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Doctoral thesis

NTNU
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Thesis for the Degree of Philosophiae Doctor
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Sammendrag på norsk

Livsløps- og generasjonsstudier av muskel- og skjelettsmerter i HUNT-studien

Kroniske muskel- og skjelettsmerter er blant de fremste årsakene til redusert livskvalitet, sykefravær og uførhet i den vestlige verden. Forekomsten er høy også blant ungdom og unge voksne. I tillegg til den individuelle belastningen, har kroniske muskel- og skjelettsmerter en stor samfunnsøkonomisk betydning relatert til behandling, arbeidsevne og sykefravær. Kunnskap som kan gi mulighet for bedre forebygging og behandling er derfor viktig. Studier har vist at både miljømessige og arvelige faktorer spiller en rolle for utviklingen av kroniske muskel- og skjelettsmerter, og familiestudier har vist en sammenheng i smerte mellom foreldre og deres barn. Det er likevel uklart om denne sammenhengen vedvarer inn i barnas voksenliv.

Ved bruk av data fra Helseundersøkelsen i Nord-Trøndelag (HUNT) koblet til Familieregisteret hos Statistisk Sentralbyrå har vi undersøkt hvorvidt det finnes en sammenheng mellom foreldre og deres voksne barn når det gjelder forekomst av kroniske muskel- og skjelettsmerter. Vi har også studert foreldre-barn sammenhenger i smerte lokaliserte til nakke/øvre rygg og/eller korsrygg for å vurdere om disse assosiasjonene er spesifikke når det gjelder smertelokalisasjon. I tillegg har vi prospektivt undersøkt om barnas risiko for smerte, assosiert med foreldresmerte, kan være modifisert av barnas kroppsmasseindeks og fysiske aktivitet.

Resultatene fra disse familiestudiene viste at kroniske muskel- og skjelettsmerter blant både mødre og fedre er assosiert med høyere forekomst av kroniske muskel- og skjelettsmerter hos deres voksne barn. Assosiasjonene var sterkest når begge foreldrene rapporterer smerte. Vi observerte ingen klar spesifisitet i sammenhengene knyttet til lokalisasjon, men dersom foreldrene hadde smerte både i nakke/øvre rygg og korsrygg var det assosiert med høyere forekomst av smerte blant barna sammenlignet med smerte i bare en lokalisasjon. Resultatene fra den prospektive studien tyder på at normal kroppsvekt reduserte risikoen for å utvikle kroniske muskel- og skjelettsmerter blant barn av foreldre som rapporterte smerte, mens den modifiserende effekten av fysisk aktivitet var mindre klar.

Studiene bidrar til kunnskap om familiære sammenhenger av kroniske muskel- og skjelettsmerter, og at slike sammenhenger er til stede også når barna er voksne. Dette kan være av betydning for valg av forebyggende strategier og terapeutiske tilnærminger for kroniske muskel- og skjelettsmerter. I tillegg tyder resultatene på faktorer som overvekt/fedme og fysisk aktivitet kan påvirke risikoen, særlig i familier som er rammet av kroniske muskel- og skjelettsmerter.

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Finansiering: Samarbeidsorganet Helse Midt-Norge RHF og NTNU

English summary

A life course and intergenerational approach to the study of musculoskeletal pain: The HUNT Study

Chronic musculoskeletal pain is among the leading causes of reduced quality of life, sick leave, and disability in Western industrialized countries, with a high prevalence, also among adolescents and young adults. In addition to the individual costs of chronic musculoskeletal pain, there is a substantial economic burden to the society related to treatment, work ability, and sickness absence. Thus, knowledge leading to improved prevention and treatment is important. It has been shown that both environmental and heritable factors have a role in the development of chronic musculoskeletal pain, and family studies have shown associations in pain between parents and children. However, it is not clear if this association persists into the offspring's adult life.

Based on Data from the HUNT Study, linked with the Family registry at Statistics Norway, we investigated potential associations between parental chronic musculoskeletal pain and occurrence of chronic musculoskeletal pain in their adult offspring. We also investigated parent-offspring associations of pain localized to the neck/upper back and/or low back in order to assess if the specificity of these associations in terms of pain localization. Additionally, we have prospectively examined if the risk of offspring pain associated with parental pain is modified by offspring body mass index and physical activity.

The results from these family-based studies showed that chronic musculoskeletal pain in mothers and fathers was consistently associated with higher occurrence of chronic musculoskeletal pain in the adult offspring, especially if both parents reported pain. We did not observe any clear specificity in the associations regarding pain localizations. However, concurrent neck/upper back and low back pain in parents was more strongly associated with occurrence of pain in the offspring compared to pain in only one of the localizations. The results from the prospective analyses showed that a normal body weight reduced the risk of musculoskeletal pain in offspring of pain-afflicted parents, while a modifying effect by physical activity was less clear.

The results from our studies contribute to the understanding that chronic musculoskeletal pain track across generations, also into offspring's adulthood. This could be of significance when considering different prevention strategies and therapeutic approaches to chronic musculoskeletal pain. Additionally, the results also indicate that factors like overweight/obesity and physical activity may influence the risk, especially in families with a history of chronic musculoskeletal pain.

To
Tonje and Heine

Contents

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This work was financially supported by a grant from the Liaison Committee between the Central Norway regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU). The research is based on data from The HUNT Study, linked with the Family Registry at Statistics Norway. I acknowledge the important work of many people who have contributed to these data. The work was carried out during the years 2011 to 2016 at the Department of Human Movement Science, and at the Department of Public health and general Practice, NTNU.

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I am very grateful to my co-author Professor Andreas Holtermann for his valuable contributions to Paper III, and for being an excellent host during our visits to *Det Nationale Forskningscenter for Arbejdsmiljø* in Copenhagen. I am also very grateful to my co-author Professor Ottar Vasseljen for important and helpful feedback and contributions on Paper II.

I would like to especially thank my "officemates" Kirsti Vik Hjerkind, Børge Moe, and Eivind Schjelderup Skarpsno for many productive discussions, both professional and personal. They have made the everyday life in the office very joyful.

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Last but not least, I want to thank my partner Tonje, for her love and support, and our wonderful son Heine, for making me feel so grateful and proud.

Trondheim, June 2016

Ragnhild Lier

List of papers

This thesis is based on the following publications:

Paper I: Lier R, Nilsen TI, Mork PJ. (2014). Parental chronic pain in relation to chronic pain in their adult offspring: family-linkage within the HUNT Study, Norway. *BMC Public Health*, 14(797):1471–2458.

Paper II: Lier R., Nilsen TIL, Vasseljen O, Mork PJ. (2015). Neck/upper back and low back pain in parents and their adult offspring: Family linkage data from the Norwegian HUNT Study. *European Journal of Pain*, 19: 762–771.

Paper III: Lier R, Mork PJ, Holtermann A, Nilsen TIL. (2016). Familial Risk of Chronic Musculoskeletal Pain and the Importance of Physical Activity and Body Mass Index: Prospective Data from the HUNT Study, Norway. *PLoS ONE*, 11(4): e0153828.

1 Introduction

Chronic musculoskeletal pain (CMP) is among the leading causes of reduced quality of life, sick leave, and disability in Western industrialized countries, and the economic burden to the society is substantial [1-3]. CMP is one of the most common reasons to seek medical consultation [4, 5], and in Norway, pain in the musculoskeletal system accounted for ~46% of all sickness leave of longer duration than 16 days in 2002, amounting to an estimated direct cost of ~21 billion NOK [6]. Additionally, a study from 2002 showed that 80% of the general Norwegian population reported musculoskeletal complaints [7]. In the Global Burden of Disease Study 2010, musculoskeletal pain was one of the main contributors to "disability-adjusted life years" [1] and "years lived with disability" [2], with low back and neck pain being among the leading specific causes. The high global burden of neck and low back pain is also reported elsewhere [8-10]. Recent reviews indicate that the global mean prevalence of low back pain between 1980 and 2009 was approximately 23%, while the mean prevalence for neck pain was ~25%. In general, the prevalence of both low back and neck pain is higher in women, in high-income countries, and in urban areas [11, 12]. More specific, the prevalence of CMP in the general adult population in Norway is substantially higher among women than men for moderate to severe pain in neck (25 vs. 11%), shoulders (27 vs. 13%), and low back (23 vs. 14%) [7]. The large proportion of people suffering from CMP calls for increased understanding of causes and mechanisms, and, in turn, successful preventive strategies [13].

1.1 Chronic musculoskeletal pain

CMP is a complex sensory and emotional experience that varies between individuals due to pain perception, attention or emotional states, among others [14]. In general, acute pain is

considered to be a normal physiological response to a stimulus associated with for example surgery, trauma or illness [15]. However, acute pain could develop into a more chronic state, and it is not completely understood why this happen in some individuals and not in others [16]. The most commonly used definition of CMP is pain that lasts longer than the expected healing time or more than a 3-months period. Pain that becomes chronic is considered to be a disease in itself with serious clinical, social, psychological, and economic impact [17]. However, the definition of CMP varies between studies, and this is evident by the difference in prevalence reported. For instance, around 33% of a community sample reported having experienced low back pain in the past month, while between 39% and 67% reported an episode during the past 12 month [18]. Musculoskeletal pain conditions are characterized by a gradual onset. Further, such conditions follow a complex episodic course with remittance and recurrence of symptoms. For example, a history of previous low back pain was found to increase the risk of a new episode of low back pain compared to those with no low back pain in the past [19]. Thus, it is uncertain whether measures of pain captures initial onset of the condition (incidence) or the onset of a new episode of an already prevalent condition. Therefore, prevalence has been suggested to be the preferred measure for the burden of generalized musculoskeletal pain conditions [20].

Several underlying mechanisms can be operative in chronic pain states: peripheral/nociceptive (for example osteoarthritis, rheumatoid arthritis, or cancer pain), peripheral neuropathic (i.e. damage or dysfunction of peripheral nerves), or central neuropathic (for example fibromyalgia, tension headache, or irritable bowel syndrome). CMP has often been considered as an effect of some ongoing peripheral nociceptive input, for instance damage or inflammation in the region of the body where the individual is experiencing pain. However, recent findings indicate that the central nervous system also play an important role in determining which nociceptive input being detected by sensory nerves in

the peripheral tissues will lead to the perception of pain [21]. For example, an individual with osteoarthritis may have centralized the pain even though the underlying mechanism of the pain is located in the peripheral nervous system. This suggests that the central nervous system is more prominently involved in maintaining the pain than the peripheral nervous system. Thus, the precise mechanisms for CMP states are unclear, and this has implications for prevention and treatment [21].

Multiple musculoskeletal pain sites are frequent among adults [22] and adolescents [23]. More precisely, a review of prevalence studies done by McBeth and Jones indicated that one-fifth of adult populations reports widespread chronic pain (fibromyalgia) [18]. An increasing number of pain sites is associated with increased risk of poor prognosis and poor overall function [24, 25]. In other studies it has also been indicated a continuum between reporting of several musculoskeletal pain sites and the later development of chronic widespread pain [26, 27]. It has been shown that 40% of people reporting musculoskeletal complaints in neck and low back also have pain at other locations. Those who reported low back as the primary pain site had a high probability of co-complaints in other spinal sites (i.e. neck, shoulders, or upper back), as well as pain across the entire body, compared to persons with other primary pain sites [28]. Data from Norway show that 31% of persons with low back pain also reported pain in up to four other body areas, suggesting that one of the reasons why treatment of low back pain have limited success is the possibility that the patients suffer from widespread pain [29]. A similar tendency was also shown in a study of neck pain [30].

1.2 Risk factors for chronic musculoskeletal pain

It is well known that CMP is more frequently reported among women compared to men, and that the prevalence of CMP increases up to about 65 years of age [3]. On the other hand, a

recent study among Finnish adolescents showed that musculoskeletal pain is substantial in a young population as well. The results from this study showed that 43% of the boys and 63% of girls at age 16, and 61% of boys and 81% of girls at age 18, reported musculoskeletal pain at two or more body sites during the last 6 months [31].

Low education, depression, anxiety, sleep disturbance, and manual work are additional risk factors for CMP [32, 33]. It has been shown that preexisting anxiety and depression is associated with increased risk for incident musculoskeletal disorders [34]. More specifically, individuals with symptoms of depression have an increased risk of developing low back pain in the future [35]. There is also evidence of an association between sleep problems and risk for CMP in the low back and neck/shoulders [36]. Further, psychosocial aspects of work such as job demands, control, support and satisfaction, imbalances between effort and reward, monotony of occupational tasks have also been associated with CMP [37]. Haukka and colleagues [38] found that high physical work load predicted persistence of multisite musculoskeletal pain, whereas obesity and low leisure time physical activity was associated with increased prevalence. Physical work demands were classified according to heavy lifting, working with hands above the shoulder level, repeated bending and straightening of the elbow, repeated wrist-hand movement and kneeling, squatting or climbing stairs [39]. Heavy domestic physical activity (i.e. vigorous gardening/heavy yard work) has also been associated with low back pain [40].

It is well established that physical inactivity [3, 41-43] and obesity [44-46] represent independent risk factors for CMP. Prospective studies have shown that regular physical exercise can prevent development of symptoms in the neck/shoulders [47-49], low back [50, 51], and upper limbs [52]. Likewise, individuals who maintain a normal body weight have lower risk of chronic pain in the neck/shoulders [41], low back [41] and upper limbs [52] compared to obese individuals. These lifestyle factors may be of particular importance in

individuals that are susceptible to develop CMP due to for example a genetic predisposition. Regular leisure time physical exercise is recommended to prevent obesity and reduce risk of several chronic diseases in adulthood [53]. However, there is conflicting evidence concerning the relation between leisure time physical exercise in adolescents and young adulthood and prevention of CMP, since both inverse [23] and positive [54] associations have been reported, as well as no association [55, 56]. A recent study indicates that the relation may be non-linear, with increased risk among both those who perform very vigorous physical activity and those who are sedentary [57]. At present, there is limited knowledge about long-term effects of regular exercise in adolescence and young adulthood on risk of CMP in later adulthood [58]. Exercise habits during youth are likely to persist into adulthood and may also be amplified by parental encouragement [59]. Thus, early established exercise habits may have profound consequences on risk of developing overweight or obesity during adulthood. It has been shown that overweight/obesity represented an independent risk factor for future development of fibromyalgia among adult women [60]. The study also showed that overweight or obese women who exercised ≥1 hour per week had >30% lower risk of chronic pain compared to overweight and obese women who were inactive. Thus, exercise may to some extent compensate for the adverse effect of overweight and obesity on future development of CMP.

Several well-known risk factors for CMP are modifiable, such as obesity, physical inactivity, and physical work demands. A more thorough understanding of familial aggregation of CMP may provide a foundation for implementing preventive strategies by identifying families and persons at high risk of CMP.

1.3 Family studies

Family studies, or intergenerational studies, include participants from more than one generation within the same family. This could for instance be parents and their children. This

study design is relevant in understanding the effect of exposures across generations, and has the potential to explore possible underlying associations in life course epidemiology [61]. They can also constitute a foundation for population-wide prevention strategies by identifying families and persons at high risk, because risk factors that cluster within families are often modifiable [62].

Familal associations of CMP indicate a heritable component, and results from twin studies provide convincing evidence of genetic susceptibility for CMP in different spinal regions, particularly for concurrent pain in the neck and low back [63-66]. Twin studies are useful for disentangling the relative contribution of genetic and environmental factors to the development of CMP. However, to optimize prevention and management of CMP it is equally relevant to gain knowledge about the overall extent of the transmission of CMP across generations in the general population. Idiopathic pain syndromes such as fibromyalgia and headache have been shown to strongly co-aggregate in individuals and families [67]. Further, it has been suggested sets of genes that have an effect on an individual's pain sensitivity and their increased likelihood of developing one or more chronic pain states. In addition, as with most illnesses that may have a familial or genetic underpinning, environmental factors may trigger the development of CMP [21].

Some studies have shown that CMP may cluster within families [68-71], while conflicting results have been reported for parent-offspring associations of pain. A study of UK schoolchildren and their parents found no evidence of parent-offspring associations of pain [72], whereas occurrence of chronic non-specific pain in Norwegian adolescents was positively associated with parental chronic pain [73]. Both these studies investigated a young offspring population, i.e. offspring aged 12-18 years. CMP is likely to develop over several years and it is therefore conceivable that parent-offspring associations become stronger when the offspring reach adulthood. Despite the fact that adult offspring create their own

environment outside their family, it has been shown that intergenerational transmissions of lifestyle behaviour manifests in late adolescence and extends into adulthood [74, 75]. Thus, if the development of CMP depends on gene-environment interactions, it is possible that the parent-offspring associations become stronger with increasing offspring age.

The genetic influence is suggested to be more pronounced in severe and activity-interfering pain conditions [70, 76]. It is plausible that offspring who carry an inherited susceptibility to develop CMP may be even more vulnerable to other risk factors for CMP. Moreover, there are conflicting evidence regarding the sex-specific heritable influence on CMP from twin studies [63, 64, 76], whereas results from family studies show that familial clustering of CMP is mainly explained by associations between female relatives [69, 77]. The "developmental origins of adult disease" hypothesis states that adverse influences early in development, and particularly during intrauterine life, can result in permanent changes in foetal physiology and metabolism, and that these changes potentially can result in increased risk of diseases, such as coronary heart disease, in adulthood [78]. For instance, low birth weight can be a proxy measure of poor intrauterine environment, and in a study by Mallen and colleagues [79] there were indications of associations between pain status and low birthweight. As a result of this it may be assumed that the mother-offspring associations of CMP could be stronger than father-offspring associations. Contradictory, another study did not find any associations between low birth weight and musculoskeletal pain. However, there were some indications of an association between low 5-minute Apgar score and chronic pain [80].

Whether or not the risk leads to disease may depend on the interaction between genes and environmental influences in a life course (the "developmental origins of adult disease" hypothesis) [78]. As mentioned, twin studies are useful in order to decide the relative contribution of genetic and environmental factors to the development of CMP. On the other

hand, it is still unknown how much of associations of pain among other family members than among twins that can be attributed to environmental effects. Especially, it is difficult to decide how much is due to maternal genetic effects (i.e. intrauterine environment) and fetal genetic effects (i.e. effects due to fetal genes transmitted from both the mother and father) [81]. Anyhow, one may speculate that the occurrence of CMP in the adult offspring is strongly influenced by genetic factors in interplay with environmental factors. It has been suggested that children of parents who display pain behavior adopt similar behaviors and are also more likely to report pain than their peers [82, 83]. As a result of this, it may be assumed that the parent-offspring association is more pronounced if both parents have a history of CMP compared to only one parent.

It may be speculated that offspring who carry an inherited susceptibility to develop pain are more vulnerable to other risk factors for pain, such as physical inactivity [3, 41-43], obesity [44, 45, 84], or a summation of life events [85]. Additionally, a positive family history of CMP has been shown to predict disability level and the extent of body area affected by CMP [83]. The variation in individual basal pain sensitivity and reduced pain-inhibitory capacity could act as a diathesis for CMP. Studies have shown that children of parents who display pain behavior learn to display similar pain behavior and are also more likely to report pain [82, 83, 86]. Moreover, offspring with parents reporting a history of musculoskeletal pain syndromes could be genetically predisposed to the development of a chronic condition of such syndromes, whereas offspring with parents reporting no pain are not [87, 88]. In this case, genetically predisposition is required for developing CMP. Thus, associations found in family studies of pain are assumingly explained by the way genetic and environmental factors interact [89, 90], and not solely a result of either of the two.

Most previous intergenerational studies have investigated the relation of pain between parents and young children and adolescents [72, 73], and there is a lack of large scale

population based studies of the intergenerational association in pain between parents and their adult offspring. Musculoskeletal pain conditions are characterized by a gradual onset, and are often established by early adult life [20]. Thus, associations between parents and their young offspring may be underestimated. It could be hypothesized that the offspring become more similar to their parents in health and lifestyle factors as they approach adulthood themselves. Because of this it is conceivable that they are more likely to take on lifestyle habits common to their parents, i.e. level of physical activity, diet, education, or profession, in their adult life [84]. Additionally, possible associations could be less influenced by offspring and parents sharing environment since the offspring are more likely to live apart from their parents when they are adults [91].

2 Aims

The aim of this thesis was to investigate intergenerational relations of CMP between parents and their adult offspring. We have used data from the HUNT Study, which is a large longitudinal population based study of Norwegian men and women, and retrieved parental and offspring information from separate surveys of the HUNT Study. A linkage with the Family Registry at Statistics Norway was used to establish family relations between parents and their offspring.

More specifically, we aimed at the following:

- To investigate the independent and combined association of maternal and paternal CMP with occurrence of CMP in their adult offspring, and if the putative parent-offspring association for CMP is modified by parental and offspring age and sex (Paper I).

- To investigate the mother-offspring and father-offspring associations of CMP localized in the neck/upper back and/or low back (spinal pain), to examine specificity of CMP (i.e. association between the same location of CMP in parents and offspring), and to investigate if presence of chronic spinal pain in both parents could be more detrimental than having only one pain-afflicted parent (Paper II).
- To prospectively examine the risk of offspring CMP associated with parental CMP, and to examine if this risk is modified by offspring body mass index (BMI) and physical activity (Paper III).

3 Material and methods

The HUNT Study is a large population based health study conducted within the county of Nord-Trøndelag, Norway, that has been carried out in three consecutive surveys, first in 1984-86 (HUNT1), then in 1995-97 (HUNT2), and last in 2006-08 (HUNT3). At all three surveys, all residents age 20 years and older were invited to participate, and information on lifestyle and health related factors were collected by questionnaires and clinical examination. More detailed information about the HUNT Study can be retrieved from http://www.hunt.ntnu.no/edu/.

The challenges of family studies lie in identifying populations with required data and sufficient numbers of people in order to estimate precise associations [61]. The HUNT Study meets these requirements, and should be considered an important source for designing and analyzing family studies.

3.1 Record linkage

The papers are all based on information from HUNT2 and HUNT3 as no information on musculoskeletal pain was obtained at HUNT1. The unique personal identification number

held by all Norwegian citizens was used to link each participant's record to information from the Family Registry at Statistics Norway, and thus establish a link between parents and offspring who had participated in one or both of the HUNT surveys. At HUNT2, 93,898 persons were invited to participate and 65,237 (70%) attended the study, whereas 93,860 persons were invited to HUNT3 and 50,807 (54%) chose to participate [92, 93]. In total, 25,493 parent-offspring pairs (offspring linked with either mother or father) were eligible for analyses.

In paper I we selected 22,162 parent-offspring pairs with complete information about CMP using parental data from HUNT2 and offspring data from HUNT3. Further, we investigated 11,248 parent-offspring trios (i.e., father, mother, and child).

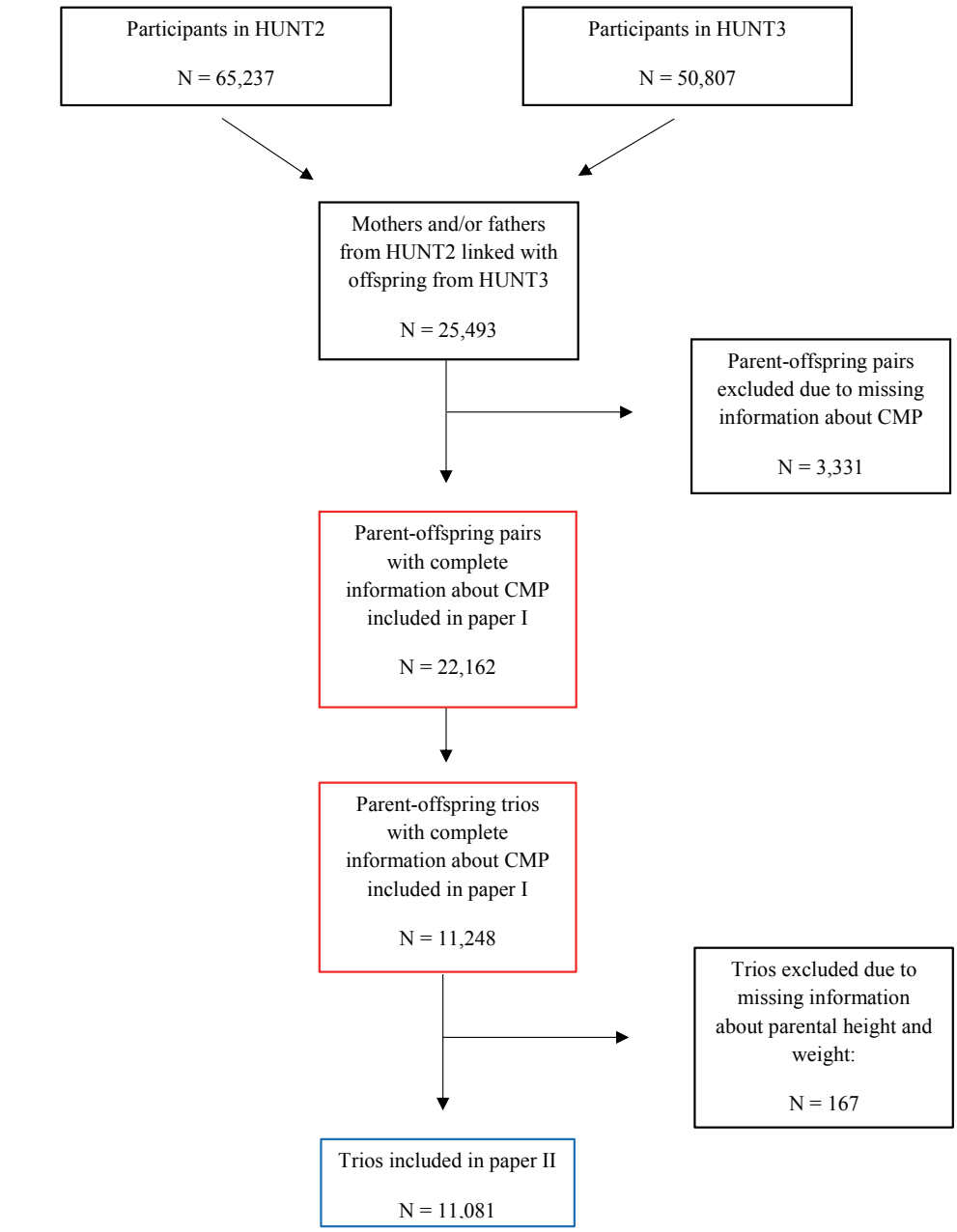

Fig 1. Flow chart showing selection procedures in Paper I and II.

CMP: chronic musculoskeletal pain.

In paper II we included all parent-offspring trios (i.e., mother, father, and adult offspring) with complete information on chronic musculoskeletal pain. However, 167 parent-offspring trios were excluded due to missing data on parental body height and weight from the clinical examination. This left 11,081 trios with parental data from HUNT2 and offspring data from HUNT3 for statistical analyses.

In paper III we used a prospective study design and selected 7,520 adult offspring who participated in both HUNT2 and HUNT3 with complete baseline (HUNT2) information about CMP, BMI, and leisure time physical activity, and where both parents had participated in HUNT2. We excluded 2,778 offspring with CMP at baseline (HUNT2), resulting in a study population of 4,742 trios available for follow-up on risk of CMP.

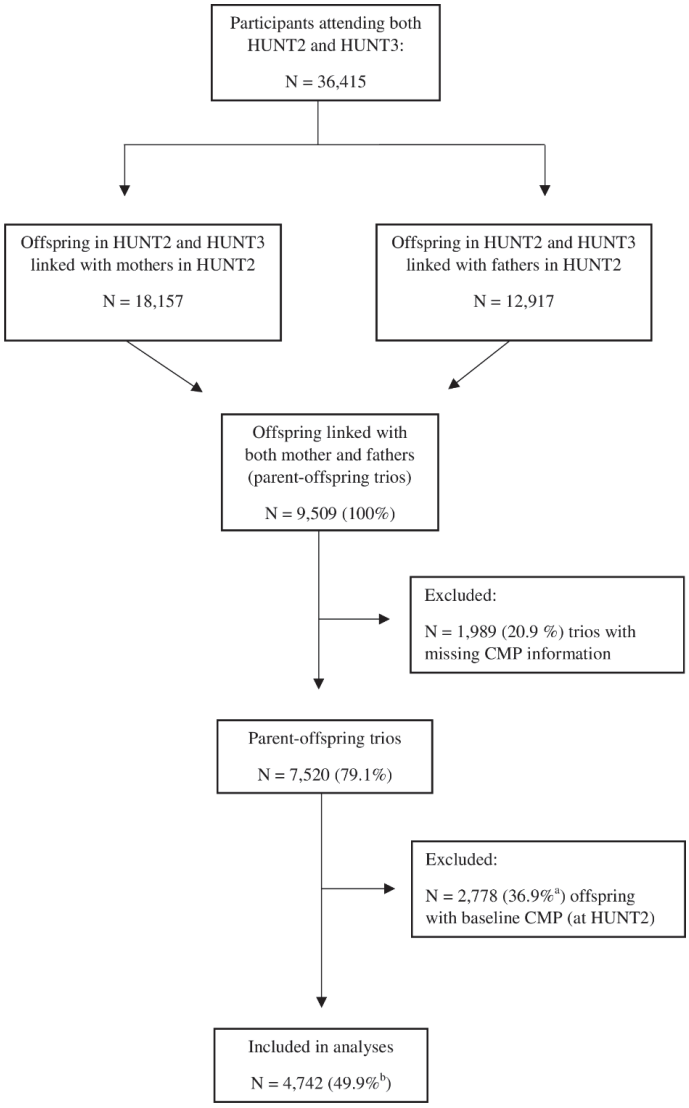

Fig 2. Flow chart showing selection procedures in Paper III.
CMP: chronic musculoskeletal pain. [a]Percentage of N=7,520 trios. [b]Percentage of 9,509 trios.

3.2 Study variables

3.2.1 Musculoskeletal pain

The participants were asked to complete a questionnaire that included items on musculoskeletal pain adopted from the Standardized Nordic Questionnaire [94], which has

been evaluated and found to have acceptable reliability and validity for upper limb and neck pain, and likely to have a high utility in screening and surveillance [95, 96]. The key question in both HUNT2 and HUNT3 was: "During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?" (response options: "no" and "yes"). We use the term "any CMP" to denote participants who answered "yes" to this question, whereas those who answered "no" formed the reference category for all comparisons. Participants with "any CMP" were also asked to indicate the affected body area(s), and in paper II spinal pain was defined as reporting neck/upper back pain and/or low back pain. Further, concurrent neck/upper back and low back pain was defined as having "multilevel spinal pain". Among offspring, non-cases for each of the outcomes neck/upper back pain, low back pain, and multilevel spinal pain were those with complete information about musculoskeletal pain who reported no chronic pain in the specified localization. Participants with any CMP were also asked to indicate if the CMP had led to reduced leisure time activity (response options: "no", and "yes") or reduced their work ability (response options: "no", "to some extent", "considerably", or "don't know"). Participants, who answered "yes" to the question on reduced leisure time activity and "to some extent" or "considerably" on reduced work ability, were classified as having "activity-interfering CMP".

3.2.2 Body mass index and physical activity

Standardized measurements of body height and body mass obtained at the clinical examination in both HUNT2 and HUNT3 were used to calculate body mass index (BMI) as mass divided by the square of height (kg/m^2). In paper I and II we adjusted for parental BMI as a continuous variable, whereas in paper III offspring BMI was adjusted for using BMI categories according to the cut-off points suggested by the World Health Organization [97]: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI

25.0-29.9 kg/m^2), and obese (BMI ≥30.0 kg/m^2). In the combined analyses of parental CMP and offspring BMI we did not include offspring who were classified as underweight. Participants in HUNT3 were also asked about their height and weight at 18 years of age. Based on the above information we also classified offspring into normal weight (BMI <25 kg/m^2) and overweight/obese (BMI ≥25 kg/m^2) at both baseline (i.e., HUNT2) and at age 18 years.

Leisure time physical activity was assessed from the HUNT2 question: "How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time)". The participants reported the number of hours of light (no sweating or heavy breathing) and/or hard (sweating and heavy breathing) activity using the response options "none", "less than 1 hour", "1-2 hours", and "3 or more hours" for both light and hard activity. Based on this information, we constructed a new variable with four categories combining information on light and hard activity; 1) "inactive" (no light or hard activity), 2) "low activity" (<3 hours light and no hard activity), 3) "moderate activity" (≥3 hours light and/or <1 hour hard activity), and 4) "high activity" (any light and ≥1 hour hard activity). In paper III the categories "inactive" and "low activity" were merged into one category of "low activity" for the analyses involving offspring level of physical activity.

3.2.3 Other variables

Physical work demands were assessed from the question: "If you have paid or unpaid work, how would you describe your job?" with four mutually exclusive response options; 1) "mostly sedentary" (e.g., at a desk, on an assembly line), 2) "much walking" (e.g., delivery work, light industrial work, teaching), 3) "much walking and lifting" (e.g., postman, nurse, construction

work), and 4) “heavy physical work” (e.g., forestry work, heavy agricultural work, heavy construction work).

Psychological wellbeing was assessed from the question: “Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?” The participants were classified into three groups; 1) “satisfied” (response options “very satisfied” and “satisfied”), 2) “somewhat satisfied” (response options “somewhat satisfied”, “neither satisfied nor dissatisfied”, and “quite dissatisfied”), and 3) “dissatisfied” (response options “dissatisfied” and “very dissatisfied”).

Information about education was available from HUNT2, and classified as “primary and lower secondary school” (0 to 9 years), “upper secondary school” (10 to 12 years), and “college or university” (>12 years). Information about education was not available in HUNT3 since this was not included in the survey questionnaire.

3.3 Statistical methods

In paper I and II we used logistic regression models to estimate adjusted odds ratios (ORs) of CMP among offspring in association with CMP in their parents. Due to the prospective design in paper III, we used Poisson regression models to estimate relative risks (RRs) of CMP in offspring associated with parental CMP. Precision of ORs and RRs was assessed by 95% confidence interval (CI). If parents had multiple offspring in the data (i.e. siblings), this could lead to inflated precision of the estimates due to reduced inter-individual variation caused by shared childhood environment and possible genetic inheritance. Thus, all standard errors were adjusted for within-family clustering using the vce(cluster) option in Stata, treating observations between families as independent and within families as dependent [98].

Potential confounders were selected after construction of directed acyclic graphs (DAGs) [99] based on a priori knowledge of possible risk factors for CMP. From this procedure, parental characteristics where chosen as possible confounders in paper I and II since they are likely to be associated with both the exposure (i.e., parental CMP) and the outcome (i.e., offspring CMP), whereas offspring characteristics may only be associated with the outcome or act as mediating factors. Moreover, parental and offspring lifestyle factors such as BMI and leisure time physical activity may be highly correlated [100], and factors such as education and psychological well-being are related to CMP in both parents and offspring [3]. In paper III the parent-offspring association of CMP was examined prospectively. We also examined if these associations were modified by offspring body mass index and leisure time physical activity. Thus, due to the nature of the design, offspring characteristics were chosen as possible confounders.

All statistical tests were two-sided, and all analyses were conducted using Stata for Windows, V.11.0 (StataCorp LP, Texas, USA).

3.3.1 Paper I

All analyses were performed on 11,248 trios consisting of adult offspring linked to both their mother and father, and conducted separately for daughters and sons. Logistic regression was used to estimate ORs of CMP in offspring associated with maternal and paternal CMP, and trios where none of the parents reported CMP defined the reference category in all analyses. Since the nature and symptom burden of CMP can differ between younger and older adults [3, 101], and because genetic influence is reported to become less important with increasing age [63], we conducted a stratified analysis by parental age <65 years and ≥ 65 years. Additionally, likelihood ratio tests were used to examine possible effect modification by offspring age (<40 years and ≥ 40 years). Possible differences in mother-offspring and father-

offspring association was also investigated due to indications of association between pain status and intrauterine environmental factors [79].

The main multivariable models were adjusted for the following paternal and maternal characteristics as potential confounders: age (continuous), BMI ([kg/m^2], continuous), leisure time physical activity (inactive, low, moderate, high, unknown), education (< 10 years, 10-12 years, ≥ 13 years, unknown), and psychological well-being (satisfied, somewhat satisfied, dissatisfied, unknown). Additionally, paternal and maternal CMP were mutually adjusted when assessing their independent association with offspring CMP by including both as covariates in the regression model. Although not argued for by DAGs, we also assessed potential confounding by the same offspring characteristics, except education, in supplementary analyses. To assess possible influence of pain severity, we conducted supplementary analyses of activity-interfering CMP in parents. Since this exposure was partly defined by work ability, these analyses were conducted on trios where both parents were ≤ 65 years.

3.3.2 Paper II

All analyses were performed on 11,081 parent-offspring trios, and firstly, logistic regression was used to estimate adjusted ORs for chronic spinal pain in the adult offspring associated with chronic spinal pain in parents. First, we conducted analyses stratified by offspring sex to examine maternal-offspring and paternal-offspring associations of spinal pain (i.e., neck/upper back, low back, and multilevel spinal pain). Linear combinations of estimates were calculated as the difference between maternal-offspring and paternal-offspring associations. This tests the null hypothesis that the difference between the maternal-offspring coefficient and the paternal-offspring coefficient equals zero. Maternal and paternal pain were mutually adjusted in these analyses. The multivariable models were adjusted for paternal and

maternal age (continuous), BMI ([kg/m^2], continuous), leisure time physical activity (inactive, low, moderate, high, unknown), physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, unknown), education (<10 years, 10-12 years, ≥ 13 years, unknown), and psychological well-being (satisfied, somewhat satisfied, dissatisfied, unknown). Although not supported by DAGs, we conducted additional analyses controlling for offspring psychological well-being and physical work demands, using the same categories as above. First incidence of spinal pain typically peaks between 25 and 40 years of age [102]. Additionally, it has been shown that the genetic influence becomes less important with increasing age [63]. Thus, possible effect modification by offspring age (<40 years and ≥ 40 years) was tested by including a product term in the regression model.

Secondly, we used logistic regression to examine the joint association of maternal and paternal spinal pain with offspring spinal pain using four categories of parental pain; parents with no pain (reference), maternal pain, paternal pain, and both maternal and paternal pain. This analysis was adjusted for offspring sex in addition to the confounders described above. A possible excess effect of spinal pain in both parents was calculated using the equation for estimating the relative excess risk due to interaction (RERI) with 95% CIs: RERI =RR_{ab} –RR_a – RR_b + 1 [103, 104]. This equation was modified in order to fit with the odds ratios (ORs) provided by the logistic regression model used in this study; $OR_{\text{Both parents}} - OR_{\text{Mother}} - OR_{\text{Father}}$ + 1. RERI >0 indicate a synergistic effect of maternal and paternal pain on the occurrence of offspring spinal pain.

3.3.3 Paper III

In paper III we used a Poisson regression model to estimate RRs of CMP in offspring, as well as activity-interfering CMP, associated with parental CMP. Further, we estimated offspring

risk of CMP associated with a combination of parental CMP and offspring physical activity, as well as of parental CMP and offspring BMI.

It has been suggested that familial clustering of CMP is mainly explained by associations between female relatives [69, 77]. Thus, possible effect modification by offspring sex was tested in addition to possible difference between maternal and paternal associations, which was evaluated using paternal CMP as the reference category in the regression model. Possible interaction (i.e. departure from additivity) between parental associations was estimated as RERI with 95% CIs from the following equation: $RERI = RR_{\text{both parents}} - RR_{\text{mother}} - RR_{\text{father}} + 1$ [103]. RERI >0 indicate a synergistic effect of maternal and paternal pain. A similar approach was used to assess possible interaction between parental pain and offspring physical activity, as well as between parental pain and offspring BMI.

The main analyses were adjusted for possible confounding by offspring sex (male, female), age (continuous), BMI (underweight, normal weight, overweight, or obese), level of physical activity (inactive, low activity, moderate activity, high activity or unknown), physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, unknown), education (< 10 years, 10-12 years, ≥ 13 years, or unknown), and psychological well-being (satisfied, somewhat satisfied, dissatisfied, or unknown). Analysis of the combined associations of parental pain and offspring physical activity or BMI did not include adjustment for the variable under study.

Ethics

All participants in HUNT2 and HUNT3 signed a written informed consent upon participation. The current project was approved by the Regional Committee for Medical Research Ethics (project no. 2011/1455/ REK midt).

4 Main results

4.1 Paper I

Parental chronic pain in relation to chronic pain in their adult offspring: family-linkage within the HUNT Study, Norway

In the first study, the population comprised 11,248 trios including 6,307 daughters and 4,941 sons linked with both their mother and father. The prevalence of any parental CMP at HUNT2 (1995-97) was 56.7% among mothers and 51.4% among fathers while the offspring prevalence of any CMP at HUNT3 (2006-08) was 47.3% among daughters and 39.3% among sons.

Overall, the multivariably-adjusted analyses showed that both maternal and paternal CMP were associated with increased odds of offspring CMP, and the ORs were largely similar between the parental age strata. Mean age for offspring, mothers, and fathers in the strata of parental age ≤ 65 years were 35.4 (standard deviation [SD] 8.5) 49.4 (SD 8.1) and 52.2 (SD 8.2), respectively. In the strata of parental age >65 years the corresponding mean ages were 54.2 (SD 6.4), 72.0 (SD 4.8), and 75.2 (SD 5.1). For example, in the analyses that included all parents, the ORs for CMP in daughters associated with maternal and paternal CMP were 1.4 (95% CI 1.2 to 1.5) and 1.2 (95% CI 1.1 to 1.3), respectively. The corresponding ORs among sons were 1.3 (95% CI 1.1 to 1.5) associated with maternal CMP and 1.2 (95% CI 1.1 to 1.4) associated with paternal CMP. Although the difference between mother-offspring and father-offspring association was slightly larger among daughters than among sons, these differences were not statistically significant (P-value, 0.08 in daughters and 0.54 in sons). Correspondingly, we did not observe any statistical interaction (i.e., departure from a multiplicative effect) between parental sex and occurrence of CMP in either daughters (P=0.97) or sons (P=0.28).

Further, we analysed any offspring CMP in association with a combined variable of any paternal and maternal CMP. Compared to the reference group of no CMP in any of the parents, the OR for CMP in offspring was 1.6 (95% CI 1.4 to 1.9) in both sons and daughters if both parents reported any CMP. Stratified analyses according to offspring age (±40 years) showed no large difference in the parent-offspring associations, and a likelihood-ratio test of the interaction between any parental CMP and offspring age gave P-values of 0.18 in daughters and 0.94 in sons.

In a supplementary analysis we examined if pain severity could influence these associations by restricting the exposure to activity-interfering CMP in parents aged ≤ 65 years. The presence of interfering CMP in either mother or father was associated with 30-50% increased odds of any CMP in the offspring. When both parents reported interfering CMP, the OR was 1.9 (95% CI 1.5 to 2.4) among daughters and 1.6 (95% CI 1.3 to 2.2) among sons.

4.2 Paper II

Neck/upper back and low back pain in parents and their adult offspring: Family linkage data from the Norwegian HUNT Study

In the second study, we wanted to investigate if specificity of pain contributed to any changes in the parent-offspring associations in pain we found in the first study. Among 11,081 parent-offspring trios 3654 (33%) offspring reported spinal pain (i.e. pain localized in neck/upper back and/or low back).

Overall, maternal and paternal spinal pain at all localizations was associated with increased occurrence of offspring spinal pain. Comparing the strength of mother-offspring and father-offspring associations suggests no large differences for any of the localizations under study, except that maternal low back pain showed a stronger relation to spinal pain in

daughters than did paternal low back pain (*P*-value for homogeneity of estimates, 0.02). The strongest parent-offspring associations were observed for parental multilevel spinal pain; mother-offspring associations gave adjusted ORs of 1.7 for spinal pain, both in daughters and sons (95% CIs, 1.4 to 2.1 and 1.3 to 2.1, respectively) whereas father-offspring associations gave adjusted ORs of 1.4 (95% CI, 1.1 to 1.7) in daughters and 1.7 (95% CI, 1.3 to 2.1) in sons. There was no large difference in the parent-offspring associations between daughters and sons, as supported by *P*-values ≥ 0.26 for all tests of interaction between parental pain and offspring sex. Sensitivity analyses were we excluded trios where one or both parents suffered from Bechterew's disease or rheumatoid arthritis did not change the results.

If both parents reported chronic neck/upper back or low back pain, the OR for chronic spinal pain in the offspring was twofold higher than if none of the parents reported spinal pain. Overall, multilevel spinal pain in both parents showed the strongest association with offspring neck/upper back, low back, and multilevel spinal pain with adjusted ORs of 2.6 (95% CI, 2.1 to 3.3), 2.4 (95% CI, 1.9 to 3.0), and 3.1 (95% CI, 2.2 to 4.4), respectively. As indicated by the estimates of RERI, a synergistic effect of pain in both parents was observed for neck/upper back (RERI 0.4, 95% CI, 0.1 to 0.8) and multilevel spinal pain (RERI 1.0, 95% CI, 0.3 to 1.6).

4.3 Paper III

Familial risk of chronic musculoskeletal pain and the importance of physical activity and body mass index: prospective data from the HUNT Study, Norway

In this prospective family-linkage study of 4,742 parent-offspring trios (2,592 daughters and 2,150 sons) 1,700 offspring (35.8%) developed CMP during the follow-up period of approximately 11 years.

Overall, both maternal (RR, 1.26; 95% CI, 1.03 to 1.55) and paternal CMP (RR, 1.29; 95% CI, 1.06 to 1.57) was associated with increased risk of offspring CMP, with no difference in the strength of the association between parents ($P_{difference}$=0.78). The risk of CMP was not stronger if both parents reported CMP (RR, 1.29; 95% CI, 1.06 to 1.57), which was also reflected in the estimates of RERI (-0.28; 95% CI, -0.66 to 0.09). Analyses of offspring risk of activity-interfering CMP gave somewhat stronger associations than for overall CMP, especially related to maternal CMP. RR for offspring CMP was 1.38 (95% CI, 1.13 to 1.68) if only mothers reported CMP and 1.08 (95% CI, 0.86 to 1.35) if only fathers reported CMP ($P_{difference}$=0.02). Corresponding RRs for offspring activity-interfering CMP were 1.42 (95% CI, 1.16 to 1.75) and 1.04 (95% CI, 0.82 to 1.32), respectively ($P_{difference}$=0.01). As indicated by the estimates of RERI there was no statistical evidence of a synergistic effect of CMP in both vs. only one parent.

Compared to offspring with high physical activity and no parental CMP, offspring with CMP present in both parents and who reported low levels of physical activity had a RR of 1.82 (95% CI, 1.32 to 2.52). Offspring with CMP present in both parents, but who reported high levels of physical activity had a RR of 1.32 (95% CI, 0.95 to 1.84). Although the risk was higher among those with low levels of physical activity, estimates of RERI indicate no synergistic effect between parental CMP and offspring physical activity (RERI=0.24; 95% CI, -0.32 to 0.79)

A similar pattern, but with somewhat stronger associations, were observed for the combined effect of parental CMP and offspring BMI. Compared to normal weight offspring (BMI <25 kg/m^2) without parental CMP, offspring of parents who both reported CMP had a RR of 2.33 (95% CI 1.68 to 3.24) if the offspring were obese (BMI ≥ 30 kg/m^2). There was also weak evidence of a synergistic effect of parental CMP and offspring obesity that extends beyond an additive effect (RERI=0.88; 95% CI, -0.03 to 1.73).

In supplementary analyses we further explored the combined effect of BMI and parental CMP using self-reported information on BMI from 18 years. Compared to normal weight offspring without parental CMP, offspring were both parents reported CMP had a RR of 2.01 (95% CI 1.17 to 3.48) if they had a BMI ≥ 25 kg/m^2, and a RR of 1.31 (95% CI, 0.89 to 1.93) if the BMI was <25 kg/m^2.

5 Discussion

5.1 Summary of main findings

The three papers forming this thesis are all family studies designed to investigate the association of CMP in parents and their adult offspring. Moreover, the results from all three papers show that CMP track across generations. More specific, the main findings of the thesis were:

- Both any CMP and activity-interfering CMP in mothers and fathers was associated with increased occurrence of CMP in the offspring, and this association was particularly strong when CMP was present in both parents (Paper I).
- Consistent positive parent-offspring associations between chronic spinal pain (i.e. pain in neck/upper back and/or low back), in particular for parental multilevel spinal pain (i.e. concurrent pain in neck/upper back and low back) (Paper II).
- No indication that specificity of pain increased the parent-offspring associations (Paper II).
- In a prospective design parental CMP was positively associated with risk of CMP in the offspring (paper III).
- The adverse effect of parental CMP was somewhat stronger among offspring who reported a low level of leisure time physical activity compared to a high physical

activity level, and among overweight and obese offspring compared to normal weight offspring (Paper III).

In all three studies, the results showed no evidence that offspring or parental age or sex modified the parent-offspring association of CMP. The associations persisted also after adjusting for parental or offspring characteristics, as well as mutual adjustment for the other parent's CMP. However, as in all observational studies, we cannot rule out residual confounding due to unmeasured or unknown factors. In family study designs of generations, there will always be some genetic and some environmental component causes acting together [105].

5.2 Methodological considerations

The studies in this thesis are all epidemiologic intergenerational studies. Participant in both HUNT2 and HUNT3, who later on were linked as parents and offspring, reported individual information about pain and lifestyle related factors. The personal identification number held by all Norwegian citizens was used to link each participant's record to information from the Family Registry at Statistics Norway in order to establish parent-offspring linkage. In an epidemiologic study, the overall goal is to distinguish chance findings from findings that might be replicated upon repetition. It is important to obtain unbiased and accurate estimates with limited errors. Thus, when interpreting the results, it should be noted that they could be distorted by random error, which reduces the precision of the associations, or by systematic error which interferes with the validity of the results. We can take steps in measurements and analyses to reduce random and systematic errors, and these topics are further discussed below [105, 106].

5.2.1 Random error (lack of precision)

The error that remains after controlling for systematic error is called random error or variability in the data. The major contributor to random error is the process of sampling study subjects, and a common way of reducing random error, and thereby increase precision, is to increase the study size. The size of the HUNT Study is in general large and satisfactory, with 65,237 participants in HUNT2 and 50,807 participants in HUNT3. However, restricting the analyses in our studies to parent-offspring trios resulted in a somewhat reduced study size (11,248 trios in Paper I, 11,081 trios in Paper II, and 4,742 trios in Paper III).

Quantification of random error is usually obtained through tests of statistical significance indicating the probability (P-value) that the observed association could be explained by chance alone, given that the null hypothesis is true. However, if the sample size is sufficiently large, even small differences may be statistically significant, and vice versa, large effects may not be statistically significant in small samples. Thus, it is argued that P-values are confounded since it is influenced by both effect size and precision [107]. Instead, information about effect size and precision could be reported separately as point estimates with confidence intervals, where a narrow confidence interval indicates little variability in the data and high precision of the estimate. Thus, we have used 95% confidence intervals rather than p-values to assess the influence of random error in our studies. Most of the analyses in this thesis were based on a relatively large sample, and together with the high number of people reporting CMP, this ensures high precision of the estimated associations. Nevertheless, some of the more infrequent exposure categories had relatively few cases, leading to less precise estimates for some comparisons, indicated by wider CIs. It should also be noted that our studies included several statistical tests, and thus some statistically significant results could be due to chance.

5.2.2 Systematic error (lack of validity)

It is important to obtain valid and precise estimates with limited bias in order to make general statement about nature. Thus, it is essential to prevent and control for such systematic errors. Systematic errors in estimates could have several sources, such as how the subjects were selected, how the study variables were measured, and by incomplete control of confounding factors [105, 106].

Selection bias

In the HUNT Study, all persons in the population were eligible for selection into the study, and thereafter classified by exposure status, rather than assigned to exposure groups. Thus, since an exposure cannot be assigned to the participants in a non-experimental study, the investigator has to rely on accurately selecting the subjects. Selection bias would be present if the observed associations were different for the participants of our studies and the non-participants [106], i.e. differences between participants and non-participants may enhance real differences between participants and the eligible study population [108]. In HUNT2 the participation rate was 71%, whereas in HUNT3 the participation rate was substantially lower (54%). Thus, loss to follow-up could have influenced the results of paper III, particularly if participation in HUNT3 was related to the probability of having CMP. Overall, the participation rates are still high, and this may indicate that the study cohort is fairly representative for the underlying population, although non-participants in HUNT3 had less musculoskeletal symptoms, lower BMI, and lower socioeconomic status than participants [93]. However, the sample used in our studies, consisting of families in which both parents and offspring participated in the HUNT Study, may represent a selected and possibly more health-conscious sample than the general population. It has been argued that representativeness is not a prerequisite for valid associations of biological phenomena [100]

and unless parent-offspring associations in pain are different between participants and non-participants, it is not likely that selection bias has influenced our results.

Information bias

Information bias, or misclassification, would influence the validity of our results if the variables under study have been measured randomly or systematically wrong. The assessment of self-reported information on CMP, leisure time physical activity, BMI, education, and psychological well-being, could all be prone to misclassification.

Self-reported information about CMP was retrieved from the questions about pain adopted from the Standardized Nordic Questionnaire [94], which has been evaluated and found to have acceptable reliability and validity for upper limb and neck pain, and likely to have a high utility in screening and surveillance [95, 96]. It should be mentioned that the information given by the participants does not include any further information about the medical history of their experienced pain. It could be speculated that some participants may have suffered from disc degeneration, osteoporosis, fractures or other conditions such as malignant disorders or inflammatory joint disease [109]. On the other hand, the Standardized Nordic Questionnaire was also designed to obtain reports about minor symptoms [94]. The participants are asked about "…pain and/or *stiffness* in your muscles and joints…". Thus, the definition of CMP could include people with minor and less painful symptoms that may result in weaker intergenerational associations than more severe pain conditions. To accommodate this, we also conducted analyses of activity-interfering CMP. These associations were somewhat stronger than those obtained for overall CMP.

We included pain in upper back to be part of neck/upper back pain (paper II) under the rational that these regions could be difficult to separate when filling in a questionnaire. However, we cannot rule out that this could have led to some misclassification. Nevertheless,

a sensitivity analysis excluding participant with only upper back pain gave similar results as for neck/upper back pain.

A number of risk factors, such as standardised measures of anthropometry, were measured objectively by trained personnel in the HUNT surveys. Compared to other studies this is an advantage since self-reported measures of similar variables could lead to bias [110]. Information about physical activity was obtained from a self-reported questionnaire that have been validated in separate studies of young adult men by comparison with more objective measures of fitness and activity, such as VO2max and ActiReg [111, 112]. A more recent study has shown that the questions used in the HUNT Study were a good long-term predictor of cardiorespiratory fitness [113]. However, misclassification of physical activity due to over- or underestimation of own activity level, or subjective interpretations of questions and response options is conceivable. Additionally, in Paper III we merged the offspring categories "inactive" and "low activity" into one category of "low activity" to increase statistical power in the combined analysis of parental CMP and offspring level of physical activity. Thus, the possibility for misclassification of physical activity is higher in these analyses, and possible effects at the extreme ends of the physical activity spectrum could have been masked.

Further, we have used categorization of BMI established by The World Health Organization where a BMI of 30 kg/m^2 has been defined as obesity based on the relation to disease risk and mortality [16]. Possible misclassification could have occurred since BMI is influenced by both fat mass and fat free mass. For instance, a lean person with low fat mass but high muscle mass may wrongly be classified as overweight or obese [110], particularly among men.

Information bias arising from non-paternity, where the biological father is not the same as the reported father in the Family Registry, was not assessed in our studies. However, this could lead to a biased parent-offspring association were maternal associations are found

to be stronger than paternal associations if pain has a strong genetic component. Estimates of non-paternity do not exist in the Norwegian population. Additionally, we found that maternal and paternal pain was associated with largely similar risk for offspring pain, contrary to the weaker father-offspring association that would be expected if the proportion of non-biological fathers was high.

In paper I and II, parental information about CMP was collected from HUNT2, whereas offspring information about pain was retrieved from HUNT3. This was done in order to limit the possibility of shared events within the family, such as injury, death or disease that could have had an effect on reporting of pain. In addition, the fact that the offspring were adults at the time the information was collected, limits possible confounding by a shared environment between offspring and their parents. On the other hand, we did not have information about whether the offspring shared environment with one or both of their parents growing up. This could have had an effect on the results since the intergenerational association could be stronger among offspring who shared an environment with their parents during childhood [90].

Confounding

Confounding can be understood as confusion of effects. In other words, if the effect of the exposure on the outcome is distorted because it is mixed together with the effect of another variable, or totally or partly due to some other extraneous factor(s) not controlled for in the analyses, confounding would influence the validity of the results, either by overestimating or underestimating the associations. The extraneous factor(s) must be associated both with the exposure and the outcome, but the association must be through a different causal pathway than the one under study. If a factor is on the same causal pathway as the one under study, this factor will be a mediator, or a mediating part of the effect we want to study. In

intergenerational studies of parents and offspring, confounding could be present due to shared environment and family characteristics. In our studies, selection of possible confounders was done based in a priori knowledge about factors that could be related to CMP. Factors such as physical activity and body mass have been shown to correlate between parents and offspring [100], and together with factors such as education, physical work demands, and psychological well-being, these factors may also be associated with the development of pain [84, 114].

In all three papers, we constructed directed acyclic graphs (DAGs) in order to select appropriate potential confounders. A DAG is a diagram that identifies confounders and common causes by linking variables by arrows that represent direct causal effects [99]. From this procedure, parental characteristics where chosen as possible confounders in Paper I and II since they are likely to be associated with both the exposure (i.e., parental CMP) and the outcome (i.e., offspring CMP), whereas offspring characteristics may only be associated with the outcome or act as mediating factors. Moreover, parental lifestyle factors such as BMI, leisure time physical activity, education, physical work demands, and psychological well-being were identified as possible confounders. Additionally, in analyses of maternal or paternal CMP associated with offspring CMP, maternal and paternal CMP were mutually adjusted. Overall, the observed parent-offspring associations in CMP were only slightly attenuated after adjustment for potential confounding by parental characteristics. Although not argued for by DAGs, we also assessed potential confounding by the same offspring characteristics in supplementary analyses. In paper I we also assessed possible influence of pain severity by conducting supplementary analyses of activity-interfering CMP in parents. In Paper III we evaluated possible confounding by the corresponding offspring factors except education, due to the prospective study design. We chose not to adjust for both parental and offspring factors at the same time since adjusting for an excessive amount of confounders could introduce a problem of co-linearity if certain factors tend to be correlated, like parental

and offspring physical activity level and BMI [100]. Following, it could be difficult to separate the effects of those variables statistically, and this could again introduce a problem resulting in unstable effect estimates [115].

CMP is associated with increased age [10, 11], and is also suggested to vary according to sex [3]. A difference between maternal-offspring and paternal-offspring associations in pain has also been reported [116]. The nature and symptom burden of CMP can differ between younger and older adults [3, 101], and genetic influence is reported to become less important with increasing age [63]. Thus, in Paper 1 we stratified the analysis of parent-offspring association of pain by parental age <65 years and ≥ 65 years. Further, all analyses in all three papers were adjusted for parental (Paper I and II) or offspring (Paper III) sex and age, either as stratified analyses by sex, or by including sex and age as covariates in the analyses.

Despite extensive information on possible confounders, we cannot rule out residual confounding due to unmeasured or unknown factors in our studies, such as whether the offspring shared environment with none, one, or both of their biological parents during childhood. Unmeasured genetic factors could have had an effect on the results from our studies. On the other hand, although we were not able to decide the relative contribution of genetic and environmental factors or possible epigenetic effects, the sparse attenuations in the results after adjusting for the potential confounders described above might indicate that parental lifestyle, psychological factors, and socioeconomic status have minor influence on the parent-offspring association of CMP.

Moreover, the family design we have used makes it less likely that our results are influenced by confounding. As mentioned, a confounder is associated with both the exposure and the outcome, and since information about the exposure and the outcome are separated by one generation, one could expect that the potential association with a confounder is weaker.

Effect measure modification (interaction)

Effect measure modification or interaction occurs when there is an interplay between two risk factors, and the effect of one risk factor on the outcome is modified by the value of another risk factor. In other words, interaction is present if the combined effect of two exposures deviates from the sum or product of their separate effect [104, 105]. Statistical interaction can be evaluated on both a multiplicative scale and on an additive scale, depending on the model used. In all three papers we assessed interaction on a multiplicative scale by comparing a model with main effects only, against a model with main effects and a product term of the variables in which there could be an interaction. In Paper I and II we tested for possible interaction between parental CMP and offspring age (<40 years and ≥ 40 years). This analysis was done based on studies showing that the nature and symptom burden of CMP can differ between younger and older adults [3, 101], and because genetic influence is reported to become less important with increasing age [63]. There was no indication of interaction between parental CMP and offspring age when assessed by including a product term in the regression model. Neither did we observe interaction between parental sex and parental CMP on the occurrence of offspring CMP in Paper I. Similarly, there was no evidence of statistical interaction between parental CMP and offspring physical activity, nor between parental CMP and offspring BMI in Paper II.

If a statistical model is based on additivity of effects, interaction is present if the separate effects of two or more exposures are not additive when presented in the same model [105]. The term "biological interaction" has been used when interaction is evaluated on an additive scale. Biological interaction between two causes occurs when the effect of one factor is dependent on the presence of another factor. However, it should be noted that an observed interaction not necessarily reflect biological mechanisms [104]. In our studies interaction on an additive scale relates to a situation where the effect of maternal CMP on offspring

development of CMP would be dependent of the presence of paternal CMP, or where the effect of parental CMP would be even stronger in combination with unfavorable levels of offspring leisure time activity or BMI. In Paper II and III we estimated the relative excess risk due to interaction (RERI) [103, 104] on an additive scale by using relative measures derived from multiplicative models. RERI is calculated from Estimating relative excess risk due to interaction (RERI) is one of these procedures by using the following equation: $RR_{\text{both parents}} - RR_{\text{mother}} - RR_{\text{father}} + 1$, where RERI >0 would indicate a synergistic effect beyond an additive effect of maternal and paternal CMP [103, 104]. Since data in Paper II were analyzed using logistic regression, we adapted the equation to ORs ($OR_{\text{both parents}} - OR_{\text{mother}} - OR_{\text{father}} + 1$). The results showed that there was a synergistic effect of CMP in both parents when the pain was localized in neck/upper back, and when the parents reported concurrent pain in neck/upper back and low back. In Paper III there was no statistical evidence of a synergistic effect of CMP in both vs. only one parent. However, there was weak evidence of a synergistic effect of parental CMP and offspring obesity on risk of offspring CMP.

5.3 Interpretation of main findings

In this thesis, all three papers have investigated the development of CMP among adult offspring by the presence of CMP in one or both of their parents. In general, the results showed that both any CMP and activity-interfering CMP in mothers and fathers were associated with increased occurrence of CMP in their offspring; that there were consistent positive associations between chronic spinal pain (i.e. pain in neck/upper back and/or low back) in parents and their offspring; and that this association was particularly strong when CMP was present in both parents. The final paper also implies that a possible genetic predisposition for CMP has a higher penetrance among offspring with a physical inactive lifestyle and/or who are overweight or obese.

5.3.1 Parent-offspring association of chronic musculoskeletal pain

It is well established that independent pain reports from parents and offspring are necessary to achieve acceptable validity in family-linkage studies [83]. We are only aware of two previous studies that have investigated parent-offspring associations within the same study population using independent pain reports from parents and offspring [72, 73]. Parent-offspring association of pain may change with increasing age in the offspring, and it has been shown that the transmission of lifestyle behaviour across generations manifests itself more strongly in late adolescence and extends into adulthood [74, 75]. Thus, we chose to investigate adult offspring, and the results showed that CMP in mothers and fathers was consistently associated with higher occurrence of CMP in their offspring.

Previous family linkage studies and twin studies have provided conflicting results regarding the effect of sex on heritability of CMP. While some studies have reported sex-dependent associations [69, 70, 77], large-scale twin studies have shown minor [63, 64] or no [76] sex-specific genetic influence on chronic pain conditions. It has also been shown that there is an associations between low birth weight and development of pain (poor intrauterine environment) [79]. Our results showed that there was no clear difference between the maternal-offspring and paternal-offspring associations of CMP, and we found no evidence of interaction with parental sex and occurrence of CMP in sons and daughters.

It has been suggested that children of parents who display pain behavior adopt similar behaviors and are also more likely to report pain than their peers [82, 83]. As a results of this, it may be assumed that the parent-offspring association is more pronounced if both parents have a history of CMP compared to only one parent, and some of the results from our studies did in fact show that the parent-offspring association of CMP was stronger if both parents reported CMP. It should be mentioned that we had no information about whether the offspring lived with their biological parents in their upbringing or not, and that the effect of shared

lifestyle and societal factors could have influenced the association of CMP between parents and their adult offspring. However, since the offspring are adults at the time they participated, they are less likely to share environmental factors with their parents.

Our data did not allow us to decide the relative contribution of genetic and environmental factors to CMP. It has been suggested that inheritance of CMP is more pronounced in severe and disabling pain conditions with widespread pain, such as fibromyalgia [69, 85], compared to conditions with milder and more localized symptoms [70]. We had no information about pain intensity in the current study, but supplementary analysis restricted to both parents and offspring with CMP that interfered with work ability and leisure time activity gave largely similar results as the main analyses.

5.3.2 Specificity of parental pain

CMP is often diagnosed and treated as localized pain [24], with pain arising from low back and neck being the most common locations [2, 117-119]. Studies have indicated common genetic basis for pain in different spinal regions, such as neck and low back [63, 120]. Additionally, it has been shown that genetic factors are of great importance for the occurrence of concurrent pain in low back and neck [121]. This is in accordance with studies showing that CMP is more likely to occur in several locations or regions [24, 122-125], and some studies have also shown that persons reporting pain in neck or low back along with widespread pain reported lower functioning compared to those who reported localized pain in the same locations [29, 30]. Concurrent pain in the low back and neck substantially decrease the likeliness of restoring normal function compared to an incident episode with localised pain in the low back or neck [126]. Thus, in Paper II we aimed at investigating whether specificity of parental CMP in spinal localizations would increase the association with offspring CMP in the same localizations.

Spinal pain has a multitude of environmental and individual risk factors as well as genetic susceptibility [127]. Twin studies have shown that genetic factors may account for 24-60% of the total variance in neck pain and/or low back pain [63, 64]. Our results showed that parental concurrent neck/upper back and low back pain (i.e. multilevel spinal pain) is more strongly associated with offspring multilevel spinal pain than parental pain localized in the neck/upper back or low back, and that this association was strongest when pain was present in both parents. This excess effect of two pain afflicted parents was particularly strong for neck/upper back and multilevel spinal pain in both parents on offspring neck/upper back pain, with statistical evidence of a synergistic effect (i.e., interaction on an additive scale). However, for other pain localizations the evidence of synergistic effects of paternal and maternal pain was weak or absent, suggesting that specificity of pain is not detrimental for the parent-offspring association of chronic pain. Anyhow, the results from Paper II may indicate that parental pain that occur in more than one body area is more severe than having pain in only one body area, and that this is reflected in the stronger parent-offspring association for multilevel spinal pain.

5.3.3 Offspring lifestyle

It may be speculated that offspring who carry an inherited susceptibility to develop CMP are more vulnerable to other risk factors for CMP, such as physical inactivity [3, 41-43] and obesity [44, 45]. Prospective studies have shown that regular physical exercise and a normal body weight is associated with a reduced risk of pain in neck/shoulders [47-49], low back [50, 51], and upper limbs [52]. Thus, in Paper III we aimed at investigating the offspring's susceptibility for CMP, and we hypothesized that the adverse effect of parental CMP on risk of CMP in offspring is amplified by physical inactivity and obesity in the offspring. The estimates from the analysis in Paper III suggest that parental CMP was more strongly

associated with offspring risk of CMP if the offspring reported low level of leisure time physical activity compared to moderate or high levels. Similarly, parental CMP was more strongly associated with offspring risk of CMP among offspring who were classified as overweight or obese compared to those who were normal weight. However, there was only statistical evidence of a weak synergistic effect of parental CMP and offspring obesity on risk of offspring CMP. Although genetics and early environmental factors have been suggested as possible mechanisms underlying the relationship between obesity and pain, there are still uncertainties about the direct causal link [46].

The parent-offspring associations that we have found in our studies could be viewed in an epigenetic perspective, where gene expression is influenced by environmental factors. Thus parental CMP or unfavourable life style factors, such as inactivity and obesity, could trigger epigenetic alterations in gene expression [61]. Although this could imply that adiposity in adolescence and early adulthood could modify the risk of CMP among persons with a heritable component of CMP, it cannot rule out the possibility that such factors are a common cause of both parental and offspring CMP.

5.4 Conclusions and implications

The results from these family-based studies show that CMP in mothers and fathers was consistently associated with higher occurrence of CMP in the adult offspring, especially if both parents reported CMP. Chronic spinal pain in parents is also associated with increased occurrence of chronic neck/upper back and low back pain in the adult offspring. This association is stronger when parents suffer from multilevel spinal pain compared to localized pain in the neck/upper back or low back. Further, prospective analyses showed that a favorable lifestyle with regular physical activity and maintenance of normal body weight may reduce the risk of CMP in offspring of pain-afflicted parents. Moreover, the associations persisted after adjusting for parental or offspring characteristics, and they were not modified by parental or offspring age. The high prevalence of CMP in both parents and offspring, also for activity interfering CMP, suggests that not all cases are clinically relevant. Nevertheless, despite that the relative contribution of genetic and environmental factors could not be decided in these studies, our data clearly demonstrate family clustering that is in agreement with a heritable component of CMP.

The results from our studies contribute to the understanding that CMP track across generations and suggest that public health initiatives aimed at prevention of CMP should consider the family history of CMP to target persons with known increased risk. Additionally, the importance of a healthy lifestyle (i.e. regular physical activity and maintenance of a normal body weight) should be emphasized, especially in families with a history of CMP.

6 References

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PAPER I

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Parental chronic pain in relation to chronic pain in their adult offspring: family-linkage within the HUNT Study, Norway

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Abstract

Background: Little is known about the association between parental chronic musculoskeletal pain (CMP) and occurrence of CMP in the adult offspring. The main objective of this study was to assess the parent-offspring association of CMP, and also to examine possible modifying effects of age and sex.

Methods: The study includes 11 248 parent-offspring trios from the Norwegian HUNT Study with information on parental CMP obtained in 1995–97 and offspring CMP obtained in 2006–08. Logistic regression was used to calculate adjusted odds ratios (ORs) for offspring CMP associated with parental CMP.

Results: Maternal and paternal CMP was associated with 20-40% increased odds of CMP in sons and daughters. Both sons and daughters had an OR of 1.6 (95% CI 1.4 to 1.9) when both parents reported CMP, compared to when none of the parents had CMP. Restricting the analyses to parental CMP that was associated with limited work ability and leisure time activity did not change the strength of the association. Further, analyses stratified by parental age ±65 years showed no clear difference in the estimated associations, and there was no evidence of interaction for parental sex ($P \geq 0.39$) or offspring age ±40 years ($P \geq 0.26$).

Conclusions: This large family-linkage study show that maternal and paternal CMP are positively associated with CMP in the adult offspring, irrespective of parental and offspring age, and that the associations are strongest when both parents have CMP. Although the high prevalence of CMP in both parents and offspring suggests that not all cases are clinically relevant, the results suggest that chronic pain has a heritable component.

Keywords: Chronic pain, Epidemiology, Family study, Heritability

Background

Chronic musculoskeletal pain (CMP) is among the leading causes of reduced quality of life and disability in Western countries [1-3]. Several modifiable risk factors have been identified, including physical inactivity [4,5], obesity [6,7], and sleep problems [8], although the causal relations are not firmly established. Aggregation of CMP within families also suggests a heritable component [9-11], possibly involving polymorphisms related to catecholamine metabolism [12,13]. However, while one study using independent pain reports from parents and adolescent offspring found associations in CMP [14], a similar study showed that there was no associations [15]. Hence, there are conflicting results regarding a parent-offspring association of CMP, especially in young offspring. Despite the fact that adult offspring create their own environment outside their family, it has been shown that intergenerational transmissions of lifestyle behaviour manifests in late adolescence and extends into adulthood [16,17]. Thus, if the development of CMP depends on gene-environment interactions, it is possible that the parent-offspring associations become stronger with increasing offspring age. We are not aware of any population-based study that has examined the parents-offspring association of CMP using offspring data from both early and late adulthood. Moreover, family studies have shown that family aggregation of chronic pain and related conditions is mainly

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attributable to associations between female relatives [9,18], while twin studies have shown inconsistent results regarding a sex-specific genetic influence on heritability of chronic pain conditions [19-21]. The independent influence of maternal versus paternal CMP on the occurrence of CMP is still undecided, although the difference between twin studies and other family studies suggest that genetic effects are not sex-dependent whereas environmental influences might be differential between mothers and fathers.

The current study utilizes family linkage data from a large population-based health survey in Norway to investigate both the independent and the combined association of paternal and maternal CMP with occurrence of CMP in the adult offspring. We also examined whether the putative parent-offspring association for CMP interacts with parental and offspring age and sex.

Methods

Study population

The HUNT Study is a large population-based health survey conducted in Nord-Trøndelag County, Norway. The study has been carried out in three waves, first in 1984–86 (HUNT1), then in 1995–97 (HUNT2), and last in 2006–08 (HUNT3). At all three waves, all residents aged 20 years and older were invited to participate, and information on lifestyle and health related factors were collected by questionnaires, whereas anthropometric data, blood pressure, and a venous blood sample were obtained at a clinical examination. More detailed information about participation, questionnaires, and procedures in the HUNT study can be read elsewhere [22].

The current study is based on information from HUNT2 and HUNT3 as no information on musculoskeletal pain was obtained at HUNT1. At HUNT2, 93 898 persons were invited to participate and 65 237 (70%) attended the study, whereas 93 860 persons were invited to HUNT3 and 50 807 (54%) chose to participate [23,24]. The unique personal identification number held by all Norwegian citizens was used to link each participant's record to information from the Family Registry at Statistics Norway, and thus establish a linkage between parents and offspring in the HUNT Study. For the purpose of the present study, we selected all 11 248 parent-offspring trios (i.e., father, mother, and child) with complete information on CMP using parental data from HUNT2 (1995–97) and offspring data from HUNT3 (2006–08).

Participation in the HUNT Study was voluntary and each participant signed a written consent. The study was approved by the Regional Committee for Ethics in Medical Research, (ref.no 2011/1455/REK midt), and carried out according to the Declaration of Helsinki.

Chronic musculoskeletal pain

The participants were asked to complete a questionnaire that included items on musculoskeletal pain adopted from the Standardized Nordic Questionnaire [25], which has been evaluated and found to have acceptable reliability and validity for upper limb and neck pain, and likely to have a high utility in screening and surveillance [26,27]. The key question in both HUNT2 and HUNT3 was:" During the last year, have you had pain and/or stiffness in your muscles and joints that lasted for at least three consecutive months?" (response options: "no" and "yes"). We use the term "any CMP" to denote participants who answered "yes" to this question, whereas those who answered "no" formed the reference category for all comparisons. Participants with CMP were also asked to indicate if the pain had led to reduced leisure time activity (response options: "no", and "yes") or reduced their work ability (response options: "no", "to some extent", "considerably", or "don't know"). Participants, who answered "yes" to the question on reduced leisure time activity and "to some extent" or "considerably" on reduced work ability, were classified as having "activity-interfering CMP".

Other variables

Standardized measurements of body height (to the nearest centimetre) and body mass (to the nearest kilogram) obtained at the clinical examination were used to calculate body mass index (BMI) as mass divided by the square of height (kg/m^2).

Leisure time physical activity was assessed from the question: "How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time)". The participants should report the number of hours of either light (no sweating or heavy breathing) or hard (sweating and heavy breathing) activity using the response options "none", "less than 1 hour", "1-2 hours", and "3 or more hours" for each type of activity. Based on this information, we constructed a new variable with four categories combining information on light and hard activity: 1) "no light or hard activity", 2) "<3 hours light and no hard activity", 3) "≥3 hours light and/or <1 hour hard activity", and 4) "any light and ≥1 hour hard activity".

Psychological wellbeing was assessed from the question: "Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?" The participants were classified into three groups: 1) "satisfied" (response options "very satisfied" and "satisfied"), 2) "somewhat satisfied" (response options "somewhat satisfied", "neither satisfied nor dissatisfied", and "quite dissatisfied"), and 3) "dissatisfied" (response options "dissatisfied" and "very dissatisfied").

Statistical analysis

Logistic regression was used to estimate odds ratios (ORs) of CMP in offspring associated with maternal and paternal CMP. Since the nature and symptom burden of CMP can differ between younger and older adults [2,28], and because genetic influence is reported to become less important with increasing age [21], we conducted a stratified analysis by parental age <65 years and ≥65 years. Additionally, a likelihood ratio test was used to examine possible effect modification by offspring age (<40 years and ≥40 years), and also by parental sex. Trios where none of the parents reported CMP defined the reference category in all analyses. All analyses were conducted separately for daughters and sons. Potential confounders were selected after construction of directed acyclic graphs (DAGs) [29] based on a priori knowledge of possible risk factors for CMP. From this procedure, parental characteristics where chosen as possible confounders since they are likely to be associated with both the exposure (i.e., parental CMP) and the outcome (i.e., offspring CMP), whereas offspring characteristics may only be associated with the outcome or act as mediating factors [29]. Moreover, parental and offspring lifestyle factors such as BMI and leisure time physical activity may be highly correlated [30], and factors such as education and psychological well-being are related to pain in both parents and offspring [2]. Thus, the main multivariable models were adjusted for the following paternal and maternal characteristics as potential confounders: age (continuous), BMI ([kg/m^2], continuous), leisure time physical activity (inactive, low, moderate, high, unknown), education (<10 years, 10-12 years, ≥13 years, unknown), and psychological well-being (satisfied, somewhat satisfied, dissatisfied, unknown). Paternal and maternal CMP were mutually adjusted for when assessing their independent association with offspring CMP by including both as covariates in the regression model. Although not argued for by DAGs, we also assessed potential confounding by the same offspring characteristics in supplementary analyses. Precision of ORs was assessed by 95% confidence interval (CI). All standard errors were adjusted for within-family clustering (i.e., siblings) using the vce (cluster) option in Stata, treating observations between families as independent and within families as dependent, and thus avoiding inflated precision of the estimated associations [31]. To assess possible influence of pain severity, we conducted supplementary analyses of activity-interfering CMP in parents. Since this exposure was partly defined by work ability, these analyses were conducted on trios where both parents were ≤65 years. Finally, to assess if parent-offspring associations are different for more severe CMP we conducted a sensitivity analysis where offspring CMP was restricted to activity-interfering CMP (i.e. pain that caused reduced activity in work and/or leisure time). All statistical tests were two-sided, and all analyses were conducted using Stata for Windows, V.11.0 (StataCorp LP, Texas, USA).

Results

The study population comprises 11 248 trios including 6 307 daughters and 4 941 sons linked with both their mother and father. Characteristics of the study population are presented in Table 1. The prevalence of any parental CMP at HUNT2 (1995–97) was 56.7% among mothers and 51.4% among fathers while the offspring prevalence of any CMP at HUNT3 (2006–08) was 47.3% among daughters and 39.3% among sons. The prevalence of interfering CMP was somewhat lower (51.4% in mothers, 45.5% in fathers, and 32.2%, and 25.5% in daughters and sons, respectively).

Table 2 shows ORs for CMP in daughters and sons associated with any CMP in mothers and fathers, both overall and stratified by parental age ±65 years. The multivariable-adjusted analyses showed that both maternal and paternal CMP were associated with increased odds of offspring CMP, and the ORs were largely similar between the parental age strata. Mean age for offspring, mothers, and fathers in the strata of parental age ≤65 years were 35.4 (standard deviation [SD] 8.5) 49.4 (SD 8.1) and 52.2 (SD 8.2), respectively. In the strata of parental age >65 years the corresponding mean ages were 54.2 (SD 6.4), 72 (SD 4.8), and 75.2 (SD 5.1). In the analyses that included all parents, the ORs for CMP in daughters associated with maternal and paternal CMP were 1.4 (95% CI 1.2 to 1.5) and 1.2 (95% CI 1.1 to 1.3), respectively. The corresponding ORs among sons were 1.3 (95% CI 1.1 to 1.5) associated with maternal CMP and 1.2 (95% CI 1.1 to 1.4) associated with paternal CMP. Although, the difference between mother-offspring and father-offspring association was slightly larger among daughters than among sons, these differences were not statistically significant (P-value, 0.08 in daughters and 0.54 in sons). Correspondingly, we did not observe any statistical interaction (i.e., departure from a multiplicative effect) between parental sex and occurrence of CMP in either daughters (P = 0.97) or sons (P = 0.28). Overall, multivariable adjustment for possible confounders only slightly attenuated the results. The results from supplementary analyses adjusted for offspring characteristics were largely similar to the results presented above. Among daughters the ORs for CMP associated with maternal and paternal CMP were 1.4 (95% CI 1.2 to 1.5) and 1.2 (95% CI 1.1 to 1.3), and the corresponding ORs among sons were 1.2 (95% CI 1.1 to 1.4), and 1.2 (95% CI 1.1 to 1.3), respectively.

Table 3 shows ORs for offspring CMP associated with a combined variable of paternal and maternal CMP. Compared to the reference group of no CMP in any of the parents, the OR for CMP in offspring was 1.6 (95%

Table 1 Baseline characteristics of 11 248 parent-offspring trios, Nord-Trøndelag Health Study

	Data from HUNT2 (1995–97)		Data from HUNT3 (2006–08)	
Characteristics	**Mother**	**Father**	**Daughter**	**Son**
Participants, no.	11 248	11 248	6 307	4 941
Age, mean (SD), years	57.2 (12.2)	60.5 (12.5)	41.1 (11.3)	43.1 (11.1)
Body mass index, mean (SD), kg/m^2	27.2 (4.5)	26.8 (3.4)	26.1 (4.8)	27.2 (3.8)
Higher education[a], no. (%)	1 587 (14.1)	1 806 (16.1)	N/A	N/A
Physically inactive[b], no. (%)	858 (7.6)	856 (7.6)	73 (1.2)	116 (2.4)
Any CMP[c], no. (%)	6 377 (56.7)	5 783 (51.4)	2 984 (47.3)	1 943 (39.3)
Interfering CMP[d], no. (%)	5 099 (51.4)	4 567 (45.5)	1 575 (32.2)	1 025 (25.5)

Abbreviations: CMP, chronic musculoskeletal pain; HUNT, The Nord-Trøndelag Health Study; SD, standard deviation.
[a]Education ≥13 years.
[b]No sessions with leisure time physical activity.
[c]CMP with duration ≥3 months during the last year at any location.
[d]CMP that interfere with work ability and/or leisure time activity.

Table 2 Odds ratios for offspring chronic musculoskeletal pain (CMP) associated with any maternal or paternal CMP

	Any maternal CMP		Any paternal CMP		P-value
	No	**Yes**	**No**	**Yes**	**Difference[c]**
Daughters					
All parents					
Cases/non-cases	1 110/1 599	1 834/1 684	1 315/1 685	1 629/1 598	
Age-adjusted OR[a] (95% CI)	1.0	1.6 (1.4 to 1.7)	1.0	1.3 (1.1 to 1.4)	0.003
Multivariably-adjusted OR[b] (95% CI)	1.0	1.4 (1.2 to 1.5)	1.0	1.2 (1.1 to 1.3)	0.080
Both parents ≤65 years					
Cases/non-cases	631/1 193	995/1 151	699/1 206	927/1 138	
Age-adjusted OR[a] (95% CI)	1.0	1.6 (1.4 to 1.8)	1.0	1.3 (1.2 to 1.5)	0.044
Multivariably-adjusted OR[b] (95% CI)	1.0	1.4 (1.2 to 1.6)	1.0	1.2 (1.1 to 1.4)	0.138
Both parents >65 years					
Cases/non-cases	349/272	547/320	398/315	598/277	
Age-adjusted OR[a] (95% CI)	1.0	1.3 (1.1 to 1.6)	1.0	1.4 (1.2 to 1.7)	0.629
Multivariably-adjusted OR[b] (95% CI)	1.0	1.3 (1.0 to 1.6)	1.0	1.4 (1.1 to 1.7)	0.612
Sons					
All parents					
Cases/non-cases	736/1 370	1 166/1 582	868/1 529	1 034/1 423	
Age-adjusted OR[a] (95% CI)	1.0	1.3 (1.2 to 1.5)	1.0	1.2 (1.1 to 1.4)	0.355
Multivariably-adjusted OR[b] (95% CI)	1.0	1.3 (1.1 to 1.5)	1.0	1.2 (1.1 to 1.4)	0.542
Both parents ≤65 years					
Cases/non-cases	367/852	576/956	402/938	541/870	
Age-adjusted OR[a] (95% CI)	1.0	1.3 (1.1 to 1.6)	1.0	1.4 (1.2 to 1.6)	0.792
Multivariably-adjusted OR[b] (95% CI)	1.0	1.3 (1.1 to 1.5)	1.0	1.3 (1.1 to 1.6)	0.756
Both parents >65 years					
Cases/non-cases	261/364	401/402	321/415	341/351	
Age-adjusted OR[a] (95% CI)	1.0	1.3 (1.1 to 1.6)	1.0	1.2 (0.9 to 1.5)	0.510
Multivariably-adjusted OR[b] (95% CI)	1.0	1.4 (1.1 to 1.7)	1.0	1.3 (1.0 to 1.6)	0.587

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for parental age (continuous) in HUNT2, and mutually adjusted for maternal and paternal CMP.
[b]Adjusted for factors in [a] and parental factors in HUNT2; body mass index ([kg/m^2] continuous), leisure time physical activity (inactive, low, moderate, high, unknown), psychological well-being (satisfied, somewhat satisfied, dissatisfied, unknown), and education (<10 years, 10–12 years, ≥13 years, unknown).
[c]P-value for the estimated difference between mother-offspring and father-offspring associations.

Table 3 Odds ratio for offspring chronic musculoskeletal pain (CMP) associated with any parental CMP

	No CMP	Any Maternal CMP	Any Paternal CMP	Any CMP in both parents
Daughters				
Cases/non-cases	535/884	780/801	575/715	1 054/883
Age-adjusted OR[a] (95% CI)	1.0	1.6 (1.4 to 1.8)	1.3 (1.1 to 1.5)	1.9 (1.7 to 2.3)
Multivariably-adjusted OR[b] (95% CI)	1.0	1.4 (1.2 to 1.6)	1.2 (1.0 to 1.4)	1.6 (1.4 to 1.9)
Sons				
Cases/non-cases	367/785	501/744	369/585	665/838
Age-adjusted OR[a] (95% CI)	1.0	1.5 (1.2 to 1.7)	1.4 (1.1 to 1.6)	1.7 (1.4 to 2.0)
Multivariably-adjusted OR[b] (95% CI)	1.0	1.4 (1.2 to 1.7)	1.3 (1.1 to 1.6)	1.6 (1.4 to 1.9)

Abbreviations: *CI*, confidence interval; *OR*, odds ratio.
[a]Adjusted for parental age (continuous) in HUNT2.
[b]Adjusted for parental factors in HUNT2; age (continuous), body mass index ([kg/m^2] continuous), leisure time physical activity (inactive, low, moderate, high, unknown), psychological well-being (satisfied, somewhat satisfied, dissatisfied, unknown), and education (<10 years, 10–12 years, ≥13 years, unknown).

CI 1.4 to 1.9) in both sons and daughters if both parents reported any CMP. Moreover, if only mothers reported any CMP, the OR for offspring CMP was 1.4 (95% CI 1.2 to 1.6) in daughters and 1.4 (95% CI 1.2 to 1.7) in sons. Correspondingly, CMP in only fathers was associated with an OR of 1.2 (95% CI 1.0 to 1.4) in daughters and 1.3 (95% CI 1.1 to 1.6) in sons. Stratified analyses according to offspring age (±40 years) showed no large difference in the parent-offspring associations (data not shown). CMP in both parents was associated with an OR of 1.7 (95% CI 1.4 to 2.2) among daughters <40 years and 1.5 (95% CI 1.2 to 1.8) among daughters ≥40 years. Among sons, the corresponding ORs were 1.7 (95% CI 1.3 to 2.3) and 1.5 (95% CI 1.2 to 1.9), respectively. A likelihood-ratio test of the interaction between parental CMP and offspring age gave P-values of 0.18 in daughters and 0.94 in sons.

In a supplementary analysis (Table 4) we examined if pain severity could influence these associations by restricting the exposure to activity-interfering CMP in parents aged ≤65 years. The presence of interfering CMP in either mother or father was associated with 30-50% increased odds of CMP in the offspring. When both parents reported interfering CMP, the OR was 1.9 (95% CI 1.5 to 2.4) among daughters and 1.6 (95% CI 1.3 to 2.2) among sons. These associations were slightly strengthened in a sensitivity analysis restricting the outcome to activity-interfering CMP in offspring, with an OR of 2.4 (95% CI 1.8 to3.1) among daughters, and 1.8 (95% CI 1.2 to 2.5) among sons (data not shown).

Discussion and conclusion

In this large population-based family linkage study we found that both paternal and maternal CMP was associated with increased occurrence of CMP in the adult offspring, and this association was particularly strong when CMP was present in both parents. Restricting the analyses to CMP that interfered with work ability and leisure time activity did not materially change the odds of CMP in the offspring. Further, we found no evidence

Table 4 Odds ratio for offspring chronic musculoskeletal pain (CMP) associated with activity-interfering CMP in parents aged ≤65 years

		Activity-interfering CMP		
	No CMP	Maternal	Paternal	Both parents
Daughters				
Cases/non-cases	297/675	305/407	261/404	407/373
Age-adjusted OR[a] (95% CI)	1.0	1.7 (1.4 to 2.1)	1.5 (1.2 to 1.8)	2.5 (2.0 to 3.0)
Multivariably-adjusted OR[b] (95% CI)	1.0	1.4 (1.1 to 1.7)	1.3 (1.0 to 1.6)	1.9 (1.5 to 2.4)
Sons				
Cases/non-Cases	169/486	190/355	160/283	219/324
Age-adjusted OR[a] (95% CI)	1.0	1.5 (1.2 to 2.0)	1.6 (1.3 to 2.1)	1.9 (1.5 to 2.5)
Multivariably-adjusted OR[b] (95% CI)	1.0	1.3 (1.3 to 1.8)	1.5 (1.1 to 1.9)	1.6 (1.3 to 2.2)

Abbreviations: *CI*, Confidence interval; *OR*, Odds ratio.
[a]Adjusted for parental age (continuous) in HUNT2.
[b]Adjusted for parental factors in HUNT2; age (continuous), body mass index ([kg/m^2] continuous), leisure time physical activity (inactive, low, moderate, high, unknown), psychological well-being (satisfied, somewhat satisfied, dissatisfied, unknown), and education (<10 years, 10–12 years, ≥13 years, unknown).

that offspring age or parental sex modified the parent-offspring association of CMP.

It is well established that independent pain reports from parents and offspring are necessary to achieve acceptable validity in family-linkage studies [32]. We are only aware of two previous studies that have investigated parent-offspring associations within the same study population using independent pain reports from parents and offspring [14,15]. Both studies investigated the influence of parental pain on occurrence of chronic pain in young, adolescent offspring. While Hoftun and colleagues [14] reported a moderate parent-offspring association for chronic pain, Jones and colleagues [15] found no association between parent and offspring pain. Based on the findings in the latter study the authors suggested that pain behaviour is not learned, but is rather attributable to individual factors and the social environment. However, it is also possible that the parent-offspring association of pain changes with increasing age in the offspring. It has been shown that the transmission of lifestyle behaviour across generations manifests itself more strongly in late adolescence and extends into adulthood [16,17] and may encompass risk factors for CMP such as physical inactivity and obesity [7,16,17]. Thus, we hypothesised that offspring and parents would become more alike with respect to CMP after the offspring approach middle-age compared to younger adulthood. However, we found no evidence of an interaction between offspring age (<40 years versus ≥40 years) and occurrence of offspring CMP, and stratified analyses gave largely similar associations.

Previous family linkage studies and twin studies have provided conflicting results regarding the effect of sex on heritability of CMP. While some studies have reported sex-dependent associations [9,10,18], large-scale twin studies have shown minor [20,21] or no [19] sex-specific genetic influence on chronic pain conditions. In the present study, there was no clear difference between the maternal-offspring and paternal-offspring associations of CMP, and we found no evidence of interaction with parental sex and occurrence of CMP in sons and daughters.

The current results suggest a stronger parent-offspring association if both parents report CMP than if only one parent have CMP. Thus, one may speculate that the occurrence of CMP in the adult offspring is strongly influenced by genetic factors. Conversely, it has been suggested that children of parents who display pain behavior adopt similar behaviors and are also more likely to report pain than their peers [32,33]. However, our data did not allow us to decide the relative contribution of genetic and environmental factors to CMP. It has been suggested that inheritance of CMP is more pronounced in severe and disabling pain conditions with widespread pain, such as fibromyalgia [9,34], compared to conditions with milder and more localized symptoms [10]. We had no information about pain intensity in the current study, but supplementary analysis restricted to both parents and offspring with CMP that interfered with work ability and leisure time activity gave largely similar results as the main analyses. Although our results are not directly comparable with previous studies regarding the impact of symptom severity on parent-offspring associations, they indicate no different associations for CMP that limits activity and non-interfering CMP. Musculoskeletal disorders are the most frequent cause of sick leave and disability in Norway [35]. However, many people do not consult their doctor with their complaints [36], and it is likely that the definition of CMP used in the current study embrace a large variation of severity levels that could be relevant in a public health perspective irrespective of their health seeking behaviour.

There are several strengths to the current study, including the large number of parent-offspring trios, the population-based nature of the data, and the ability to link family members using the Family Registry at Statistics Norway. In contrast to previous studies using extended families [9,10] or family history of pain reported by the young offspring [18], we investigated the parent-offspring association using independent pain reports from parents at HUNT2 (1995–97) and from adult offspring at HUNT3 (2006–08). Another strength of this study was the ability to adjust for parental characteristics associated with CMP, including age [2], BMI [6,7,37,38], leisure time physical activity [4,7], psychological well-being [8,39], and education [10,40]. It may be argued that offspring characteristics are more likely to be associated with offspring CMP, but results from additional analyses adjusted for offspring characteristics were similar to those adjusted for parental characteristics. However, as in all observational studies, residual confounding due to unmeasured and unknown factors cannot be ruled out. Although we are not able to decide the relative contribution of genetic and environmental factors or possible epigenetic effects [41,42], the sparse attenuations in the results after adjusting for potential confounders might indicate that parental lifestyle, psychological factors, and socioeconomic status have minor influence on the parent-offspring association of CMP. This is in agreement with a recent study on adolescents from the same population [14]. Although self-reported information on CMP, leisure time physical activity, education, and psychological well-being could be prone to misclassification [43], it is not likely that such misclassification is differential between pain-afflicted and pain-free individuals. Nevertheless, when generalizing these results to a broader population it should be noted that the trios included in the current study may constitute a selected sample in terms of family structure and health status. The participation rate was substantially lower at HUNT3 (54%) than at HUNT2 (71%), and non-

participants in HUNT3 are reported to have less musculoskeletal symptoms, lower BMI, and lower socioeconomic status than participants [24].

In conclusion, this family-linkage study shows that CMP in mothers and fathers was consistently associated with higher occurrence of CMP in the adult offspring, especially if both parents reported CMP. These associations persisted also after adjusting for parental or offspring characteristics and they were not modified by offspring age. Moreover, restricting the analyses to parental activity-interfering CMP did not change the strength of the associations. The high prevalence of CMP in both parents and offspring, also for activity interfering CMP, suggests that not all cases are clinically relevant. Nevertheless, despite that the relative contribution of genetic and environmental factors could not be decided in this study, our data clearly demonstrate family clustering that is in agreement with a heritable component of CMP.

Abbreviations

BMI: Body mass index; CI: Confidence interval; CMP: Chronic musculoskeletal pain; OR: Odds ratio.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TILN acquired the data. RL was involved in the data preparation, performed the statistical analysis, and wrote the first draft of the paper. TILN and PJM revised the manuscript, and all authors contributed to the final draft. All authors read and approved the final manuscript.

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PAPER II

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PAPER III

PLOS ONE

RESEARCH ARTICLE

Familial Risk of Chronic Musculoskeletal Pain and the Importance of Physical Activity and Body Mass Index: Prospective Data from the HUNT Study, Norway

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Abstract

The main objectives of the current study was i) to prospectively examine if chronic musculoskeletal pain in parents is associated with risk of chronic musculoskeletal pain in their adult offspring, and ii) to assess if these parent-offspring associations are modified by offspring body mass index and leisure time physical activity. We used data on 4,742 adult offspring linked with their parents who participated in the population-based HUNT Study in Norway in 1995–97 and in 2006–08. Family relations were established through the national Family Registry. A Poisson regression model was used to estimate relative risk (RR) with 95% confidence interval (CI). In total, 1,674 offspring (35.3%) developed chronic musculoskeletal pain during the follow-up period of approximately 11 years. Both maternal (RR: 1.26, 95% CI: 1.03, 1.55) and paternal chronic musculoskeletal pain (RR: 1.29, 95% CI: 1.06, 1.57) was associated with increased risk of offspring chronic musculoskeletal pain. Compared to offspring of parents without chronic musculoskeletal pain, the adverse effect of parental pain was somewhat stronger among offspring who reported a low (RR: 1.82, 95% CI: 1.32, 2.52) versus high (RR: 1.32, 95% CI: 0.95, 1.84) level of leisure time physical activity. Offspring of parents with chronic musculoskeletal pain and who were classified as obese had more than twofold increased risk (RR: 2.33, 95% CI: 1.68, 3.24) of chronic musculoskeletal pain compared to normal weight offspring of parents without pain. In conclusion, parental chronic musculoskeletal pain is positively associated with risk of chronic musculoskeletal pain in their adult offspring. Maintenance of normal body weight may reduce the risk of chronic musculoskeletal pain in offspring of pain-afflicted parents.

Introduction

Recent family linkage studies have shown that parental pain is strongly associated with the prevalence of chronic musculoskeletal pain (CMP) in offspring, both during adolescence [1] and in later adulthood [2]. Although the importance of family history of CMP has been

no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

recognized for decades [3], no previous study has prospectively examined offspring risk of CMP in relation to parental pain reporting.

Inter-generational transfer of chronic musculoskeletal pain could be explained by both genetic heritability [4, 5] and shared environment [3, 6–8]. However, it has been suggested that the genetic influence is larger in more severe pain conditions, such as chronic widespread pain and pain conditions that interfere with daily activities [4, 5]. It may be speculated that offspring who carry an inherited susceptibility to develop CMP are more vulnerable to other risk factors for CMP, such as physical inactivity [9–12] and obesity [13, 14]. Prospective studies have shown that regular physical exercise and a normal body weight is associated with a reduced risk of pain in neck/shoulders [15–17], low back [18, 19], and upper limbs [20]. It may therefore be hypothesized that the adverse effect of parental CMP on risk of CMP in offspring is amplified by physical inactivity and obesity in the offspring.

In a family linkage study of parents and their adult offspring we prospectively examined the risk of offspring CMP in relation to parental pain reporting, and if these parent-offspring associations are modified by offspring body mass index (BMI) and leisure time physical activity.

Materials and Methods

Study population

The HUNT Study is a large population based longitudinal health study conducted within the county of Nord-Trøndelag, Norway. The study has been carried out in three consecutive surveys, first in 1984–1986 (HUNT1), then in 1995–1997 (HUNT2), and last in 2006–2008 (HUNT3). In all three surveys, all residents 20 years of age and older were invited to participate, and information on lifestyle and health related factors were collected by questionnaires and a clinical examination. Since no information on musculoskeletal pain was obtained at HUNT1, those who were eligible for inclusion in the current study had participated at either HUNT2 or HUNT3. At HUNT2, 93,898 persons were invited to participate, and 65,237 (70%) attended the study, whereas at HUNT3 93,860 were invited and 50,807 (54%) chose to participate [21, 22]. A total of 36,415 participated at both HUNT2 and HUNT3. More detailed information about the HUNT study can be retrieved from http://www.hunt.ntnu.no/edu/.

Each participant signed a written consent, and the study was approved by the Regional Committee for Medical and Health Research Ethics Central Norway (project no. 2011/1455/REC Central).

Record linkage

The unique personal identification number held by all Norwegian citizens was used to link each participant's record to information from the Family Registry at Statistics Norway, and thus establish family data of biological parents and their offspring in the HUNT Study. For the purpose of the present study we identified 9,509 parent-offspring trios where the offspring had family linkage to both their mother and father. 1,989 (20.9%) of these trios were excluded due to incomplete information about CMP. Parental information about CMP was retrieved from HUNT2.Due to the prospective nature of the data, we excluded 2,778 (36.9%) trios where offspring reported CMP at baseline (HUNT2), resulting in a study population of 4,742 offspring available for follow-up on risk of CMP. The complete inclusion and exclusion process is shown in Fig 1.

Outcome measure

The participants were asked to complete a questionnaire that included items on musculoskeletal pain adopted from the Standardized Nordic Questionnaire [23]. These questions have

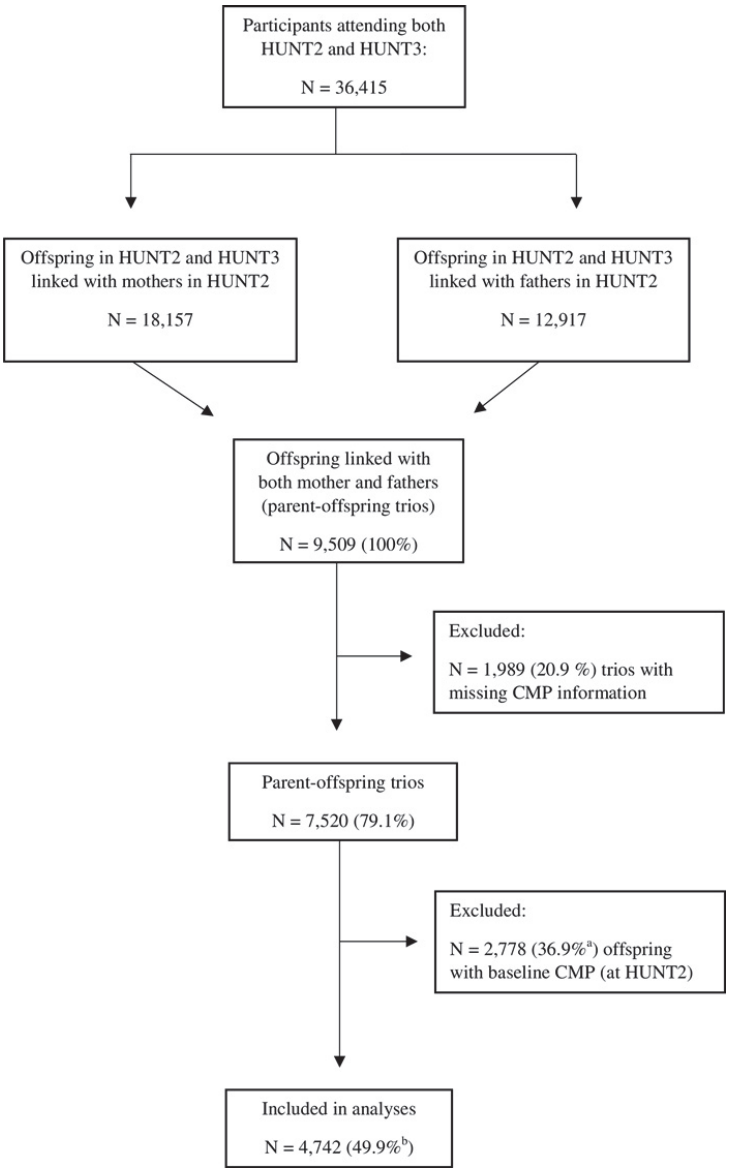

Fig 1. Flow chart showing selection procedures into the study. CMP: chronic musculoskeletal pain. [a]Percentage of N = 7,520 trios. [b]Percentage of 9,509 trios.

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acceptable reliability and validity for upper limb and neck pain [24], and are suggested to have a high utility in screening and surveillance [25]. In both HUNT2 and HUNT3 the participants were asked the following question about CMP:"During the last year, have you had pain and/or

stiffness in your muscles and joints that lasted for at least three consecutive months?". The response options were "yes" and "no", and those who reported CMP were also asked to indicate if the pain had led to reduced leisure time activity (response options: "yes", and "no") or reduced their work ability (response options: "no", "to some extent", "considerably", or "don't know"). Offspring who answered "yes" to the question on reduced leisure time activity and/or reported work ability to be reduced "to some extent" or "considerably" were classified as having "activity-interfering CMP".

Exposure measures

Information on parental CMP was obtained from the same question as described above, and based on this we constructed a variable with four mutually exclusive categories reflecting parental reporting of CMP: "none", "mother", "father", and "both parents". As for offspring, we also constructed a variable indicating activity-interfering CMP in parents, with the same categories as for overall CMP: "none", "mother", "father", and "both parents".

Leisure time physical activity was assessed by the question "How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the year. Your commute to work counts as leisure time)". The participants reported number of hours of either light (no sweating or heavy breathing) or hard (sweating and heavy breathing) activity using the response options "none", "less than 1 hour", "1–2 hours", and "3 or more hours" for each type of activity. Based on this information, we constructed a new variable with five categories combining information on light and hard activity: 1) "inactive" (no light or hard activity), 2) "low activity" ($<$3 hours light and no hard activity), 3) "moderate activity" ($\geq$3 hours light and/or $<$1 hour hard activity), 4) "high activity" (any light and $\geq$1 hour hard activity), and 5) "unknown". In the combined analyses of parental CMP and offspring physical activity the categories "inactive" and "low activity" were collapsed into one category labeled "low activity".

Standardized measurements of body height (to the nearest centimeter) and body weight (to the nearest half kilogram) were obtained at the clinical examination. BMI was calculated as weight divided by the square of height (kg/m^2), and the participants were then classified into four BMI groups according to the cut-off points suggested by the World Health Organization [26]: underweight (BMI $<$18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI $\geq$30.0 kg/m^2). Participants in HUNT3 were also asked about their height and weight at 18 years of age. Based on the above information we also classified offspring into normal weight (BMI $<$25 kg/m^2) and overweight/obese (BMI $\geq$25 kg/m^2) at both baseline (i.e., HUNT2) and at age 18 years.

Statistical analysis

A Poisson regression model was used to estimate relative risk (RR) of CMP in offspring associated with parental CMP. We also assessed the combined effect of parental CMP and offspring leisure time physical activity, as well as of parental CMP and offspring BMI, on risk of CMP in offspring. Precision of RR was assessed by 95% confidence interval (CI). All standard errors were adjusted for within-family clustering (i.e., siblings) using the vce(cluster) option in Stata, treating observations between families as independent and within families as dependent, and thus avoiding inflated precision of the estimated associations [27].

The possible difference between maternal and paternal associations was evaluated using paternal CMP as the reference category in the regression model. Possible statistical interaction (i.e., departure from additivity) between mother-offspring and father-offspring associations was estimated as relative excess risk due to interaction (RERI). We calculated RERI estimates with 95% CIs from the following equation: $\text{RERI} = \text{RR}_{\text{both parents}} - \text{RR}_{\text{mother}} - \text{RR}_{\text{father}} + 1$ [28],

i.e., RERI >0 indicate a synergistic effect beyond an additive effect. This approach was also used to assess possible interaction between parental pain and offspring physical activity, as well as between parental pain and offspring BMI. Additionally, statistical interaction was also assessed on a multiplicative scale by a likelihood ratio test of a product term in the model (without cluster-adjusted standard errors) as well as in analyses stratified by offspring physical activity and BMI categories (data not shown).

The main analyses were adjusted for possible confounding by offspring sex (male, female), age (continuous), BMI ("underweight", "normal weight", "overweight", "obese", or "unknown"), leisure time physical activity ("inactive", "low activity", moderate activity", "high activity" or "unknown"), physical work demands ("mostly sedentary", "much walking", "much walking and lifting", "heavy physical work", or "unknown"), education ("<10 years", "10–12 years", "≥13 years", or "unknown"), and psychological well-being ("satisfied", "somewhat satisfied", "dissatisfied", or "unknown"). Analysis of the combined associations of parental pain and offspring physical activity or BMI did not include adjustment for the variable under study.

All statistical tests were two-sided, and all analyses were conducted using Stata for Windows, V.11.0 (StataCorp LP, Texas, USA).

Results

In this prospective family-linkage study of 4,742 parent-offspring trios (2,592 daughters and 2,150 sons), a total of 1,700 offspring (35.8%) developed CMP during the follow-up period of approximately 11 years. The mean age at baseline was 33.3 (8.2) years among daughters and 35.1 (8.4) years among sons. Additional baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline characteristics of the study population at HUNT2.

Variables	Daughters	Sons	Mothers	Fathers
Participants, no.	2,592	2,150	4,742	4,742
Age, mean (SD)	33.3 (8.2)	35.1 (8.4)	60.7 (9.9)	64.1 (10.2)
Categories of body mass index[a]				
Normal weight, % (no.)	60.4 (1,545)	41.6 (887)	28.7 (1,354)	27.5 (1,301)
Overweight, % (no.)	29.9 (765)	48.7 (1,039)	43.5 (2,052)	54.5 (2,579)
Obese, % (no.)	8.9 (227)	9.8 (209)	27.1 (1,278)	17.1 (810)
Unknown, % (no.)	0.8 (20)	0.3 (7)	0.7 (31)	0.8 (39)
Leisure time of physical activity[b]				
Inactive, % (no.)	2.8 (73)	6.1 (130)	8.0 (381)	7.6 (363)
Low activity, % (no.)	25.4 (659)	19.2 (413)	37.4 (1,771)	26.3 (1,246)
Moderate activity, % (no.)	35.3 (915)	32.2 (692)	26.3 (1,247)	33.2 (1,574)
High activity, % (no.)	35.3 (916)	41.5 (892)	9.7 (461)	19.9 (944)
Unknown, % (no.)	1.1 (29)	1.1 (23)	18.6 (882)	13.0 (615)
Chronic musculoskeletal pain[c]				
Any pain, % (no.)	[e]	[e]	56.9 (2,699)	52.0 (2,464)
Activity interfering pain[d], % (no.)	[e]	[e]	51.5 (2,171)	46.5 (1,981)

SD: standard deviation.

[a]Categories defined by WHO. The category "underweight" is not included.

[b]"Inactive" defined as no light or hard activity, "low" defined as <3 hours light and no hard activity, "moderate" defined as ≥3 hours light and/or <1 hour hard activity, and "high" defined as any light and ≥1 hour hard activity.

[c]Pain with duration ≥3 months during the last year at any location.

[d]Pain that interfere with work ability and/or leisure time activity.

[e]Offspring with pain at baseline (HUNT2) were excluded from the analyses.

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Table 2. Risk for offspring chronic musculoskeletal pain associated with chronic musculoskeletal pain in one or both parents.

	Any offspring CMP				Offspring activity-interfering CMP			
Variables	**Case/Non-case**	**RR[a]**	**RR[b] (95% CI)**	**RERI (95% CI)**	**Case/Non-case**	**RR[a]**	**RR[b] (95% CI)**	**RERI (95% CI)**
Any parental CMP								
No CMP	320/735	1.00	1.00 (Ref.)		137/735	1.00	1.00 (Ref.)	
Maternal	439/744	1.28	1.26 (1.03, 1.55)		209/744	1.38	1.38 (1.13, 1.68)	
Paternal	337/613	1.31	1.30 (1.04, 1.62)		133/613	1.11	1.08 (0.86, 1.35)	
Both parents	578/885	1.30	1.29 (1.06, 1.57)	-0.28 (-0.65, 0.09)	268/885	1.47	1.40 (1.15, 1.69)	-0.07 (-0.40, 0.26)
Parental activity-interfering CMP								
No CMP	320/735	1.00	1.00 (Ref.)		137/735	1.00	1.00 (Ref.)	
Maternal	353/595	1.27	1.25 (1.01, 1.56)		176/595	1.43	1.42 (1.16, 1.75)	
Paternal	263/495	1.26	1.25 (0.99, 1.57)		103/495	1.07	1.04 (0.82, 1.32)	
Both parents	393/569	1.36	1.35 (1.09, 1.67)	-0.15 (-0.54, 0.24)	188/569	1.56	1.48 (1.21, 1.81)	-0.02 (-0.35, 0.38)

CMP: chronic musculoskeletal pain, CI: confidence interval, RERI: relative excess risk due to interaction, RR: relative risk.

[a]Adjusted for offspring age (continuous) and sex in HUNT2.

[b]Adjusted for offspring factors in HUNT2; age (continuous), sex, body mass index (underweight, normal weight, overweight, obese, or unknown), leisure time physical activity (inactive, low, moderate, high, or unknown), physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, or unknown), psychological well-being (satisfied, somewhat satisfied, dissatisfied, or unknown), and education (<10 years, 10–12 years, ≥13 years, or unknown).

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Table 2 shows the RRs for CMP and activity-interfering CMP in offspring associated with parental CMP. Both maternal (RR: 1.26, 95% CI: 1.03, 1.55) and paternal (RR: 1.29, 95% CI: 1.06, 1.57) CMP was associated with increased risk of offspring CMP, with no difference in the strength of the association between parents ($P_{difference}$ = 0.78). The risk of CMP was not stronger if both parents reported CMP (RR: 1.29, 95% CI: 1.06, 1.57), which was also reflected in the estimates of RERI (-0.28, 95% CI: -0.66, 0.09). Offspring risk of activity-interfering CMP was more strongly associated with maternal (RR: 1.3842, 95% CI: 1.13, 1.68) than paternal (RR: 1.08, 95% CI: 0.86, 1.35) CMP ($P_{difference}$ = 0.02). These associations remained largely similar when the analysis was restricted to parental activity-interfering CMP, with RRs of 1.42 (95% CI: 1.16, 1.75) and 1.04 (95% CI: 0.82, 1.32), respectively ($P_{difference}$ = 0.01). As indicated by the estimates of RERI there was no statistical evidence of a synergistic effect of CMP in both vs. only one parent (-0.02, 95% CI: -0.35, 0.38).

Table 3 shows the combined effect of parental CMP and offspring leisure time physical activity on offspring risk of activity-interfering CMP. Offspring with CMP present in both parents and who reported a low level of physical activity had a RR of 1.82 (95% CI: 1.32, 2.52) compared to offspring with high physical activity and no parental CMP. Offspring with CMP present in both parents, but who reported a high level of physical activity had a RR of 1.32 (95% CI: 0.95, 1.84). Although the offspring risk was higher among those with low physical activity, the estimate of RERI (0.24, 95% CI: -0.32, 0.79) indicated no synergistic effect between parental CMP and offspring physical activity. The analyses of parental-offspring CMP stratified by high, moderate, or low level of offspring physical activity showed that offspring where both parents reported CMP had RRs of 1.34 (95% CI:0.96, 1.86), 1.50 (95% CI:1.05, 2.13), and 1.43 (95% CI:1.05, 1.94), respectively (data not shown). We did not observe any statistical interaction (i.e., departure from a multiplicative effect) between parental pain and offspring physical activity (P = 0.15).

Table 3. Risk for offspring chronic musculoskeletal pain associated with the combined effect of parental chronic musculoskeletal pain and offspring leisure time physical activity.

	Offspring activity-interfering CMP		
Variables	**High leisure time physical activity**	**Moderate leisure time physical activity**	**Low leisure time physical activity**
No CMP			
Cases/non-cases	49/301	38/239	48/188
Age-adjusted RR	1.00	0.96	1.40
RR[a]	1.00 (Ref.)	0.91 (0.62, 1.36)	1.29 (0.89, 1.87)
Any CMP, one parent			
Case/non-case	215/894	241/780	202/659
Age-adjusted RR	1.36	1.61	1.56
RR[a]	1.30 (0.97, 1.75)	1.51 (1.13, 2.03)	1.38 (1.03, 1.87)
Any CMP, both parents			
Case/non-case	86/352	82/307	96/217
Age-adjusted RR	1.39	1.45	2.12
RR[a]	1.32 (0.95, 1.84)	1.34 (0.96, 1.86)	1.82 (1.32, 2.50)

CMP: chronic musculoskeletal pain, CI: confidence interval, RR: relative risk.

[a]Adjusted for offspring factors in HUNT2; age (continuous), sex, body mass index (underweight, normal weight, overweight, obese, or unknown), physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, or unknown), psychological well-being (satisfied, somewhat satisfied, dissatisfied, or unknown), and education (<10 years, 10–12 years, ≥13 years, or unknown).

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A similar pattern, but with somewhat stronger associations, where observed for the combined effect of parental CMP and offspring BMI (Table 4). Compared to normal weight offspring of pain-free parents, obese offspring of pain-afflicted parents had a RR of 2.33 (95% CI:

Table 4. Risk for offspring chronic musculoskeletal pain associated with the combined effect of parental chronic musculoskeletal pain and offspring body mass index.

		Offspring activity-interfering CMP		
Variables		**Normal weight**	**Overweight**	**Obese**
No CMP				
	Cases/non-cases	67/399	57/265	11/57
	Age-adjusted RR	1.00	1.30	1.15
	RR[a]	1.00 (Ref.)	1.24 (0.91, 1.70)	1.12 (0.63, 1.98)
Any CMP, one parent				
	Case/non-case	282/928	282/928	87/254
	Age-adjusted RR	1.36	1.66	1.75
	RR[a]	1.34 (1.04, 1.71)	1.57 (1.23, 2.02)	1.60 (1.19, 2.15)
Any CMP, both parents				
	Case/non-case	113/454	113/349	41/71
	Age-adjusted RR	1.37	1.78	2.57
	RR[a]	1.32 (1.00, 1.74)	1.67 (1.27, 2.20)	2.33 (1.68, 3.24)

CMP: chronic musculoskeletal pain, CI: confidence interval, RR: relative risk.

[a]Adjusted for offspring factors in HUNT2; age (continuous), sex, leisure time physical activity (inactive, low, moderate, high, or unknown), physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, or unknown), psychological well-being (satisfied, somewhat satisfied, dissatisfied, or unknown), and education (<10 years, 10–12 years, ≥13 years, or unknown).

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1.68, 3.24) while normal weight offspring of pain-afflicted parents had a RR of 1.32 (95% CI: 1.00, 1.74). An additional analysis adjusted for parental BMI did not alter the results (RRs of 2.29 [1.63, 3.20], and 1.32 [1.00, 1.75], respectively). There was weak evidence of a synergistic effect of parental CMP and offspring obesity on risk of offspring CMP with RERI of 0.88 (95% CI: 0.03, 1.73). The analyses of parental-offspring CMP stratified by offspring BMI showed that offspring where both parents reported CMP had RRs of 1.30 (95% CI: 1.03, 1.70) for normal weight offspring, 1.34 (95% CI: 1.01, 1.79) for overweight offspring, and 2.17 (95% CI: 1.22, 3.85) for obese offspring (data not shown). There was no statistically significant interaction on a multiplicative scale between parental pain and offspring physical activity (P = 0.51).

In supplementary analyses we further explored the combined effect of BMI and parental CMP using information on offspring BMI at age 18 years (data not shown). Offspring were both parents reported CMP had a RR of 2.01 (95% CI: 1.17, 3.48) if they had a BMI $\geq$25 kg/m^2 and a RR of 1.31 (95% CI: 0.89, 1.93) if the BMI was $<$25 kg/m^2 compared to normal weight offspring of pain-free parents.

Discussion

In this prospective family-linkage study we found that parental CMP was positively associated with risk of CMP in the adult offspring. There were no clear differences between father-offspring and mother-offspring associations for any CMP. However, when the analyses were restricted to offspring risk of activity-interfering CMP, the association was stronger for maternal than paternal CMP. The results of the combined analyses showed that offspring risk of activity-interfering CMP associated with parental CMP was somewhat higher among offspring who reported a low level of leisure time physical activity compared to a high physical activity level. However, the results did not suggest association above additivity. The adverse association of parental CMP with offspring activity-interfering CMP was somewhat stronger among overweight and obese offspring compared to normal weight offspring, suggesting that offspring BMI may modify parent-offspring association of CMP.

Parental pain has been associated with increased occurrence of offspring pain in childhood and adolescence in some studies [1, 29, 30], but not in others [31, 32]. Inconsistent results could be explained by the different definitions of (chronic) pain, the type and pain sites under study, and the different methods for pain reporting (i.e., own reporting vs. from other family members) [31, 33]. Only a few studies [3, 31, 32] have used independent information on pain from both parents and offspring; however, it has been argued that this is a crucial advantage in studies of intergenerational associations of pain to avoid bias and misclassification in pain reporting [34]. Based on independent data on pain from parents and offspring, we have in a recent cross-sectional study showed that presence of parental CMP was associated with increased occurrence of CMP in the adult offspring [35]. The current study extends on the abovementioned findings, showing that presence of parental CMP is prospectively associated with risk of CMP in the adult offspring.

The inter-generational transfer of CMP is likely related to both genetic factors and environmental influences. A few studies have pointed at specific genetic markers that are involved in the etiology of chronic pain [5], disabling low back pain [36] and fibromyalgia [33, 37]. However, leisure time physical activity [38], obesity [38], socioeconomic status [39], and psychological wellbeing [40] are factors that track across generations, and these factors have also been associated with development of CMP [9–14, 41, 42]. Thus, shared lifestyle and societal factors could contribute to the association of CMP between parents and their adult offspring; however, adult offspring are less likely to share environmental factors with their parents than are children and adolescents. Importantly, the current study indicates that the lifestyle of the adult offspring modify the parent-to-offspring transfer of CMP.

Both physical inactivity and obesity have been related to increased risk of CMP [9–14], but whether lifestyle factors such as obesity and inactivity could modify the association between parental and offspring CMP has not previously been examined. Although the association between parental CMP and offspring risk of activity-interfering CMP was higher in offspring who reported low level of leisure time physical activity compared to moderate or high levels, there was no evidence of synergistic effects above what could be expected from the additive effect of each risk factor. However, inconsistent associations between physical activity and CMP has been reported [43], suggesting that both low and high levels of physical activity can increase the risk of CMP. If such differential associations with physical activity exist this could mask a possible modifying effect of physical activity in our analyses. There was evidence that offspring BMI could be an effect modifier on the parent-offspring association of CMP, with somewhat stronger associations among offspring who were classified as overweight or obese than those who were normal weight. It has been suggested that inter-individual differences in pain sensitivity and endogenous pain-inhibitory capacity could reflect variations in the inherent susceptibility for chronic pain [44, 45], but that a triggering insult or exposure is required for the development of chronic pain [37, 46]. This could imply that a possible genetic predisposition for CMP [47, 48] has a higher penetrance among offspring with a physically inactive lifestyle and/or who are overweight or obese. Moreover, it has been shown that factors early in life is associated with risk of pain [49], and in the present study, a BMI $\geq$25 kg/m^2 at the age of 18 years was associated with a particularly detrimental effect of parental pain compared to those who reported a BMI $<$25 kg/m^2 at 18 years. Although this could imply that adiposity in adolescence and early adulthood could modify the risk of CMP among persons with a heritable component of chronic pain, it cannot rule out the possibility that such factors are a common cause of both parental and offspring pain.

We observed that mother-offspring and father-offspring associations were equally related to offspring risk of any CMP, whereas the risk of more severe and activity interfering CMP was more strongly related to maternal than paternal CMP. Information bias arising from non-paternity [50], where the biological father is not the same as the reported father could result in a weaker association through the paternal line compared with the maternal line. A recent study from the same population estimated the influence of various non-paternity rates on parent-offspring associations in continuously measured cardiovascular disease risk factors [35]. A stronger maternal-offspring than paternal-offspring association for some of the risk factors were cancelled out when assuming non-paternity rates of 3–5%. The possible influence of non-paternity was not assessed in the current study due to the nature of the data (i.e. binary exposures and outcomes). However, the somewhat differential associations with mother's and father's CMP could reflect non-paternity, but could also imply that the maternal influence is higher than paternal influences, particularly through environmental and behavioral factors [50]. Studies have shown that children of parents who display pain behavior learn to display similar pain behavior and are also more likely to report pain [6, 8, 51].

Important strengths of the current study include the prospective design, excluding offspring with CMP at baseline, the registry based information on family relations, the information on CMP obtained from parents and offspring independently and at different time points, and the inclusion of adult offspring who predominantly will not share household with their parents. Moreover, we were able to adjust for several offspring characteristics that could confound the parent-offspring associations of CMP, such as age [11], BMI [14], leisure time physical activity [12], physical work demands [52], psychological well-being [53, 54], and education [5, 55]. Nevertheless, possible residual confounding due to unknown or unmeasured factors cannot be ruled out.

There are some limitations that should be considered when interpreting the results of this study. Information on CMP was only reported at baseline and at follow-up 11 years later, with no information on possible changes in CMP during the follow-up period. Thus, some offspring could have experienced intermittent CMP that was not captured upon participation in the health survey. However, it is not likely that this was differential between offspring with parents who reported CMP and those who did not. Similarly, information on leisure time physical activity and BMI was only assessed at baseline, with no information on possible changes throughout the follow-up period. The questions about leisure time physical activity used in this study has been validated against more objective measures of fitness and activity, such as VO_2max and ActiReg in a subsample of young men [56]. Although the questionnaire has been reported to have good repeatability and provide useful measures of leisure time physical exercise, subjective interpretations of the activity questions could have influenced the results. Moreover, a premise for inclusion into this study was that the mother, father and offspring all had to participate in the health survey. This may have resulted in a somewhat selected and more health conscious sample than the general population. However, it is disputable whether representativeness is a prerequisite for making valid risk assessments in epidemiological studies [57].

In conclusion, this prospective study shows that parental CMP is positively associated with risk of CMP in the adult offspring. There was no clear evidence of effect modification by offspring leisure time physical activity, but maintenance of normal body weight may reduce the risk of CMP in offspring of pain-afflicted parents. Community-based measures aimed at reducing the incidence of CMP should therefore emphasize the importance of a healthy lifestyle, especially in families with a history of CMP.

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Author Contributions

Conceived and designed the experiments: TILN. Analyzed the data: RL. Wrote the paper: RL PJM AH TILN.

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