. It could be that females in general are more aware and better at reporting adverse life events than males, suggesting a recall bias among the male participants.

5.2 Association between multisite musculoskeletal pain and adverse childhood experiences (ACE)

The main goal of this study was to explore the association between multisite musculoskeletal pain and the extent of ACE in adolescents controlling for sociodemographic, physical, and psychosocial factors.

We found a linear relationship between the increasing number of pain sites and the associating factors. There was an increasing prevalence of adverse life events for those reporting an increasing number of musculoskeletal pain sites. The reports of adverse life events were particularly high for the participants reporting four pain sites. This indicates that those experiencing more adverse life events also experience more musculoskeletal pain sites. This suggest that there is an important relationship between the two, and that ACE may lead to musculoskeletal pain in adolescents. This finding supports several previous studies (16-20). However, most of these studies discuss fibromyalgia syndrome and chronic pain as a result of adverse life events and not multisite pain specifically. Especially conflict or fight with parents, peer problems, and serious disease or injury to someone close to you was highly associated with multisite pain in our study. These are important findings, as all three adverse life events were common among the participants.

There was a similar linear relationship between increasing pain sites and increase in psychosocial factors and mental health problems, and a reduction in self-efficacy. School-related stress, lack in parental support, and anxiety/depression were especially important factors associated with multisite pain. Psychosocial factors have been found associated with

musculoskeletal pain in several other studies (3;8). This suggest that psychosocial factors during adolescents could have an important effect on musculoskeletal pain, or vice versa. It is a matter of concern that school-related stress seems to have such a big impact on the experience of musculoskeletal pain, and notable that females report more school related stress than males. As mentioned earlier, we found a high prevalence of shoulder and neck pain among the participants, comparable to previous studies (2;7;9), and it was especially high among females. Shoulder and neck pain is often associated with stress, and in the multivariable analysis we found that school-related stress was highly associated with musculoskeletal pain, especially for females. These findings could suggest that adolescents experience increasing amount of school-related stress, and that this might lead to more musculoskeletal pain.

In the multivariable analysis adverse life events could alone explain 7.5% of the variance for musculoskeletal pain in the total sample. Evaluation of the multivariable models explaining variance was done by Cohen's criteria where 2–13% is small, 13–26% is medium and ≥ 26% is large (35). The variance is thus small, but still emphasizes the importance of ACE when it comes to musculoskeletal pain and suggest an important association between musculoskeletal pain and adverse life events. This is in agreement with Imbierowicz and Egle who found that patients with fibromyalgia had more frequent and/or more severe adversities during childhood (16), and with McBeth and colleagues who found that persons with chronic widespread pain reported more ACE (17). Our findings are also comparable to the findings in the British Birth Cohort study, were both physical and social adversity prior to the age seven years was associated with an increase in the risk of chronic widespread pain (19). Also General et al (20), and Andreucci et al (8) found similar associations. These studies were however mostly conducted on adults, while our findings shed some new light on the important association between ACE and multisite pain in adolescents. This emphasizes the importance of early intervention when it comes to ACE. There was a notable gender difference on the association between musculoskeletal pain and adverse life events. For females' adverse life events could alone, significantly, explain 10.3% of the variance for musculoskeletal pain, whereas for males only 2.4% and not significantly. This gender difference is comparable to other studies (3;6;10;11).

Sociodemographic factors and physical factors had no mediating effect in the multivariable analysis. Physical factors had a minor mediating effect on the relationship for males, but not

for females. A possible explanation might be that males reported being more exposed to violence than females.

Psychosocial factors explained an additional 7.1% of the variance for the total sample and this indicates an important relationship between psychosocial factors and multisite musculoskeletal pain in adolescents. The psychosocial factors had a mediating effect on the association between ACE and musculoskeletal pain for both males and females separately. This is supported by the findings of Eckhoff and Kvernmo who found a strong dose-response association between widespread musculoskeletal pain and psychosocial factors (3). Also Hoftun and colleagues found that symptoms of anxiety and depression showed strong association with pain, including multisite pain (11). In their three-year follow-up study, Lien et al. found a strong association between pain at 15/16 years and mental distress at 18/19 years of age suggesting that musculoskeletal pain in adolescents can lead to mental distress later in life (36). These are important findings, accentuating that clinicians should take both pain complaints and signs of mental distress among adolescents more seriously and examine for potential psychosocial problems.

The final model explained 14.5% for the total sample, 7.1% for males and 17.1% for females of the total variance for musculoskeletal pain. For males, psychosocial factors could explain an additional 2.9% of the total variance, and for females an additional 7.3%. This change suggests that psychosocial factors had a stronger impact for females. However, the reduction for adverse life events was about the same for males and females, suggesting that psychosocial factors have a similar mediating effect on the association between multisite musculoskeletal pain and adverse life events for both genders. Anxiety/depression was the variable most associated with musculoskeletal pain for males, followed by adverse life events and sedentary activity. For females' school-related stress was the variable most associated with multisite pain, followed by anxiety/depression and adverse life events. Anxiety and depression where found by many authors to have an important association with musculoskeletal pain for both males and females (3;11). Hoftun and colleagues found that boys with symptoms of anxiety and depression had 5.3 times higher odds of multisite pain, and girls had 4.5 times higher odds of multisite pain compared to those without anxiety and depression (11). High amounts of sedentary activity have also been shown to have an important association with multisite pain (37-39). The difference between males and females considering school-related stress was quite large, suggesting that females are more affected by

this factor than males. Females also reported a higher prevalence of school-related stress. These are importing and interesting findings suggesting that females are more troubled with school-related stress and their consequences.

Anxiety/depression, school-related stress and sedentary activity were important factors associated with multisite musculoskeletal pain. Adverse life events appeared to be an important factor, but the association with multisite musculoskeletal pain may in part be mediated by other psychosocial factors. This is an important finding comparable to existing literature where psychosocial factors (3;11;36) and sedentary activity (37-39) where found to have the most important associations with multisite musculoskeletal pain. Our study suggests that the consequences of adverse life events in childhood could be multisite musculoskeletal pain and that symptoms could appears already during adolescence. Our findings emphasize the findings of the big ACE study from California, were ACE appears to be a risk factor for health problems and illnesses in general (5). These are important findings emphasizing the necessity of early intervention and treatment by pediatricians and other clinicians in contact with children and adolescents.

5.3 **Study strengths and weaknesses**

There were several strengths with this study. One important strength was that several important ACE and psychosocial factors associated with musculoskeletal pain was incorporated in an integrated model. Another strength was that the study had a high participant rate and a high number of participants from all the junior high schools in North Norway. It is known that non-responders might be more troubled than responders, still the missing data were few regarding each question which suggest that the questions were well understood. This contributes to the internal validity of the study.

There were also weaknesses to recognize with this study. No causal direction of the association could be described due to the study's cross-sectional design and when it comes to psychosomatic problems reverse causality is always possible. This study also relies on self-reports and there was thus a risk of information bias. There was also a risk of recall bias as the dependent pain question had the specification of one year, and it is likely that answers truly represent a shorter time period of 3-6 months. Some of the scales incorporated in the study did not have a defined time period and the HSCL-10 measured only anxiety/depression

symptoms during the last week. Some scales from the study are not frequently used in other studies, making it hard to replicate our findings. One might also argue that some of the adverse life events incorporated in the study was a little too broad. For example, conflict or fights with parents and peer problems. These variables, some would argue, are too common among adolescents to be considered adverse life events. The questions may also be considered unspecific as most of them were yes or no questions. These types of questions give concrete answers but says little of the extent. Also, the answer "several times" is objectively vague and could have been interpreted different among the participants. It does indicate some regularity and seriousness of pain and thus the importance of multisite pain is still emphasized. The data set used in the study is from 2003–2005 which means it is almost 20 years old. This adds the question if the study is still even relevant as big societal changes have happened during the last two decades.

The explained variance of the multivariable model might be considered low. However, explained variance is a relative value, dependent on the nature of the associations examined. For most of the factors in this study it was not possible to say whether they appeared before or after musculoskeletal pain which makes it difficult to decipher whether the psycho- social factors are confounders or mediators. If they were mediators, then the multivariable model is at risk of over-adjustment bias.

5.4 Clinical implications

This study suggests an association between ACE and multiple musculoskeletal pain sites presented by adolescents. This implies that multisite musculoskeletal pain may be a result of ACE. It also suggests an important gender difference, as females report both more adverse life events, musculoskeletal pain, and psychosocial factors than males. Physicians meeting young people should ask the patient about different adverse life events as prevention and treatment at an early age could prevent the development of multisite musculoskeletal pain later in life.

6 Conclusion

We found a high prevalence of both musculoskeletal pain and ACE among adolescents in this study especially for females. Participants reporting more than one pain sites reported an increasing proportion of ACE, with high reports for the participants reporting four

musculoskeletal pain sites. This shows an important association between the extent of ACE and the experience of multisite musculoskeletal pain. Psychosocial factors seemed to have a mediating effect on the association, and anxiety/depression symptoms and school related stress were the most important psychosocial factors associated with musculoskeletal pain.

7   References

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8 Tables

8.1 Table 1. Prevalence of musculoskeletal pain and adverse life events by gender (%)

	N	Male	Female	Total	Gender diff. (X_2)
Site of pain					
Head	4728	38.5	63.0	50.8	282.593[p<.001]
Neck/shoulder	4667	27.7	42.7	35.2	115.210[p<.001]
Arms/legs/knees	4649	30.7	33.2	31.9	3.337[p=.068]
Back	4669	31.1	37.2	34.1	19.053[p<.001]
Adverse life events					
Parental unemployment or social care	4808	9.7	10.8	10.3	1.570[p=.210]
Serious illness or injury to yourself	4813	7.5	8.2	7.8	.633[p=.426]
Serious disease or injury to someone close to you	4811	28.3	39.5	33.9	66.560[p<.001]
Death to someone close to you	4803	23.6	27.9	25.8	11.576[p<.001]
Sexual assault	4805	1.9	7.1	4.5	74.704[p<.001]
Bullied	4823	15.4	13.8	14.6	2.094[p=.148]
Exposed to violence	4787	22.0	13.8	17.9	53.844[p<.001]
Conflict or fights with your parents	4806	72.3	88.3	80.4	194.499[p<.001]
Parental mental health problems	4780	6.0	10.7	8.4	33.409[p<.001]
Peer problems	4770	29.6	57.1	43.5	367.570[p<.001]
Parental financial problems	4783	18.9	28.4	23.7	59.985[p<.001]
Parental drug problems	4783	4.1	4.6	4.3	.564[p=.453]

Note: Analysis was carried out using Chi-square test.

8.2 Table 2. Number of musculoskeletal pain sites by adverse life events and stratified by gender (%)

| Adverse life events (%) | N | Number of musculoskeletal pain sites | | | | | | Statistics |
		0	1	2	3	4	Total	Value
Parental unemployment or social care	4512	7.9	10.1	11.4	11.7	13.4	10.3	14.481[p=.006]
Males	2262	7.6	10.9	10.9	10.2	12.9	9.8	7.388[p=.117]
Females	2250	8.5	9.1	11.9	12.5	13.7	10.7	8.644[p=.071]
Serious illness or injury to yourself	4516	4.9	5.1	8.8	11.6	16.3	7.7	83.847[p<.001]
Males	2264	4.8	5.6	8.6	14.9	12.9	7.2	36.601[p<.001]
Females	2252	5.1	4.5	9.1	9.8	18.2	8.2	54.212[p<.001]
Serious disease or injury to someone close to you	4508	24.7	30.7	36.1	44.5	50.6	33.8	136.651[p<.001]
Males	2260	21.6	26.9	32.6	37.0	43.2	28.1	44.886[p<.001]
Females	2248	29.5	35.0	39.1	48.6	54.5	39.4	63.679[p<.001]
Death to someone close to you	4506	20.7	25.3	27.1	28.6	33.5	25.6	33.332[p<.001]
Males	2258	20.9	24.4	24.5	25.9	27.3	23.6	5.238[p=.264]
Females	2248	20.2	26.4	29.3	30.1	36.7	27.6	26.569[p<.001]
Sexual assault	4506	2.3	2.8	3.5	7.5	13.0	4.3	107.853[p<.001]
Males	2265	1.2	1.6	1.1	2.8	7.1	1.8	26.674[p<.001]
Females	2241	4.1	4.3	5.6	10.1	16.2	6.9	54.622[p<.001]
Bullied	4515	9.5	12.9	16.5	21.7	20.8	14.6	69.427[p<.001]
Males	2262	9.7	15.2	17.5	25.6	21.4	15.1	42.716[p<.001]
Females	2253	9.3	10.2	15.6	19.6	20.5	14.1	36.725[p<.001]
Exposed to violence	4481	11.7	15.1	17.4	24.7	33.3	17.5	124.197[p<.001]
Males	2236	14.0	19.0	24.1	38.7	41.5	21.5	98.505[p<.001]
Females	2245	8.1	10.6	11.7	17.1	29.1	13.6	76.569[p<.001]
Conflict or fights with your parents	4489	73.2	77.1	85.5	88.0	90.2	80.4	111.980[p<.001]
Males	2245	65.1	71.2	79.3	81.9	81.2	72.3	46.292[p<.001]
Females	2244	86.2	83.9	90.7	91.3	95.0	88.5	31.578[p<.001]
Parental mental health problems	4465	5.7	6.3	8.2	12.1	17.3	8.3	70.972[p<.001]
Males	2234	5.1	5.2	6.8	7.0	9.4	5.9	5.729[p=.220]
Females	2231	6.6	7.6	9.4	14.8	21.6	10.7	53.677[p<.001]
Peer problems	4458	32.0	38.7	45.9	57.9	62.1	43.0	187.683[p<.001]
Males	2226	22.3	28.3	33.6	41.4	42.6	29.4	48.889[p<.001]
Females	2232	47.4	50.8	56.3	67.0	72.1	56.6	67.901[p<.001]
Parental financial problems	4471	16.5	20.0	25.6	29.9	41.7	23.4	131.975[p<.001]
Males	2236	15.3	16.1	20.0	25.4	32.8	18.5	33.885[p<.001]
Females	2235	18.4	24.5	30.4	32.4	46.3	28.4	73.221[p<.001]
Parental drug problems	4469	3.8	3.6	4.5	3.8	7.6	4.3	13.264[p=.010]
Males	2234	3.7	3.3	4.7	4.2	6.7	4.0	4.172[p=.383]
Females	2235	4.1	4.0	4.4	3.6	8.1	4.5	9.218[p=0.56]

Note: Analysis was carried out using Chi-square test.

8.3 Table 3. Number of musculoskeletal pain sites by associated factors; adverse life events, parental adverse events, individual adverse events, school related stress, parental support, peer support and self-efficacy

	Number of pain sites							Statistics
	N	0	1	2	3	4	Total	F
Adverse life events	4280	2.12	2.48	2.87	3.42	4.00	2.72	124.418 p<.001
Parental adverse events*	4415	1.07	1.17	1.35	1.40	1.69	1.26	50.359 p<.001
Individual adverse events**	4426	0.28	0.36	0.46	0.65	0.84	0.44	65.460 p<.001
School related stress	4508	6.53	6.89	7.48	8.07	8.38	7.20	129.444 p<.001
Parental support	4470	6.76	6.92	7.26	7.92	8.10	7.19	31.830 p<.001
Peer support	4475	5.64	5.61	5.54	5.60	5.85	5.63	1.731[p=.140]
Self-efficacy	4455	15.18	14.89	14.72	14.16	14.00	14.76	25.777 p<.001

Note: Analysis was carried out using one-way ANOVA.
* Includes parental unemployment or social care, conflict or fights with your parents, parental mental health problems, parental financial problems, parental drug problems
** Includes serious illness or injury to yourself, sexual assault, bullied, exposed to violence

8.4 Table 4. Associations between adverse life events and musculoskeletal pain in adolescents controlling for sociodemographic factors, physical factors, and psychosocial factors

	Musculoskeletal pain		
	Total sample	Males	Females
Step 1 – Adverse life events			
Adverse life events	**0.282 (<.001)**	**0.181 (.062)**	**0.332 (<.001)**
R2	*0.075 (<.001)*	*0.024 (.062)*	*0.103 (<.001)*
Step 2 – Sociodemographic factors			
Adverse life events	**0.272 (<.001)**	**0.174 (.072)**	**0.343 (<.001)**
Gender	0.049 (.453)	-	-
Socioeconomic status	-0.044 (.483)	-0.161 (.097)	0.037 (.656)
Sami	-0.029 (.649)	0.004 (.969)	-0.091 (.285)
R2	*0.069 (<.001)*	*0.031 (.099)*	*0.099 (<.001)*
Step 3 – Physical factors			
Adverse life events	**0.268 (<.001)**	**0.161 (.097)**	**0.342 (<.001)**
Gender	0.089 (.196)	-	-
SES	-0.036 (.581)	-0.160 (.110)	0.028 (.749)
Sami	-0.037 (.562)	-0.018 (.856)	-0.088 (.300)
Physical injury	0.110 (.108)	0.037 (.713)	0.139 (.112)
Sedentary activity	0.078 (.224)	0.181 (.067)	0.021 (.804)
Physical activity	-0.012 (.857)	0.093 (.352)	-0.074 (.418)
R2	*0.074 (<.001)*	*0.042 (0.110)*	*0.098 (.005)*
Step 4 – Psychosocial factors			
Adverse life events	**0.121 (.089)**	**0.074 (.484)**	**0.175 (.081)**
Gender	0.006 (.930)	-	-
SES	-0.002 (.970)	-0.117 (.252)	0.064 (.462)
Sami	-0.029 (.645)	-0.039 (.698)	-0.071 (.395)
Physical injury	0.151 (.025)	0.084 (.421)	0.171 (.046)
Sedentary activity	0.030 (.634)	0.110 (.286)	-0.030 (.721)
Physical activity	-0.026 (.697)	0.019 (.856)	-0.060 (.510)
Self-efficacy	0.013 (.851)	0.119 (.276)	-0.064 (.510)
Parental involvement	-0.023 (.746)	0.055 (.630)	-0.071 (.497)
Parental support	-0.027 (.719)	-0.046 (.684)	0.014 (.900)
Peer support	-0.058 (.375)	-0.103 (.360)	-0.026 (.772)
School-related stress	0.139 (.048)	0.063 (.556)	0.236 (.017)
Anxiety/depression symptoms	0.294 (<.001)	0.257 (.038)	0.187 (.116)
R2	*0.145 (<.001)*	*0.071 (.086)*	*0.171 (<.001)*

Note: Statistics done by hierarchical, linear multiple regression. Standardized beta values presented.