Mats Kirkeby Fjeld

Chronic hip and knee pain in parents and their adult offspring: family linkage data from the HUNT study.

NTNU
Norwegian University of Science and Technology
Faculty of Medicine
Department of Neuroscience
BEV 3901 Master Thesis in Human Movement Science

Trondheim, spring 2014
Acknowledgments

I would like to thank all of my supervisors, especially Tom Ivar Lund Nilsen, for the guidance, supervision and advice. I would also like to address my appreciation to my co-students, friends and family for their support and inspirational words through these two years.

I am humble and grateful for all of their support.
Abstract

Background: Pain is a complex subjective sensation and is considered to be a huge global health concern. Several studies have suggested pain and chronic pain to cluster within families, but these studies have mainly focused on fibromyalgia and spinal pain. However, there is little knowledge concerning intergenerational transfer of chronic pain in knees and hips.

Objective: The purpose of this study is to investigate a possible association between parents and their adult offspring occurrence of chronic knee and hip pain, and further to examine if a potential association is stronger for subjects with higher levels of pain due to osteoarthritis.

Method: This study is based on answers from 11 080 parent-offspring trios participating in the Nord-Trøndelag Health Study (HUNT). The HUNT study includes health and lifestyle related questions - including occurrence and localization of chronic pain. Through a linkage with the Family Registry at Statistics Norway, relations between adult offspring and parents in the HUNT data were established (parental data from HUNT2 (1995-97) and offspring data from HUNT3 (2006-08)). Logistic regression analysis was used to estimate odds ratio (OR) for the association between parents and their adult offspring occurrence of chronic pain in knee and hip.

Results: Overall, 4.9% (542) of the sons and 8% (886) of the daughters reported knee pain, whereas corresponding figures for hip pain are 3.6% (398) and 9.5% (1053), respectively. The OR for chronic knee pain when mothers reported chronic knee pain was 1.8 (95% CI 1.5-2.2) in daughters and 1.3 (95% CI 1.0-1.6) in sons. When father reported knee pain the OR was 1.1 (95% CI 0.9-1.4) in daughters and 1.3 (95% CI 1.0-1.6) in sons. The OR for chronic hip pain when mothers reported chronic hip pain was 1.5 (95% CI 1.3-1.8) in daughters and 1.4 (95% CI 1.1-1.8) in sons. When fathers reported hip pain the OR was 1.4 (95% CI 1.2-1.7) in daughters and 1.5 (95% CI 1.1-1.9) in sons. If the pain was accompanied by osteoarthritis, the association was somewhat stronger in sons, compared to the association from the main analyses.

Conclusion: In this present study, the results indicate an overall increased OR for chronic knee and hip pain among adult offspring of parents reporting chronic pain in the same region. Although genetic and environmental effects cannot be separated in this study, these results suggest a heritable component in the occurrence of chronic knee and hip pain.
Table of Contents

Introduction ................................................................................................................................. 5

Methods and materials ............................................................................................................... 7
  The study population ................................................................................................................. 7
  Family linkage .......................................................................................................................... 7
  Study variables ....................................................................................................................... 8
    Chronic pain .......................................................................................................................... 8
    Other variables .................................................................................................................... 8
    Statistical analysis ............................................................................................................... 9

Results ....................................................................................................................................... 10

Discussion ................................................................................................................................. 15
  Main findings .......................................................................................................................... 15
  Strength and limitations .......................................................................................................... 15
  Comparison with current literature ....................................................................................... 16
  Possible mechanisms ............................................................................................................. 18

Conclusion ................................................................................................................................ 19

Reference .................................................................................................................................. 20
Introduction

Pain is a complex subjective sensation and differs in intensity, duration, perception, region and etiology (Buskila D, 2007). In terms of duration, chronic pain is often used and defined as pain that persists for 3 to 6 months (Debono, Hoeksema, & Hobbs, 2013). Pain has vital function for the maintenance of the homeostasis in the body, but prolonged pain might also work as a forceful stressor. Several studies have shown people diagnosed with chronic pain to have an impaired health status and a reduced quality of life, as well as reduced mental and functional capacity (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Debono et al., 2013; Holliday & McBeth, 2011; Larsson, Bjork, Borsbo, & Gerdle, 2012). Additionally, chronic pain is regarded as one of the conditions responsible for the greatest challenges in disability-adjusted life years and has been commonly reported in the general population (Holliday & McBeth, 2011; Murray et al., 2012).

The incident and prevalence of chronic pain vary among countries (Breivik et al., 2006; Debono et al., 2013). In USA, it has been reported that as many as 100 million Americans suffers from chronic pain and the estimate of socioeconomic expenses due to chronic pain amounts for 560 billion to 635 billion American dollars each year (Debono et al., 2013). A large survey, done in Europe, suggests the prevalence of chronic pain among adults to be 19% (Breivik et al., 2006). The survey showed 21% to have depressive symptoms due to pain, while 19% lost their job and 13% changed their jobs due to pain. The survey further suggests Norway to be one of the countries with the highest occurrence of chronic pain, with a prevalence of 30% (Breivik et al., 2006). In a Norwegian study, using data from the Nord-Trøndelag Health Survey (HUNT), the prevalence of pain has been reported to be 52% among women and 42% among men (Hagen, Linde, Heuch, Stovner, & Zwart, 2011).

One of the three most common regions affected by chronic pain is the lower limb (Breivik et al., 2006; Hagen et al., 2011). Most research done on chronic pain and the lower limb is done in relation to osteoarthritis (Agaliotis et al., 2013; Cicuttini, Spector, & Baker, 1997; Cleveland et al., 2013; Ding et al., 2005; Litwic, Edwards, Dennison, & Cooper, 2013; Neame, Muir, Doherty, & Doherty, 2004; Valdes & Spector, 2011; Zhai, Ding, Stankovich, Cicuttini, & Jones, 2005). This degenerative condition has been predicted to become a huge health-related concern in
the future, due to the growth in the aging population and increasing incidents of obesity (Litwic et al., 2013; Murray et al., 2012). The prevalence of osteoarthritis in the US has been suggested to increase from today’s 27 million, to 67 million adults by 2030 (Neogi, 2013). Osteoarthritis is one of the main causes to knee replacement surgery and the number of knee replacements in the US has increased three-fold from 1991 to 2004 (Cicuttini et al., 1997; Neogi, 2013). The indirect costs in terms of expenses is estimated to amount for 3.4 billion USD to 13.2 billion USD per year (Neogi, 2013).

Nevertheless, site-specific pain and chronic pain has been reported to cluster within families (Arnold et al., 2004; Ferreira, Beckenkamp, Maher, Hopper, & Ferreira, 2013; Fjer R., Hartvigsen J., & Kyvik K. O., 2006; Hartvigsen et al., 2009; Hocking, Morris, Dominiczak, Porteous, & Smith, 2012; Nielsen, Knudsen, & Steingrimsdottir, 2012; Nyman, Mulder, Iliadou, Svartengren, & Wiktorin, 2011). These studies have predominately been done in relation to fibromyalgia and pain in neck and low back. However, in familial aggregation studies the associations are often explained due to genetic factors, environmental factors or in some case both (Ferreira et al., 2013; Fjer R. et al., 2006; Kamaleri, Natvig, Ihlebaek, Benth, & Bruusgaard, 2008; MacGregor, Griffiths, Baker, & Spector, 1997; Nyman et al., 2011; Valdes & Spector, 2011). Hoftun and colleagues (2013) have reported a familial history of chronic pain to be associated with the development of chronic pain. The study investigates the generational transfer of chronic pain between parents and young offspring and suggests family environment to be of great importance in the development of chronic pain. (Hoftun, Romundstad, & Rygg, 2013). Although the family clustering of chronic pain has been investigated in several studies, the inter-generational transfer of chronic pain in the lower limbs between parents and adult offspring is yet to be investigated.

The purpose of this study is to investigate the inter-generational association of chronic knee and hip pain between parents and their adult offspring, and to examine if a potential association is stronger for subjects reporting osteoarthritis.
Methods and materials

The study population

The subjects included in this study have participated in the Nord-Trøndelag Health Study (HUNT). The HUNT Study is a longitudinal population based study, where all inhabitants aged 20 years and above, living in Nord-Trøndelag were asked to participate. Nord-Trøndelag is a Norwegian county and has been considered to be fairly representative as an excerpt of Norway. The population of Nord-Trøndelag has been regarded as an ideal population for epidemiological studies as it appears to be stable and homogenous (Krokstad et al., 2013). The HUNT data is based on a self-reported questionnaire on health and lifestyle related factors, supplemented with anthropometrical measurements and gathering of biological specimens done by trained personnel (Holmen et al., 2003; Krokstad et al., 2013). For more information about the HUNT study visit [www.ntnu.no/hunt](http://www.ntnu.no/hunt).

The survey has been conducted in three waves. The first survey was carried out in 1984-86, the second in 1995-97 and third in 2006-08, respectively. In HUNT2, 93,898 were invited and 65,237 attended the study giving a participation of 70%. In HUNT3, 93,860 people invited and 50,807 responded giving the study a participation of 54% (Holmen et al., 2003; Krokstad et al., 2013). In this study, the analyses are based on data from HUNT2 and HUNT3. Parental information was collected at HUNT2, while offspring information was based on data from HUNT3. The study population consisted of 11,080 trios, where the offspring were linked to both their father and mother.

Each participant signed a written consent, and the Regional Committee of Ethics in Medical Research has approved the study.

Family linkage

The linkage was done with help from the Family Registry at Statistics Norway. The unique individual 11-digit identification number held by all Norwegian citizens was used to create a family linkage between offspring and their parents participating in the HUNT2 and HUNT3, respectively.
Study variables

**Chronic pain**
The subjects answered a questionnaire containing information on health and lifestyle factors including elements of musculoskeletal pain. The chronic pain question has been implemented from the Standardized Nordic Questionnaire (Kuorinka et al., 1987). Chronic pain was assessed by the question “During the last year, have you had pain and/or stiffness in your muscles and limbs that has lasted for at least 3 consecutive months?” with “yes” and “no” as possible options. If the subject answered “yes”, the subject was asked to answer a follow-up question to indicate afflicted regions (e.g. neck, low-back, knee, hip, etc.).

Based on this information, offspring who answered, “yes” to the chronic pain question and indicated that the pain was localized to the hip and/or the knee were classified as having chronic pain in knee and/or hip. Offspring who did not report knee or hip as the pain afflicted area, or who did not report any chronic pain were classified as having no knee or hip pain, respectively. These resulting variables were used as outcome variables in the logistic regression analyses.

Similarly, parents who answered “yes” to the chronic pain questions and also indicated that knee and/or hip were the afflicted region was classified as having chronic knee or hip pain. Parents who answered “no” to the chronic pain questions constitute the reference category in the regression analyses. Parents who reported chronic pain at other localizations than hip or knee were not included in the analyses.

Osteoarthritis was assessed based on the question “Has a doctor ever said that you have osteoarthritis?” with “yes” and “no” as possible options. We used this information to construct a variable indicating if the parents had chronic knee and/or hip pain including osteoarthritis. As for the parental variable described above, those who reported no chronic pain constituted the reference group.

**Other variables**
Height and weight were obtained during a physical examination. Height was measured to the nearest cm and weight was measured to the nearest kilogram. Body mass index (BMI) was calculated as mass divided by the squared value of height (kg/m²).
Education was assessed by the question “What is your highest level of education?” Answers were categorized into four different groups, “education ≤9 years”, “10-12 years”, “>12 years” and “unknown”.

For the assessment of physical activity the question was “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 subject answered in hours per week of low physical activity (no sweat or out of breath) and vigorous physical activity (sweating or out of breath) with following options; “none”, “<1 hour”, “1-2 hours” and “>3 hours” for each activity. These answers were stratified into five categories of physical activity, “inactive” (no low activity or vigorous activity), “low activity” (<3 hours low and no vigorous activity), “medium activity” (≥3 hours low and/or <1 hour vigorous activity), ”high activity” (any low and ≥1 hour vigorous activity) and “unknown”.

Physical activity at work was assessed by the question “How would you describe your work?” Response options were “mostly sedentary” (e.g. office), “work demanding walking” (e.g. teaching), “work demanding walking and heavy lifting“ (e.g. nurse) and ”heavy manual labor” (e.g. heavy construction laborer). These answers were stratified into four different groups “sedentary”, “walking”, “heavy lifting/heavy laborer” and “unknown”.

The subjects also answered questions on smoking history. The answers were used to form four different smoking categories “never”, “former”, “current” and “unknown”.

**Statistical analysis**

For the characteristics of the study population we used descriptive analysis. Logistic regression was used to estimate odds ratios for offspring chronic pain associated with parental chronic pain. Adjustments for potential confounding factors mainly included variables based on parental factors, as these factors are considered to have the closest relation to the exposure factor (Hernan, Hernandez-Diaz, Werler, & Mitchell, 2002; Vik, Romundstad, & Nilsen, 2013). Moreover, offspring factor are more likely to be mediators rather than confounders, and should thus not be adjusted for. Analyses included adjustments for the following parental factors: age (continuous), BMI (continuous), physical activity (“inactive”, “low activity”, “medium activity”, “high activity” and “unknown”), physical activity at work (“sedentary”, “walking”, “heavy
lifting/heavy laborer” and “unknown”), smoking (“never”, “former”, “current” and “unknown”) and education (“≤9 years”, “10-12 years”, “>12 years” and “unknown”). All main analyses were conducted separately for daughters and sons, whereas analyses of the combined effect of mothers and fathers pain were conducted on a pooled sample to increase statistical power. These analyses were adjusted for offspring sex. The precision of the odds ratio was assessed by a 95% confidence interval (CI). All statistical analysis was conducted using SPSS. vers. 21.

Results

Among the 11 080 trios who were available for statistical analyses, 9.5% (1053) of the daughters and 3.6% (398) of sons reported hip pain, while 8% (886) of daughters and 4.9% (542) of sons reported knee pain. However, in the results presented below the numbers included in the various analyses will vary slightly due to different number of parents with knee and hip pain.

Table 1 shows the characteristics of 11 080 parent-offspring trios. The mean age was 60.4 years for fathers and 57.1 years for mothers. Offspring had a mean age of 41.9 years. Mean BMI was 26.9 kg/m² for fathers, 27.2 kg/m² for mothers and 26.6 kg/m² for offspring. When stratifying the subjects into WHO categories, 60.5% of the offspring had a BMI >25 (i.e were classified as overweight or obese). Among mothers 64.8% had a BMI >25, while 70.4% amongst fathers had a BMI >25. Based on smoking, 26.7% of fathers were classified as current smokers and 25.6% amongst mothers, while 21% among offspring. As for physical activity, 17.3% were inactive among fathers and 20.1% amongst mothers and 8.5% were inactive amongst offspring. In regard to level of education 12.8% had more than 12 years among fathers and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Father</th>
<th>Mother</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>60.4 (±12.4)</td>
<td>57.1 (±12.1)</td>
<td>41.9 (±11.2)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.9 (±3.4)</td>
<td>27.2 (4.6±)</td>
<td>26.6 (±4.4)</td>
</tr>
<tr>
<td>BMI &gt;25 kg/m², %</td>
<td>70.4</td>
<td>64.8</td>
<td>60.5</td>
</tr>
<tr>
<td>Current smoking, % (n)</td>
<td>26.7 (2959)</td>
<td>25.6 (2837)</td>
<td>21 (2323)</td>
</tr>
<tr>
<td>Physically inactive, % (n)</td>
<td>17.3 (1919)</td>
<td>20.1 (2222)</td>
<td>8.5 (943)</td>
</tr>
<tr>
<td>High education (&gt;12 years), % (n)</td>
<td>12.8 (1422)</td>
<td>10.5 (1164)</td>
<td>N/A</td>
</tr>
<tr>
<td>Heavy lifting and laborer, % (n)</td>
<td>26.2 (2906)</td>
<td>27.3 (3023)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
10.5% among mothers. In physical activity at work 26.2% among fathers reported heavy lifting and laborer, while 27.3% amongst mothers.

Table 2 show the ORs for chronic knee and hip pain among sons and daughters associated with parental chronic knee and hip pain. Among daughters the OR for chronic knee pain when mothers reported chronic knee pain was 1.8 (95% CI 1.5-2.2), the association was somewhat lower in sons with an OR of 1.3 (95% CI 1.0-1.6). The OR for chronic hip pain, when mothers reported chronic hip pain, was 1.5 (95% CI 1.3-1.8) in daughters and 1.4 (95% CI 1.1-1.8) in sons. Correspondingly, the OR for chronic knee pain in presence of chronic knee pain in fathers was 1.1 (95% CI 0.9-1.4) in daughters and 1.3 (95% CI 1.0-1.6) in sons. The OR for chronic hip pain, when fathers reported chronic hip pain, was 1.4 (95% CI 1.2-1.7) in daughters and 1.5 (95% CI 1.1-1.9) in sons.

Table 3 show the OR for chronic knee and hip pain among offspring associated with their parental chronic pain, in one or both parents, a pooled analysis. When only fathers reported chronic knee pain the OR for chronic knee pain among the offspring was 1.2 (95% CI 0.9-1.6). The OR for chronic knee pain among the offspring was somewhat higher when only mothers reported knee pain with an OR of 1.8 (95% CI 1.4-2.2). If both parents reported knee pain the OR was 1.7 (95% CI 1.3-2.2). The OR for hip pain among the offspring, when only fathers reported hip pain, was 1.3 (95% CI 1.0-1.7). When only mothers reported hip pain the OR was 1.4 (95% CI 1.1-1.7). If both parents reported chronic hip pain the OR was 2.0 (95% CI 1.6-2.5) for chronic hip pain in the offspring.
Table 2 Odds ratio (OR) for offspring chronic knee or hip pain associated with parental chronic knee or hip pain.

<table>
<thead>
<tr>
<th>Parental pain</th>
<th>Daughters</th>
<th>Sons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case/Non-case</td>
<td>Age-adjusted OR</td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>No</td>
<td>296/2412</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>331/1198</td>
</tr>
<tr>
<td>Hip</td>
<td>No</td>
<td>363/2345</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>377/1386</td>
</tr>
<tr>
<td>Father</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>No</td>
<td>391/2608</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>187/940</td>
</tr>
<tr>
<td>Hip</td>
<td>No</td>
<td>433/2566</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>264/891</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval. a Adjusted for parental age. b Adjusted for parental age (continuous), parental BMI (continuous), parental PA (inactive, low activity, medium activity, high activity), parental education (≤9 years, 10-12 years, >12 years), parental physical activity at work (sedentary, walking, heavy lifting/heavy laborer and unknown), smoking (never, former, current, unknown)
Table 3 Odds ratio (OR) for knee and hip pain among offspring associated with parental pain in one or both parents, a pooled analysis.

<table>
<thead>
<tr>
<th>Parental pain</th>
<th>Offspring pain</th>
<th>Case/Non-case</th>
<th>Age-adjusted OR(^a)</th>
<th>Multi-adjusted OR(^b) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Pain</td>
<td></td>
<td>237/2333</td>
<td>1.0</td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td>Only father</td>
<td></td>
<td>93/677</td>
<td>1.3</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>Only Mother</td>
<td></td>
<td>218/1013</td>
<td>1.8</td>
<td>1.8 (1.4-2.2)</td>
</tr>
<tr>
<td>Both parents</td>
<td></td>
<td>103/453</td>
<td>1.9</td>
<td>1.7 (1.3-2.2)</td>
</tr>
<tr>
<td><strong>Hip</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Pain</td>
<td></td>
<td>241/2329</td>
<td>1.0</td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td>Only Father</td>
<td></td>
<td>111/651</td>
<td>1.5</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Only Mother</td>
<td></td>
<td>205/1177</td>
<td>1.5</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>Both parents</td>
<td></td>
<td>153/577</td>
<td>2.3</td>
<td>2.0 (1.6-2.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval. \(^a\) Adjusted for parental age. \(^b\) Adjusted for parental age (continuous), parental BMI (continuous), parental PA (inactive, low activity, medium activity, high activity), parental education (≤9 years,10-12 years, >12 years), parental physical activity at work (sedentary, walking, heavy lifting/heavy laborer and unknown), smoking (never, former, current, unknown), offspring gender.

In supplementary analyses, we also analyzed the parent-offspring associations in chronic knee and hip pain restricting parental pain to those who also reported osteoarthritis (Table 4). Among daughters, the OR for chronic knee pain when mothers reported chronic knee pain and osteoarthritis was 1.6 (95% CI 1.3-2.1), the association was somewhat stronger among sons with an OR of 1.8 (95% CI 1.3-2.3). When mothers reported hip pain and osteoarthritis the OR for hip pain was 1.4 (95% CI 1.1-1.8) in daughters and 1.4 (95% CI 1.0-1.9) in sons. Correspondingly, when fathers reported chronic knee pain and osteoarthritis the OR was 1.0 (95% CI 0.8-1.4) in daughters and 1.5 (95% CI 1.0-2.1) in sons. When fathers reported hip pain and osteoarthritis the OR in daughters was 1.3 (95% CI 1.0-1.7) and the OR in sons was 1.7 (95% 1.2-2.4).
Table 4 Odds ratio (OR) for offspring chronic knee or hip pain associated with parental chronic knee or hip pain and reported osteoarthritis.

<table>
<thead>
<tr>
<th>Parental pain</th>
<th>Daughters</th>
<th>Case/Non-case</th>
<th>Age-adjusted OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multi-adjusted OR&lt;sup&gt;b&lt;/sup&gt; (95%CI)</th>
<th>Sons</th>
<th>Case/Non-case</th>
<th>Age-adjusted OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multi-adjusted OR&lt;sup&gt;b&lt;/sup&gt; (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>484/3212</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td></td>
<td></td>
<td>282/2597</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Yes + Osteoarthritis</td>
<td>143/398</td>
<td>1.7</td>
<td>1.6 (1.3-2.1)</td>
<td>81/371</td>
<td>1.7</td>
<td>1.8 (1.3-2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>596/3328</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td>234/2777</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes + Osteoarthritis</td>
<td>144/403</td>
<td>1.5</td>
<td>1.4 (1.1-1.8)</td>
<td>58/373</td>
<td>1.4</td>
<td>1.4 (1.0-1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>519/3283</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td>304/2676</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes + Osteoarthritis</td>
<td>59/265</td>
<td>1.1</td>
<td>1.0 (0.8-1.4)</td>
<td>45/236</td>
<td>1.5</td>
<td>1.5 (1.0-2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>608/3197</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td>229/2779</td>
<td>1.0</td>
<td>1.0 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes + Osteoarthritis</td>
<td>89/260</td>
<td>1.4</td>
<td>1.3 (1.0-1.7)</td>
<td>44/265</td>
<td>1.7</td>
<td>1.7 (1.2-2.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval. <sup>a</sup>Adjusted for parental age. <sup>b</sup>Adjusted for parental age (continuous), parental BMI (continuous), parental PA (inactive, low activity, medium activity, high activity), parental education (≤9 years, 10-12 years, >12 years), parental physical activity at work (sedentary, walking, heavy lifting/heavy laborer and unknown), smoking (never, former, current, unknown)
Discussion

Main findings
The results of the current study show an increased occurrence of chronic knee and hip pain among adult offspring if parents report chronic pain in the same region. The associations appear to have roughly the same impact in sons and daughters. When only the father reported chronic pain in hip or knee there was an increased odds for offspring pain in the same region. The same appeared when only the mother reported chronic pain in the hip or knee region. The association was slightly stronger when only the mother reported pain compared to when only the father reported pain. However, when both parents reported hip pain the association was strongest. The analyses incorporating information on osteoarthritis show slightly stronger parent-son associations compared to the main analyses.

Strength and limitations
The HUNT survey covers a wide aspect of topics in regard to health and lifestyle, allowing analysis to be adjusted for several potential confounding factors such as smoking, physical activity and BMI (Holmen et al., 2003; Krokstad et al., 2013). The combination of physical examination, the high number of participants and the thorough work with the questionnaire make the study less likely to be prone to selection bias and results left to chance. Another major strength of this study is the population based study sample, which is considered to be homogenous and fairly representative for Norway (Hopper, Bishop, & Easton, 2005; Krokstad et al., 2013). Furthermore, the analyses are based on information from adult offspring, the adult offspring is more likely to live separately from their parents, thereby decreasing the possibility of shared environment as potential confounder. Additionally, the information on chronic pain was collected at separate surveys (i.e. HUNT2 and HUNT3) reducing the possibility of shared events (e.g. trauma) to affect the pain reported in parents and offspring (Hoftun et al., 2013). Finally, the family linkage allows for self-reported pain from both parents and offspring without having to rely on indirect information from relatives.

On the other hand, self-reported measures of pain and other health and lifestyle related factors could have introduced bias. Subjective reporting of pain has
both strengths and limitations (Chapman et al., 1985; Kuorinka et al., 1987; Landmark, Romundstad, Dale, Borchgrevink, & Kaasa, 2012). One advantage is the effectiveness and simplicity which may lead to a good compliance, but again these results may oversimplify the complexity of the pain experience (Chapman et al., 1985). Eriksen and Ihlebæk has described subjective health complains to be complex, as the thresholds in regard to pain and complains are individual and subjective (Eriksen & Ihleboek, 2002). However, the chronic pain question in HUNT is implemented from the Nordic Questionnaire, which has been standardized with support from the Nordic Council of Ministers (Kuorinka et al., 1987).

Furthermore, misclassification might be a limitation in this present study as the subjects are asked to report factors such as smoking, education and physical activity at work and leisure time. However, the leisure time physical activity question has been validated against objective measurements and has been regarded as a reliable tool in regard to the vigorous and the sitting category (Kurtze, Rangul, & Hustvedt, 2008). Still, the transmission from this validation study may be considered to be low as the study contains a rather small sample size of young men. However, questionnaires have been described as a useful tool in classifying subjects into broad classifications of physical activity (Shephard, 2003). Nonetheless, the effects of unmeasured variables in this study cannot be out ruled and thus the occurrence of bias in forms of misclassification.

In the analysis of osteoarthritis, we are not sure that the reporting of osteoarthritis is related to pain in hip or knees. The question on osteoarthritis is not asked in relation to chronic pain and its localization, and could be reported without any relation to pain in knees and hip. Hence, these results should be interpreted with caution. However, osteoarthritis is a phenomenon often reported in relation to the hip and knee region (Spector & MacGregor, 2004).

It should also be noted that the data consists of some siblings, and thus the precision of estimated associations could be somewhat inflated (i.e. narrow confidence intervals) due to less variation in the data than if all subjects were independent of each other.

**Comparison with current literature**

The results in this study are in accordance with other family linkage studies, showing an increased risk of chronic pain when other family members have chronic pain
Twin studies have showed spinal pain to have heritability estimates ranging from modest to high due to genetic influence (Fjer R. et al., 2006; Hartvigsen et al., 2009; Nyman et al., 2011). Additionally, both Arnold and colleagues (2004) and Buskila and co-workers (1996) have reported a family clustering of fibromyalgia (Arnold et al., 2004; Buskila, Neumann, Hazanov, & Carmi, 1996). Arnold and co-workers demonstrated through clinical testing and interviews an increased risk of fibromyalgia when a family member has reported fibromyalgia (Arnold et al., 2004). In correspondence, Hoftun and co-workers (2013) showed an association between parental chronic pain and chronic pain among young offspring (Hoftun et al., 2013). On the other hand, a population-based study done in England did not find an association between parental pain and pain in the offspring. (Jones, Silman, & Macfarlane, 2004). These conflicting results suggest no conclusive answer to the parent-offspring relation in terms of pain. However, in line with Hoftun and colleagues this current study indicates a similar inter-generational association between parental chronic pain and adult offspring chronic pain in hip and knee.

In regard to chronic knee and hip pain, most studies have been done in relation to osteoarthritis, which appears to cluster within family (Hirsch et al., 1998; Neame et al., 2004). A sibling study demonstrated an increased risk for hip osteoarthritis among siblings of patients who have undergone a hip replacement. The study showed an 11-fold greater risk for osteoarthritis in the hip among male siblings if the joint spacing was 1.5 mm or less and a four-fold increased risk in female siblings (Lanyon, Muir, Doherty, & Doherty, 2000). In another study on knee osteoarthritis, Neame and colleagues (2004) demonstrated through radiographs of the tibiofemoral joint and patella femoral joint, an increased risk of knee osteoarthritis among siblings compared to community representatives. In a pooled analysis the siblings had more than a two-fold increased risk of tibiofemoral osteoarthritis and a two-fold increased odds of patella femoral osteoarthritis (Neame et al., 2004). These results indicate an increased risk for chronic knee pain when siblings have reported osteoarthritis. In the present study, the parent-son association was slightly stronger if parental pain was restricted to those who also reported osteoarthritis. However, we were not able to separate environmental and genetic effects in these data.
An important remark when comparing the results with other studies is the usage of different definitions in terms of pain and chronic pain. Although the results appear to be in agreement with the current literature, researchers suggest the lack of standardization to cause difficulties in the comparison between studies (Chapman et al., 1985; Landmark et al., 2012). Hence, the comparisons to be interpreted with caution.

**Possible mechanisms**

The results of the present study may be explained by genetic factors, environmental factors, or a combination of the two (Kaprio J, 2000; Mogil, 2012). The environmental component may consist of several factors such as smoking, alcohol consumption, cultural differences, BMI, physical activity, socioeconomic status, quality of life and a familial history of pain (Buskila & Neumann, 2005; Ferreira et al., 2013; Kaprio J, 2000; Larsson et al., 2012). Some researchers suggest that the family environment and familial history of chronic pain to be associated with the development of chronic pain (Hoftun et al., 2013; Larsson et al., 2012). Correspondingly, MacGregor and co-workers (1997) completed a study on adult twins and pain thresholds suggesting shared environmental effects to be of importance rather than genetic effects in terms of pain thresholds. The study further suggests their results to be consistent with other observational studies suggesting pain to be induced by learned behavior within the family (MacGregor et al., 1997) However, Fjer and colleagues (2006) reports the genetic factor to be of relevance, further suggesting the environmental factor to become more dominant with increasing age (Fjer R. et al., 2006).

On the other hand, when discussing the genetic component, multiple genes may interfere with the susceptibility to develop a disease, these genes may also have an influence in other diseases or tasks within the body (Kaprio J, 2000). For chronic pain in knee and hip, several articles have suggested a possible genetic susceptibility (Ding et al., 2005; Neame et al., 2004; Spector & MacGregor, 2004; Valdes & Spector, 2010, 2011). Zhai and co-workers (2005) have investigated the heritability estimates for structural changes in the knee and muscle strength, which may contribute to chronic knee pain. The heritability estimates range from 20-73% depending on the structure examined (Zhai et al., 2005). Neame and colleagues (2004) have investigated a possible genetic influence on risk of osteoarthritis,
demonstrating an increased occurrence of osteoarthritis as a sibling reports osteoarthritis (Neame et al., 2004). Moreover, Valdes and co-workers (2011) have done a review on the subject where they showed several genes to be associated with the development of osteoarthritis. The researchers specially emphasize the gene GDF5, which is frequently reported to be association with osteoarthritis. They also highlight the lack of convincing evidence in regard to hip osteoarthritis (Valdes & Spector, 2011). Nevertheless, the genetic factor is important to consider in context to the environmental factor, as it may give a better understanding of the relative size of the genetic factor (Kaprio J, 2000).

Whether the results in this present study are explained through environmental or genetic factors are uncertain. To be able to distinguish between the two factors the study design and study sample has been reported to be two key elements (Hopper et al., 2005). However, Neogi (2013) has described the impact of pain in osteoarthritis, viewing the etiology of osteoarthritis with a multidimensional and multifactorial approach. Neogi (2013) further suggest the etiology to be more complex rather than explained by either a genetic or environmental factor (Neogi, 2013). In correspondence, Mogil (2013) describes chronic pain and the investigation to be more complex and diverse than first anticipated (Mogil, 2012).

**Conclusion**

In conclusion, there seems to be an increased occurrence of chronic knee and hip pain among adult offspring when parents report chronic pain in the hip or knee. The results also suggest slightly stronger associations, among sons, when parents also report osteoarthritis. Revealing and detecting a family pattern in pain could be of clinical importance, both for treatment and prevention. However, whether these results are explained by genetic or environmental factors are not clear, but the majority of previous family studies suggest a genetic susceptibility.
Reference


