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# BMJ Open

## The influence of family history on prognosis of spinal pain and the role of leisure time physical activity and body mass index: family-linkage data from the Norwegian HUNT Study.

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Manuscripts

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3 **The influence of family history on prognosis of spinal pain and the role of leisure time**  
4 **physical activity and body mass index: family-linkage data from the Norwegian HUNT**  
5 **Study.**  
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## ABSTRACT

**Objectives:** To investigate the influence of parental chronic spinal pain on prognosis of chronic spinal pain in adult offspring, and whether offspring physical activity level and body mass index (BMI) modified this association.

**Design:** Prospective cohort study.

**Setting:** We used family linked longitudinal data from the Norwegian HUNT study collected in HUNT2 (1995-97) and HUNT3 (2006-08).

**Participants:** A total of 1,529 offspring who reported spinal pain in HUNT2 were linked with parental data and followed-up in HUNT3.

**Outcomes:** We estimated relative risk (RR) with 95% confidence intervals (CIs) for recovery from chronic spinal pain, and also from activity limiting spinal pain, in offspring related to chronic spinal pain in parents. We also investigated whether offspring leisure time physical activity and BMI modified these intergenerational associations in spinal pain.

**Results:** Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR: 0.83, 95% CI: 0.69, 0.99) and activity limiting spinal pain (RR: 0.71, 95% CI: 0.54, 0.94), compared to offspring of parents without chronic spinal pain.

Analyses stratified by BMI and physical activity showed no strong evidence of effect modification on these associations. However, offspring who were overweight/obese and with both parents reporting spinal pain had particularly low probability of recovery from activity limiting spinal pain, compared those who were normal weight and had parents without spinal pain (RR: 0.57, 95% CI: 0.39-0.84).

**Conclusion:** Offspring with chronic spinal pain are less likely to recover if they have parents with chronic spinal pain, particularly if offspring are overweight/obese.

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5 **Key words:** Low back pain, neck pain, chronic pain, obesity, family study, physical activity.  
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### 10 **Strengths and limitations of this study**

- 12 • The HUNT Study is a large population-based health study with longitudinal data that  
13 allows prospective analysis on the prognosis of chronic spinal pain.  
14
- 15 • Chronic spinal pain was independently reported in parents and offspring; family relations  
16 was informed by a linkage with a national registry; and the data allowed us to control for  
17 a wide range of potential confounders.  
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- 19 • Information on pain status, physical activity, and body mass index was not updated  
20 throughout the follow-up period.  
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## INTRODUCTION

Spinal pain that includes low back and neck pain is highly prevalent and a common cause of disability worldwide.[1] The natural history of spinal pain is extremely variable and may last a few days or persist for many years.[2] A substantial proportion of patients recover within the first three months of a spinal pain episode, but around three quarters of the remaining patients are likely to experience pain one year after onset.[3, 4] People who fail to recover in the first few months following an acute episode are at greater risk of poor prognosis.[5] Spinal pain, especially in its chronic and disabling form, could be a significant personal and financial burden,[6] and may also influence families and society.[1] It is therefore vital to identify factors that influence prognosis of spinal pain, which in turn can inform preventive interventions to reduce chronicity.

Parental pain is strongly associated with the increased risk of chronic musculoskeletal pain in offspring, both during adolescence[7], and in later adulthood.[8] Furthermore, there is preliminary evidence that treatment response in patients with chronic low back pain is influenced by genetic factors.[9] It is, therefore, possible that parental history of spinal pain influences the prognosis of spinal pain in offspring. Conversely, several studies have shown that engagement in moderate to vigorous-intensity leisure time physical activity and maintenance of a normal body mass index (BMI) are associated with better prognosis of spinal pain.[10-14] Thus, a healthy offspring lifestyle could modify a possible adverse effect of parental spinal pain on prognosis of offspring spinal pain. Currently, there is limited knowledge about the influence of parental spinal pain on prognosis of spinal pain in offspring and whether this association is modified by offspring lifestyle.

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3 In this study, we have used population-based longitudinal data from the Norwegian HUNT Study  
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5 to investigate the influence of parental spinal pain on the prognosis of chronic spinal pain  
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7 regarding severity and activity limitation in the adult offspring. We have also investigated  
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9 whether offspring leisure time physical activity and BMI modify any of these associations.  
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## 14 **METHODS**

### 15 **Study population**

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17 The HUNT Study is a population-based health study conducted within the county of Nord-  
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19 Trøndelag, Norway. The study was performed in three consecutive waves, first in 1984–1986  
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21 (HUNT1), then in 1995–1997 (HUNT2), and last in 2006–2008 (HUNT3). In all three surveys,  
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23 all residents 20 years of age and older were invited to participate, and information on lifestyle  
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25 and health-related factors were collected by questionnaires and a clinical examination.  
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27 Information on musculoskeletal pain was not collected at HUNT1. Therefore, those who were  
28  
29 eligible for inclusion in this study had participated at HUNT2 and HUNT3. At HUNT2, 93,898  
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31 individuals were invited to participate, and 65,237 (65.5%) joined the study, while at HUNT3  
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33 93,860 were invited and 50,807 (54.1%) agreed to participate.[15, 16] Each participant signed  
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35 written consent, and the study was approved by the Regional Committee for Medical and Health  
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37 Research Ethics Central Norway (ref. no. 2011/1455). Further information about selection  
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39 procedures, participation and questionnaires used in the HUNT study can be found at  
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41 <http://www.ntnu.edu/hunt>.  
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### 51 **Patient involvement**

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3 Since historical cohort data was used in this study, patients were not involved in the conduct and  
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5 design of the study.  
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### 10 **Record linkage**

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12 The unique personal identification number held by all Norwegian citizens was used to link each  
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14 participant's record to information from the Family Registry at Statistics Norway, and therefore  
15  
16 establish a link between parents and offspring who participated in one or both of HUNT2 and  
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18 HUNT3. A total of 11,483 offspring reported spinal pain at HUNT2, and of these, 6,662 could be  
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20 followed-up on spinal pain status in HUNT3, approximately 11 years later. To be able to study  
21  
22 the association between parental spinal pain and offspring prognosis of spinal pain, we selected  
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24 all 1,529 parent–offspring trios (i.e., mother, father and adult offspring) where both the mother  
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26 and the father had information on spinal pain from HUNT2.  
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### 33 **Chronic spinal pain**

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35 At HUNT2 and HUNT3, participants were asked to complete the Standardized Nordic  
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37 Questionnaire which has acceptable reliability and validity.[17] The question regarding  
38  
39 musculoskeletal pain was as follows: “In the last year, have you had pain and/or stiffness in  
40  
41 muscles or joints that have lasted at least 3 consecutive months?” (response options: “no” and  
42  
43 “yes”). Participants who answered “yes” were asked to indicate the affected body area(s).  
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45  
46 Offspring who reported chronic neck and/or low back pain (spinal pain) at HUNT2 were  
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48 included in this study, and offspring who also reported spinal pain at HUNT3 were considered  
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50 not recovered (outcome measure). Offspring reporting spinal pain at HUNT2 were also asked to  
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52 indicate if the pain had led to reduced leisure time activity (response options: “no”, and “yes”) or  
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3 reduced their work ability (response options: “no”, “to some extent”, “considerably”, or “don’t  
4 know”). Offspring who answered “yes” to the question on reduced leisure time activity and/or  
5 reported work ability to be reduced “to some extent” or “considerably”, were classified as having  
6 “activity limiting spinal pain”. In secondary analyses, we used this information to investigate the  
7 prognosis of activity limiting spinal pain; i.e., recovery was defined as not reporting activity  
8 limiting spinal pain at HUNT3. Based on the same question as described above, we obtained  
9 information on parental chronic spinal pain. Further, we created a variable with four mutually  
10 exclusive categories for presence of parental chronic spinal pain at baseline (exposure measure):  
11 “none”, “mother”, “father”, or “both parents”.  
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### 26 **Leisure time physical activity**

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28 Leisure time physical activity was assessed by the following question “How much of your leisure  
29 time have you been physically active during the last year? (Think of a weekly average for the  
30 year. Your commute to work counts as leisure time)”. Participants reported the number of hours  
31 of either light (no sweating or heavy breathing) or hard (sweating and heavy breathing) activity  
32 using the response options “none”, “less than 1 hour”, “1–2 hours”, and “3 or more hours” for  
33 each type of activity. Based on this information, we constructed a variable with four categories  
34 (combining information on light and hard activity): 1) “inactive” (no light or hard activity), 2)  
35 “low activity” (<3 hours light and no hard activity), 3) “moderate activity” (≥3 hours light and/or  
36 <1 hour hard activity), and 4) “high activity” (any light and ≥1 hour hard activity). In the  
37 combined analyses of parental chronic spinal pain and offspring leisure time physical activity the  
38 categories “inactive” and “low activity” were collapsed into one category labelled “Physically  
39 inactive” and the categories “moderate activity” and “high activity” were collapsed into one  
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3 category labelled “Physically active”. This categorization has been used previously in other  
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5 studies based in data from HUNT.[18, 19]  
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### 10 **Body mass index**

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12 Standardized measurements of body height (to the nearest centimetre) and body weight (to the  
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14 nearest half kilogram) were obtained at clinical examination. BMI was calculated as weight  
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16 divided by the square of height ( $\text{kg}/\text{m}^2$ ), and classified into four BMI groups according to the  
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18 cut-off points suggested by the World Health Organization:[20] underweight ( $\text{BMI} < 18.5 \text{ kg}/\text{m}^2$ ),  
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20 normal weight ( $\text{BMI} 18.5\text{--}24.9 \text{ kg}/\text{m}^2$ ), overweight ( $\text{BMI} 25.0\text{--}29.9 \text{ kg}/\text{m}^2$ ), and obese ( $\text{BMI}$   
21  
22  $\geq 30.0 \text{ kg}/\text{m}^2$ ). Only 27 participants (1 %) were classified as “underweight”, and the combined  
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24 analysis of parental chronic spinal pain and offspring BMI, the categories “underweight” and  
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26 “normal weight” were collapsed into one category labelled “normal weight”. The categories  
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28 “overweight” and “obese” were collapsed into one category labelled “overweight/obese”.  
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### 35 **Statistical analysis**

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37 We used a Poisson regression model [21-24] to estimate relative risk (RR) of chronic spinal pain  
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39 and activity limiting spinal pain in offspring whose parents reported chronic spinal pain, using  
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41 parents with no chronic spinal pain as the reference category. Precision of estimates was assessed  
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43 by a 95% confidence interval (CI). All standard errors were adjusted for within-family clustering  
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45 (i.e., siblings) using the vce (cluster) option in Stata, treating observations between families as  
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47 independent and within families as dependent, and thus avoiding inflated precision of the  
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49 estimated associations.[25]  
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Possible effect modification by offspring leisure time physical activity or offspring BMI was assessed by stratified analyses (i.e. physically active vs physically inactive and normal weight vs overweight/obese) as well as by tests of the estimated relative excess risk due to interaction (RERI) (i.e., departure from additive effects). We calculated RERI estimates with 95% CIs from the following equation:  $RERI = RR_{\text{parental pain \& physically active/overweight and/or obese}} - RR_{\text{parental pain \& physically activity/ overweight and/or obese}} - RR_{\text{parental pain \& physically inactivity/normal weight}} + 1$ , [26] i.e.,  $RERI > 0$  indicate a synergistic effect beyond an additive effect. Statistical interaction was also evaluated on a multiplicative scale by a likelihood ratio test of a product term in the model (these likelihood ratio tests had to be run without cluster-adjusted standard errors to avoid misspecification of the model).

The main analyses (parental influence on risk of poor prognosis) were adjusted for possible confounding by offspring sex (male, female), age (continuous), BMI (“underweight”, “normal weight”, “overweight”, “obese”, or “unknown”), leisure time physical activity (“physically inactive” or “physically active”, or “unknown”), education (“<10 years”, “10–12 years”, “>13 years”, or “unknown”), and depression (“depressed”, or “not depressed”, or “unknown”).

Depression was assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS) using a score of 8 as a cut-off for a dichotomised variable.[27-29]

All statistical tests were two-sided, and all analyses were conducted using Stata statistical software (version 13.0, STATA Corp., College Station, TX, USA).

## RESULTS

In this prospective study of 1,529 offspring with chronic spinal pain at baseline, a total of 540 (35%) offspring were defined as recovered after approximately 11 years of follow-up.

Additionally, among 775 offspring with activity limiting spinal pain, 244 were defined as recovered at follow-up. Descriptive statistics of offspring, mothers, and fathers are shown in Table 1. The mean age at baseline was 32.8 (8.6) years among offspring. Most offspring were physically active (64.7%), and about half of the offspring (52.9%) were classified as overweight or obese. About one third (36.9%) of the offspring were current smokers, and just a small portion of offspring (18.7%) reported having a higher education degree. A small proportion (10.5%) of offspring had symptoms of depression according to the Hospital Anxiety and Depression Scale.

Table 1. Baseline characteristics of the study population at HUNT2

Variables	Offspring	Mothers	Fathers
Participants, no.	1,529	1,529	1,529
Age, mean (SD)	32.8 (8.6)	63.8 (9.4)	67.2 (9.5)
Body mass index, mean (SD)	25.9 (5.2)	28.3(7.3)	27.6 (6.9)
Overweight/obese, % (n)	42.3 (799)	70.6 (1,080)	72.2 (1,104)
Physically active <sup>a</sup> , % (n)	63.9 (977)	43.0 (510)	57.7 (716)
Current smoker, % (n)*	33.1 (506)	26.3 (400)	28.5 (434)
Higher education <sup>b</sup> , % (n)	20.7 (316)	4.5 (61)	6.0 (84)
Symptoms of depression <sup>c</sup> , %, (n)	10.4 (155)	17.0 (225)	16.5 (215)

SD, standard deviation

<sup>a</sup> Engagement in moderate ( $\geq 3$  hours light and/or  $< 1$  hour hard activity per week) or high leisure time physical activity (any light and  $\geq 1$  hour hard activity per week)

<sup>b</sup> University education or higher

<sup>c</sup> Score  $\geq 8$  on the Hospital Anxiety and Depression Scale

### Chronic spinal pain and activity limiting spinal pain

Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR: 0.83, 95% CI: 0.69, 0.99) and activity limiting spinal pain (RR: 0.71, 95% CI: 0.54-0.94) compared to offspring with no parents with chronic spinal pain (Table 2). These associations were weaker and less precise when chronic spinal pain was present in only one parent, with similar associations observed for maternal and paternal spinal pain.

Table 2. Relative risk (RR) of recovery from spinal pain and activity limiting spinal pain in adult offspring associated with parental spinal pain.

Parental spinal pain	Offspring spinal pain				Offspring activity limiting spinal pain			
	No. of persons	No. of cases	Crude RR	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Crude RR	Adjusted RR <sup>a</sup> (95% CI)
None	346	138	1.00	1.00 (Ref.)	163	66	1.00	1.00 (Ref.)
Mother	424	147	0.88	0.90 (0.75-1.07)	214	62	0.73	0.74 (0.56-0.98)
Father	272	97	0.90	0.91 (0.74-1.12)	127	40	0.77	0.78 (0.57-1.05)

Both	487	158	0.82	0.83	271	76	0.69	0.71
			(0.69-0.99)				(0.54-0.94)	

CI, confidence interval

<sup>a</sup>Adjusted for age, sex, BMI, smoking, leisure time physical activity, education and HADS score.

### Physical activity

In the stratified analysis for physical activity, there was no strong evidence of effect modification for either physically active offspring (RR: 0.78; 95% CI: 0.62, 0.98), or physically inactive offspring (RR: 0.98; 95% CI: 0.71, 1.36) (Table 3). Tests of statistical interaction indicate no departure from neither multiplicative ( $p = 0.037$ ) nor additive effects (RERI 0.19, 95% CI, -0.17, 0.55), data not shown.

Table 3. Relative risk (RR) of recovery from spinal pain in adult offspring associated with parental spinal pain; analysis stratified by leisure time physical activity.

	Physically active			Physical inactive		
	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)
Parental spinal pain						
None	229	97	1.00 (Ref.)	111	40	1.00 (Ref.)
Mother or father	434	163	0.94 (0.77-1.14)	246	74	0.82 (0.60-1.11)
Both parents	314	100	0.78 (0.62-0.98)	166	58	0.98 (0.71-1.35)

CI: confidence interval

aAdjusted for age, sex, BMI, smoking, education and HADS score.

### Body mass index

In the stratified analysis for body mass index, there was no strong evidence of effect modification. However, offspring who were overweight or obese had the lowest probability of recovery if both parents report activity limiting spinal pain or chronic spinal pain (RR: 0.57; 95% CI: 0.39, 0.84 and RR: 0.79; 95% CI: 0.61, 1.03 respectively) compared to normal weight (Table 4). In addition, there was no evidence of statistical interaction neither on the additive (estimates of RERI for chronic spinal pain and activity limiting spinal pain were -0.04; 95% CI: -0.38, 0.30 and -0.34; 95% CI: -0.91, 0.23, respectively) nor on the multiplicative scale ( $p = 0.131$  and  $p = 0.048$ , respectively).

Table 4. Relative risk (RR) of recovery from spinal pain and activity limiting spinal pain in adult offspring associated with parental spinal pain; analysis stratified by BMI.

Variables	Normal weight			Overweight/obese		
	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)
Offspring spinal pain						
Parental spinal pain						
None	168	68	1.00 (Ref.)	177	69	1.00 (Ref.)
Mother or father	316	111	0.88 (0.70-1.12)	380	133	0.89 (0.70-1.12)

Both parents	242	82	0.86	242	76	0.79
			(0.66-1.11)			(0.61-1.03)
Offspring activity limiting spinal pain						
Parental spinal pain						
None	86	34	1.00 (Ref.)	130	50	1.00 (Ref.)
Mother or father	151	42	0.72	301	98	0.72
			(0.49-1.04)			(0.51-0.99)
Both parents	129	41	0.84	188	52	0.57
			(0.57-1.24)			(0.39-0.84)

CI: confidence interval.

aAdjusted for age, sex, leisure physical activity, smoking, education and depression.

## DISCUSSION

### Summary of findings

The findings of this large population-based prospective family-linkage study indicate that offspring with both parents reporting chronic spinal pain are less likely to recover from chronic spinal pain and activity limiting spinal pain compared with offspring with no parent with spinal pain. Overall, there was no strong evidence that physical activity or body mass index modified these associations, although the results suggest that the inverse association between parental spinal pain and recovery from activity limiting spinal pain was strongest among offspring with a high BMI. This study supports the evidence from twin studies that genetics potentially influences recovery from chronic spinal pain,[30] but these intergenerational associations incorporate



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3 shared environmental factors and shared beliefs that could influence recovery. For instance, there  
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5 is evidence showing that negative beliefs about pain and negative expectations about recovery  
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7 predict chronic and disabling spinal pain.[31-33] It seems clear that it is important to consider the  
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9 family history of chronic spinal pain as well as lifestyle behaviours when identifying people at  
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11 higher risk of non-recovery.  
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### 17 **Comparison of findings with previous research**

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19 A recent systematic review showed that offspring of parents with chronic pain have poorer  
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21 outcomes regarding pain, general health, psychological, and family functioning as compared to  
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23 offspring of parents without pain.[34] The inter-generational transmission of spinal pain could be  
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25 explained by genetic heritability [35, 36] or a family shared environment.[37-40] Moreover, it  
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27 has been suggested that the genetic influence is greater in more disabling pain conditions, such as  
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29 chronic widespread pain and chronic activity limiting spinal pain, rather than in acute or sub-  
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31 acute non-debilitating pain.[35, 36] It is widely accepted that lifestyle factors, such as physical  
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33 activity and body weight, also play a significant role in the prognosis of chronic musculoskeletal  
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35 pain.[41]  
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42 Some studies have suggested that people with chronic back pain who regularly engage in leisure  
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44 time physical activity have better prognosis measured in terms of pain, disability, and quality of  
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46 life than those who are sedentary.[18, 42] However, there remains conflicting evidence regarding  
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48 how physical activity influences the prognosis of spinal pain,[43] with studies demonstrating that  
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50 both low and high levels of physical activity can negatively influence the prognosis of spinal  
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52 pain.[44, 45] For instance, a study found that high leisure time physical activity was related to  
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3 decreased prevalence of low back pain.[46] Whereas another study found that either high or low  
4 levels of leisure time physical activity was related to increased prevalence of low back pain.[44]  
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6 In contrast, a prospective study did not find any significant association between moderate/high  
7 levels of leisure physical activity and low back pain in young adults.[47] Another follow-up  
8 study found that regular habits of leisure physical activity have no effect on recovery from low  
9 back pain.[48] The inconsistency in the literature is possibly attributed to the diverse definitions  
10 and classifications of levels of physical activity. If such divergent associations with leisure time  
11 physical activity exist this could mask a possible modifying effect of physical activity in our  
12 analyses.  
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26 The literature has provided evidence that obesity is associated with poor outcomes in people with  
27 chronic widespread pain,[49, 50] as well as chronic spinal pain [18, 51, 52] and also decreases  
28 the probability of recovery from chronic spinal pain regardless of the care they receive,[14]  
29 however, whether BMI could modify [19] the relationship between parental spinal pain on  
30 offspring recovery from chronic spinal pain has not been investigated before. Our results suggest  
31 that offspring BMI may modify on the parent-offspring association of spinal pain, with  
32 somewhat stronger associations among offspring who were classified as overweight or obese  
33 than those who were underweight or normal weight. Research has shown that inter-individual  
34 differences in pain sensitivity and endogenous pain-inhibitory capacity could reflect variations in  
35 the inherent susceptibility for chronic pain,[53, 54] but that a triggering exposure is required for  
36 the development of chronic pain.[55, 56] This could suggest that a possible genetic susceptibility  
37 for poor recovery from chronic pain [57, 58] as a higher penetrance between offspring who are  
38 overweight or obese.  
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## Strengths and limitations

This study has several strengths including the prospective design utilising a large population-based sample with a long follow-up period. In addition, the registry based information on family relations allowed us to include information on chronic spinal pain obtained from parents and offspring independently and at different time points. An important aspect is that the offspring were adults at the time of data collection, indicating that the parent-to-offspring association of chronic spinal pain persists into adulthood when the offspring most likely live apart from their parents. Furthermore, we were able to adjust for several offspring characteristics that could confound the parent-offspring associations of chronic spinal pain, such as age,[59] BMI,[52] leisure physical activity,[60] smoking,[59] depression [59] and education.[36, 61] However, we cannot exclude the possible residual confounding attributable to unknown or unmeasured factors.

There are some limitations that should be taken into account. Firstly, information on chronic spinal pain was only reported at baseline and follow-up 10-11 years later, with no information on possible changes in chronic spinal pain during the follow-up period. Consequently, recovery measured at follow-up could have been related to another episode of chronic spinal pain rather than the one reported at baseline. However, it is unlikely that this was differential between offspring with parents who reported chronic spinal pain and those who did not. Likewise, information on leisure time physical activity and BMI was only assessed at baseline, with no information on possible changes during the follow-up period. Secondly, although the questions about leisure time physical activity used in this study have been reported to have good reliability and provide useful measures of leisure physical activity,[62] subjective interpretations of the

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3 activity questions could have influenced the results. Besides, it is well known that self-reports  
4 may lead to under or overestimation of the variables of interest.[63] Thirdly, a premise for  
5 inclusion into this study was that the mother, father and offspring all had to participate in the  
6 health survey. To some extent, this may have resulted in a selected and more health conscious  
7 sample than the general population. Nevertheless, it is questionable whether representativeness is  
8 a prerequisite for making valid risk assessments in epidemiological studies.[57]  
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## 19 **CONCLUSION**

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21 Offspring with chronic spinal pain are less likely to recover if they have parents with chronic  
22 spinal pain compared to offspring without parental chronic spinal pain. This association is  
23 stronger when the offspring present pain that interferes with their usual work and leisure  
24 activities (activity limiting spinal pain). The inverse association between parental chronic spinal  
25 pain on recovery was somewhat stronger among offspring who were overweight or obese. The  
26 association between parental chronic spinal pain and the prognosis of chronic spinal pain in the  
27 adult offspring underlines the importance of identifying those at high risk of non-recovery since  
28 they account for significant social and individual financial burden. Therefore, clinicians should  
29 consider family history of spinal pain when implementing strategies to improve recovery from  
30 chronic spinal pain, chronic spinal pain. For instance, the assessment of the potential risks of  
31 physical activity and education about the range of benefits, as well as highlights the importance  
32 of maintenance of a normal body weight.  
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30 interpretation of the data, or the decision to submit the paper for publication.  
31  
32

### 33 34 35 **Author Contributions** 36

37 All authors critically revised the manuscript for important intellectual content and approved the  
38  
39 final manuscript. Please find below a detailed description of the role of each author:  
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- 42  
43 - Anita B Amorim: conception and design, analysis and interpretation of data, drafting and  
44  
45 revision of the manuscript, and final approval of the version to be published.  
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3 - Ragnhild Lier: conception and design, drafting and revision of the manuscript, and final  
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# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5

1		#6b	For matched studies, give matching criteria and number of	6
2			exposed and unexposed	
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5	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	6, 7 and
6			confounders, and effect modifiers. Give diagnostic criteria, if	8
7			applicable	
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10	Data sources /	#8	For each variable of interest give sources of data and details of	See note
11	measurement		methods of assessment (measurement). Describe	1
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	8
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21	Study size	#10	Explain how the study size was arrived at	6
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23	Quantitative	#11	Explain how quantitative variables were handled in the	8
24	variables		analyses. If applicable, describe which groupings were chosen,	
25			and why	
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28	Statistical	#12a	Describe all statistical methods, including those used to control	8 and 9
29	methods		for confounding	
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32		#12b	Describe any methods used to examine subgroups and	8 and 9
33			interactions	
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35				
36		#12c	Explain how missing data were addressed	8 and 9
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	8 and 9
39				
40				
41		#12e	Describe any sensitivity analyses	8 and 9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg	9 and 10
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	9 and 10
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54		#13c	Consider use of a flow diagram	n/a
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	9 and 10
57			clinical, social) and information on exposures and potential	
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1		confounders. Give information separately for exposed and	
2		unexposed groups if applicable.	
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4		#14b Indicate number of participants with missing data for each	n/a
5		variable of interest	
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8		#14c Summarise follow-up time (eg, average and total amount)	9 and 10
9			
10	Outcome data	#15 Report numbers of outcome events or summary measures	10 and
11		over time. Give information separately for exposed and	11
12		unexposed groups if applicable.	
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15	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	10 and
16		adjusted estimates and their precision (eg, 95% confidence	11
17		interval). Make clear which confounders were adjusted for and	
18		why they were included	
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22		#16b Report category boundaries when continuous variables were	10 and
23		categorized	11
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26		#16c If relevant, consider translating estimates of relative risk into	n/a
27		absolute risk for a meaningful time period	
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30	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	10 and
31		interactions, and sensitivity analyses	11
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34	Key results	#18 Summarise key results with reference to study objectives	11 and
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38	Limitations	#19 Discuss limitations of the study, taking into account sources of	13
39		potential bias or imprecision. Discuss both direction and	
40		magnitude of any potential bias.	
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43	Interpretation	#20 Give a cautious overall interpretation considering objectives,	13 and
44		limitations, multiplicity of analyses, results from similar studies,	14
45		and other relevant evidence.	
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48	Generalisability	#21 Discuss the generalisability (external validity) of the study	13 and
49		results	14
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52	Funding	#22 Give the source of funding and the role of the funders for the	15 and
53		present study and, if applicable, for the original study on which	16
54		the present article is based	
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## Author notes



1. 6, 7 and 8

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For peer review only

# BMJ Open

## The influence of family history on prognosis of spinal pain and the role of leisure time physical activity and body mass index: family-linkage data from the Norwegian HUNT Study.

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<b>Primary Subject Heading</b>:	Epidemiology
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Keywords:	Low back pain, neck pain, chronic pain, obesity, family study, physical activity

SCHOLARONE™  
Manuscripts

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3 **The influence of family history on prognosis of spinal pain and the role of leisure time**  
4 **physical activity and body mass index: family-linkage data from the Norwegian HUNT**  
5 **Study.**  
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## ABSTRACT

**Objectives:** To investigate the influence of parental chronic spinal pain on prognosis of chronic spinal pain in adult offspring, and whether offspring physical activity level and body mass index (BMI) modified this association.

**Design:** Prospective cohort study.

**Setting:** We used family linked longitudinal data from the Norwegian HUNT study collected in HUNT2 (1995-97) and HUNT3 (2006-08).

**Participants:** A total of 1,529 offspring who reported spinal pain in HUNT2 were linked with parental data and followed-up in HUNT3.

**Outcomes:** We estimated relative risk (RR) with 95% confidence intervals (CIs) for recovery from chronic spinal pain, and also from activity limiting spinal pain, in offspring related to chronic spinal pain in parents. We also investigated whether offspring leisure time physical activity and BMI modified these intergenerational associations in spinal pain.

**Results:** Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR: 0.83, 95% CI: 0.69, 0.99) and activity limiting spinal pain (RR: 0.71, 95% CI: 0.54, 0.94), compared to offspring of parents without chronic spinal pain.

Analyses stratified by BMI and physical activity showed no strong evidence of effect modification on these associations. However, offspring who were overweight/obese and with both parents reporting spinal pain had particularly low probability of recovery from activity limiting spinal pain, compared those who were normal weight and had parents without spinal pain (RR: 0.57, 95% CI: 0.39-0.84).

**Conclusion:** Offspring with chronic spinal pain are less likely to recover if they have parents with chronic spinal pain, particularly if offspring are overweight/obese.

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5 **Key words:** Low back pain, neck pain, chronic pain, obesity, family study, physical activity.  
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### 10 **Strengths and limitations of this study**

- 12 • The HUNT Study is a large population-based health study with longitudinal data that  
13 allows prospective analysis on the prognosis of chronic spinal pain.  
14
- 15 • Chronic spinal pain was independently reported in parents and offspring; family relations  
16 was informed by a linkage with a national registry; and the data allowed us to control for  
17 a wide range of potential confounders.  
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- 19 • Information on pain status, physical activity, and body mass index was not updated  
20 throughout the follow-up period.  
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## INTRODUCTION

Spinal pain that includes low back and neck pain is highly prevalent and a common cause of disability worldwide.[1] The natural history of spinal pain is extremely variable and may last a few days or persist for many years.[2] A substantial proportion of patients recover within the first three months of a spinal pain episode, but around three quarters of the remaining patients are likely to experience pain one year after onset.[3, 4] People who fail to recover in the first few months following an acute episode are at greater risk of poor prognosis.[5] Spinal pain, especially in its chronic and disabling form, could be a significant personal and financial burden,[6] and may also influence families and society.[1] It is therefore vital to identify factors that influence prognosis of spinal pain, which in turn can inform preventive interventions to reduce chronicity.

Family studies have suggested that chronic pain aggregate in families,[7, 8] with the parent-offspring transmission of chronic pain explained by genetic heritability[9, 10] and shared environment factors.[11-14] The mean heritability of chronic low back pain is 67%,[10, 15] suggesting that a substantial proportion of the risk of developing chronic spinal pain is driven by genetics. However, families also share similar lifestyles and express similar health behaviours and beliefs. This suggests shared environmental factors[8, 16] could also have an important influence on the prognosis of spinal pain.[17, 18]

Parental pain is strongly associated with the increased risk of chronic musculoskeletal pain in offspring, both during adolescence,[7] and in later adulthood.[19] Furthermore, there is preliminary evidence that treatment response in patients with chronic low back pain is influenced by genetic factors.[20] It is, therefore, possible that parental history of spinal pain influences the

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3 prognosis of spinal pain in offspring. Conversely, several studies have shown that engagement in  
4 moderate to vigorous-intensity leisure time physical activity and maintenance of a normal body  
5 mass index (BMI) are associated with better prognosis of spinal pain.[21-25] Thus, a healthy  
6 offspring lifestyle could modify a possible adverse effect of parental spinal pain on prognosis of  
7 offspring spinal pain. Currently, there is limited knowledge about the influence of parental spinal  
8 pain on prognosis of spinal pain in offspring and whether this association is modified by  
9 offspring lifestyle.  
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21 In this study, we have used population-based longitudinal data from the Norwegian HUNT Study  
22 to investigate the influence of parental spinal pain on the prognosis of chronic spinal pain  
23 regarding severity and activity limitation in the adult offspring. We have also investigated  
24 whether offspring leisure time physical activity and BMI modify any of these associations.  
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## 33 **METHODS**

### 34 **Study population**

35 The HUNT Study is a population-based health study conducted within the county of Nord-  
36 Trøndelag, Norway. The study was performed in three consecutive waves, first in 1984–1986  
37 (HUNT1), then in 1995–1997 (HUNT2), and last in 2006–2008 (HUNT3). In all three surveys,  
38 all residents 20 years of age and older were invited to participate, and information on lifestyle  
39 and health-related factors were collected by questionnaires and a clinical examination.  
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49 Information on musculoskeletal pain was not collected at HUNT1. Therefore, those who were  
50 eligible for inclusion in this study had participated at HUNT2 and HUNT3. At HUNT2, 93,898  
51 individuals were invited to participate, and 65,237 (65.5%) joined the study, while at HUNT3  
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3 93,860 were invited and 50,807 (54.1%) agreed to participate.[26, 27] Each participant signed  
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5 written consent, and the study was approved by the Regional Committee for Medical and Health  
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7 Research Ethics Central Norway (ref. no. 2011/1455). Further information about selection  
8  
9 procedures, participation and questionnaires used in the HUNT study can be found at  
10  
11 <http://www.ntnu.edu/hunt>.  
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### 16 **Patient involvement**

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18 Since historical cohort data was used in this study, patients were not involved in the conduct and  
19  
20 design of the study.  
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### 26 **Record linkage**

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28 The unique 11-digit personal identification number held by all Norwegian citizens was used to  
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30 link each participant's record to information from the Family Registry at Statistics Norway, and  
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32 there by establish a link between parents and offspring who participated in one or both of  
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34 HUNT2 and HUNT3. The Family Registry provide data on persons registered as legal parents,  
35  
36 either as biological parents or through adoption. A total of 11,483 offspring reported spinal pain  
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38 at HUNT2, and of these, 6,662 could be followed-up on spinal pain status in HUNT3,  
39  
40 approximately 11 years later. To be able to study the association between parental spinal pain  
41  
42 and offspring prognosis of spinal pain, we selected all 1,529 parent-offspring trios (i.e., mother,  
43  
44 father and adult offspring) where both the mother and the father had information on spinal pain  
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46 from HUNT2.  
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### **Chronic spinal pain**

At HUNT2 and HUNT3, participants were asked to complete the Standardized Nordic Questionnaire which has acceptable reliability and validity.[28] The question regarding musculoskeletal pain was as follows: “In the last year, have you had pain and/or stiffness in muscles or joints that have lasted at least 3 consecutive months?” (response options: “no” and “yes”). Participants who answered “yes” were asked to indicate the affected body area(s). Offspring who reported chronic neck and/or low back pain (spinal pain) at HUNT2 were included in this study, and offspring who also reported spinal pain at HUNT3 were considered not recovered (outcome measure). Offspring reporting spinal pain at HUNT2 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”). 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 limiting spinal pain”. In secondary analyses, we used this information to investigate the prognosis of activity limiting spinal pain; i.e., recovery was defined as not reporting activity limiting spinal pain at HUNT3. Based on the same question as described above, we obtained information on parental chronic spinal pain. Further, we created a variable with four mutually exclusive categories for presence of parental chronic spinal pain at baseline (exposure measure): “none”, “mother”, “father”, or “both parents”.

### **Leisure time physical activity**

Leisure time physical activity was assessed by the following question “How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the

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3 year. Your commute to work counts as leisure time)". Participants reported the number of hours  
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5 of either light (no sweating or heavy breathing) or hard (sweating and heavy breathing) activity  
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7 using the response options "none", "less than 1 hour", "1–2 hours", and "3 or more hours" for  
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9 each type of activity. Based on this information, we constructed a variable with four categories  
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11 (combining information on light and hard activity): 1) "inactive" (no light or hard activity), 2)  
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13 "low activity" (<3 hours light and no hard activity), 3) "moderate activity" ( $\geq 3$  hours light and/or  
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15 <1 hour hard activity), and 4) "high activity" (any light and  $\geq 1$  hour hard activity). In the  
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17 combined analyses of parental chronic spinal pain and offspring leisure time physical activity the  
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19 categories "inactive" and "low activity" were collapsed into one category labelled "Physically  
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21 inactive" and the categories "moderate activity" and "high activity" were collapsed into one  
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23 category labelled "Physically active". This categorization has been used previously in other  
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25 studies based in data from HUNT.[29, 30] We did not conduct analyses stratified by physical  
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27 activity status on the outcome "activity limiting spinal pain", since people with activity limiting  
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29 spinal pain are likely to have limited engagement in leisure and work activities.  
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### 38 **Body mass index**

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40 Standardized measurements of body height (to the nearest centimetre) and body weight (to the  
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42 nearest half kilogram) were obtained at clinical examination. BMI was calculated as weight  
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44 divided by the square of height ( $\text{kg}/\text{m}^2$ ), and classified into four BMI groups according to the  
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46 cut-off points suggested by the World Health Organization:[31] underweight ( $\text{BMI} < 18.5 \text{ kg}/\text{m}^2$ ),  
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48 normal weight ( $\text{BMI} 18.5\text{--}24.9 \text{ kg}/\text{m}^2$ ), overweight ( $\text{BMI} 25.0\text{--}29.9 \text{ kg}/\text{m}^2$ ), and obese ( $\text{BMI}$   
49  
50  $\geq 30.0 \text{ kg}/\text{m}^2$ ). Only 27 participants (1 %) were classified as "underweight", and the combined  
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52 analysis of parental chronic spinal pain and offspring BMI, the categories "underweight" and  
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3 “normal weight” were collapsed into one category labelled “normal weight”. The categories  
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5 “overweight” and “obese” were collapsed into one category labelled “overweight/obese”.  
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### 10 **Statistical analysis**

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12 We used a Poisson regression model[32-35] to estimate relative risk (RR) of chronic spinal pain  
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14 and activity limiting spinal pain in offspring whose parents reported chronic spinal pain, using  
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16 parents with no chronic spinal pain as the reference category. Precision of estimates was assessed  
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18 by a 95% confidence interval (CI). All standard errors were adjusted for within-family clustering  
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20 (i.e., siblings) using the vce (cluster) option in Stata, treating observations between families as  
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22 independent and within families as dependent, and thus avoiding inflated precision of the  
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24 estimated associations.[36]  
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31 Possible effect modification by offspring leisure time physical activity or offspring BMI was  
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33 assessed by stratified analyses (i.e. physically active vs physically inactive and normal weight vs  
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35 overweight/obese) as well as by tests of the estimated relative excess risk due to interaction  
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37 (RERI) (i.e., departure from additive effects). We calculated RERI estimates with 95% CIs from  
38  
39 the following equation:  $RERI = RR_{\text{parental pain \& physically active/overweight and/or obese}} - RR_{\text{noparental pain \&}}$   
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41  $RR_{\text{physically activity/ overweight and/or obese}} - RR_{\text{parental pain \& physically inactivity/normal weight}} + 1$  ,[37] i.e.,  $RERI > 0$   
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43 indicate a synergistic effect beyond an additive effect. Statistical interaction was also evaluated  
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45 on a multiplicative scale by a likelihood ratio test of a product term in the model (these  
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47 likelihood ratio tests had to be run without cluster-adjusted standard errors to avoid  
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49 misspecification of the model).  
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3 The main analyses (parental influence on risk of poor prognosis) were adjusted for possible  
4 confounding by offspring sex (male, female), age (continuous), BMI (“underweight”, “normal  
5 weight”, “overweight”, “obese”, or “unknown”), leisure time physical activity (“physically  
6 inactive” or “physically active”, or “unknown”), education (“<10 years”, “10–12 years”, “>13  
7 years”, or “unknown”), and depression (“depressed”, or “not depressed”, or “unknown”).  
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14 Depression was assessed using the depression subscale of the Hospital Anxiety and Depression  
15 Scale (HADS) using a score of 8 as a cut-off for a dichotomised variable.[38-40]  
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21 All statistical tests were two-sided, and all analyses were conducted using Stata statistical  
22 software (version 13.0, STATA Corp., College Station, TX, USA).  
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## 28 **RESULTS**

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31 In this prospective study of 1,529 offspring with chronic spinal pain at baseline, a total of 540  
32 (35%) offspring were defined as recovered after approximately 11 years of follow-up.  
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35 Additionally, among 775 offspring with activity limiting spinal pain, 244 were defined as  
36 recovered at follow-up. Descriptive statistics of offspring, mothers, and fathers are shown in  
37 Table 1. The mean age at baseline was 32.8 (8.6) years among offspring. Most offspring were  
38 physically active (63.9%), and nearly half of the offspring (42.3%) were classified as overweight  
39 or obese. About one third (33.1%) of the offspring were current smokers, and just a small portion  
40 of offspring (20.7%) reported having a higher education degree. A small proportion (10.4%) of  
41 offspring had symptoms of depression according to the Hospital Anxiety and Depression Scale.  
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Table 1. Baseline characteristics of the study population at HUNT2

Variables	Offspring	Mothers	Fathers
Participants, no.	1,529	1,529	1,529
Age, mean (SD)	32.8 (8.6)	63.8 (9.4)	67.2 (9.5)
Body mass index, mean (SD)	25.9 (5.2)	28.3(7.3)	27.6 (6.9)
Overweight/obese, % (n)	42.3 (799)	70.6 (1,080)	72.2 (1,104)
Physically active <sup>a</sup> , % (n)	63.9 (977)	43.0 (510)	57.7 (716)
Current smoker, % (n)*	33.1 (506)	26.3 (400)	28.5 (434)
Higher education <sup>b</sup> , % (n)	20.7 (316)	4.5 (61)	6.0 (84)
Symptoms of depression <sup>c</sup> , %, (n)	10.4 (155)	17.0 (225)	16.5 (215)

SD, standard deviation

<sup>a</sup> Engagement in moderate ( $\geq 3$  hours light and/or  $< 1$  hour hard activity per week) or high leisure time physical activity (any light and  $\geq 1$  hour hard activity per week)

<sup>b</sup> University education or higher

<sup>c</sup> Score  $\geq 8$  on the Hospital Anxiety and Depression Scale

### Chronic spinal pain and activity limiting spinal pain

Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR: 0.83, 95% CI: 0.69, 0.99) and activity limiting spinal pain (RR: 0.71, 95% CI: 0.54-0.94) compared to offspring with no parents with chronic spinal pain (Table 2).

These associations were weaker and less precise when chronic spinal pain was present in only one parent, with similar associations observed for maternal and paternal spinal pain.

Table 2. Relative risk (RR) of recovery from spinal pain and activity limiting spinal pain in adult offspring associated with parental spinal pain.

Parental spinal pain	Offspring spinal pain				Offspring activity limiting spinal pain			
	No. of persons	No. of cases	Crude RR	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Crude RR	Adjusted RR <sup>a</sup> (95% CI)
None	346	138	1.00	1.00 (Ref.)	163	66	1.00	1.00 (Ref.)
Mother	424	147	0.88	0.90 (0.75-1.07)	214	62	0.73	0.74 (0.56-0.98)
Father	272	97	0.90	0.91 (0.74-1.12)	127	40	0.77	0.78 (0.57-1.05)
Both	487	158	0.82	0.83 (0.69-0.99)	271	76	0.69	0.71 (0.54-0.94)

CI, confidence interval

<sup>a</sup>Adjusted for age, sex, BMI, smoking, leisure time physical activity, education and HADS score.

### Physical activity

In the stratified analysis for physical activity, there was no strong evidence of effect modification for either physically active offspring (RR: 0.78; 95% CI: 0.62, 0.98), or physically inactive offspring (RR: 0.98; 95% CI: 0.71, 1.36) (Table 3). Tests of statistical interaction indicate no departure from neither multiplicative ( $p = 0.11$ ) nor additive effects (RERI 0.19, 95% CI, -0.17, 0.55), data not shown.

Table 3. Relative risk (RR) of recovery from spinal pain in adult offspring associated with parental spinal pain; analysis stratified by leisure time physical activity.

	Physically active			Physical inactive		
	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)
None	229	97	1.00 (Ref.)	111	40	1.00 (Ref.)
Mother or father	434	163	0.94 (0.77-1.14)	246	74	0.82 (0.60-1.11)
Both parents	314	100	0.78 (0.62-0.98)	166	58	0.98 (0.71-1.35)

CI: confidence interval

aAdjusted for age, sex, BMI, smoking, education and HADS score.

### Body mass index

In the stratified analysis for body mass index, there was no strong evidence of effect modification. However, offspring who were overweight or obese had the lowest probability of recovery if both parents report activity limiting spinal pain or chronic spinal pain (RR: 0.57; 95% CI: 0.39, 0.84 and RR: 0.79; 95% CI: 0.61, 1.03 respectively) compared to normal weight (Table 4). In addition, there was no clear evidence of statistical interaction neither on the additive (estimates of RERI for chronic spinal pain and activity limiting spinal pain were -0.04; 95% CI: -0.38, 0.30 and -0.34; 95% CI: -0.91, 0.23, respectively) nor on the multiplicative scale ( $p = 0.54$  and  $p = 0.20$ , respectively).

Table 4. Relative risk (RR) of recovery from spinal pain and activity limiting spinal pain in adult offspring associated with parental spinal pain; analysis stratified by BMI.

Variables	Normal weight			Overweight/obese		
	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)
Offspring spinal pain						
Parental spinal pain						
None	168	68	1.00 (Ref.)	177	69	1.00 (Ref.)
Mother or father	316	111	0.88 (0.70-1.12)	380	133	0.89 (0.70-1.12)
Both parents	242	82	0.86 (0.66-1.11)	242	76	0.79 (0.61-1.03)
Offspring activity limiting spinal pain						
Parental spinal pain						
None	86	34	1.00 (Ref.)	130	50	1.00 (Ref.)
Mother or father	151	42	0.72 (0.49-1.04)	301	98	0.72 (0.51-0.99)
Both parents	129	41	0.84 (0.57-1.24)	188	52	0.57 (0.39-0.84)

CI: confidence interval.

<sup>a</sup>Adjusted for age, sex, leisure physical activity, smoking, education and depression.



## DISCUSSION

### Summary of findings

The findings of this large population-based prospective family-linkage study indicate that offspring with both parents reporting chronic spinal pain are less likely to recover from chronic spinal pain and activity limiting spinal pain compared with offspring with no parent with spinal pain. Overall, there was no strong evidence that physical activity or body mass index modified these associations, although the results suggest that the inverse association between parental spinal pain and recovery from activity limiting spinal pain was strongest among offspring with a high BMI. This study supports the evidence from twin studies that genetics potentially influences recovery from chronic spinal pain,[41] but these intergenerational associations incorporate shared environmental factors and shared beliefs that could influence recovery. For instance, there is evidence showing that negative beliefs about pain and negative expectations about recovery predict chronic and disabling spinal pain.[42-44] It seems clear that it is important to consider the family history of chronic spinal pain as well as lifestyle behaviours when identifying people at higher risk of non-recovery.

### Comparison of findings with previous research

A recent systematic review showed that offspring of parents with chronic pain have poorer outcomes regarding pain, general health, psychological, and family functioning as compared to offspring of parents without pain.[45] The inter-generational transmission of spinal pain could be explained by genetic heritability[9, 10] or a family shared environment.[11-14] Moreover, it has

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3 been suggested that the genetic influence is greater in more disabling pain conditions, such as  
4 chronic widespread pain and chronic activity limiting spinal pain, rather than in acute or sub-  
5 acute non-debilitating pain.[9, 10] It is widely accepted that lifestyle factors, such as physical  
6 activity and body weight, also play a significant role in the prognosis of chronic musculoskeletal  
7 pain.[46]  
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17 Some studies have suggested that people with chronic back pain who regularly engage in leisure  
18 time physical activity have better prognosis measured in terms of pain, disability, and quality of  
19 life than those who are sedentary.[29, 47] However, there remains conflicting evidence regarding  
20 how physical activity influences the prognosis of spinal pain,[48] with studies demonstrating that  
21 both low and high levels of physical activity can negatively influence the prognosis of spinal  
22 pain.[49, 50] For instance, a study found that high leisure time physical activity was related to  
23 decreased prevalence of low back pain.[51] Whereas another study found that either high or low  
24 levels of leisure time physical activity was related to increased prevalence of low back pain.[49]  
25 In contrast, a prospective study did not find any significant association between moderate/high  
26 levels of leisure physical activity and low back pain in young adults.[52] Another follow-up  
27 study found that regular habits of leisure physical activity have no effect on recovery from low  
28 back pain.[53] The inconsistency in the literature is possibly attributed to the diverse definitions  
29 and classifications of levels of physical activity. If such divergent associations with leisure time  
30 physical activity exist this could mask a possible modifying effect of physical activity in our  
31 analyses.  
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3 The literature has provided evidence that obesity is associated with poor outcomes in people with  
4 chronic widespread pain,[54, 55] as well as chronic spinal pain[29, 56, 57] and also decreases the  
5 probability of recovery from chronic spinal pain regardless of the care they receive,[25]  
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8 however, whether BMI could modify[30] the relationship between parental spinal pain on  
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10 offspring recovery from chronic spinal pain has not been investigated before. Our results suggest  
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12 that offspring BMI may modify on the parent-offspring association of spinal pain, with  
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14 somewhat stronger associations among offspring who were classified as overweight or obese  
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16 than those who were underweight or normal weight. Research has shown that inter-individual  
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18 differences in pain sensitivity and endogenous pain-inhibitory capacity could reflect variations in  
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20 the inherent susceptibility for chronic pain,[58, 59] but that a triggering exposure is required for  
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22 the development of chronic pain.[60, 61] This could suggest that a possible genetic susceptibility  
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24 for poor recovery from chronic pain[62, 63] as a higher penetrance between offspring who are  
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26 overweight or obese.  
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### 35 **Strengths and limitations**

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37 This study has several strengths including the prospective design utilising a large population-  
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39 based sample with a long follow-up period. In addition, the registry based information on family  
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41 relations allowed us to include information on chronic spinal pain obtained from parents and  
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43 offspring independently and at different time points. An important aspect is that the offspring  
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45 were adults at the time of data collection, indicating that the parent-to-offspring association of  
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47 chronic spinal pain persists into adulthood when the offspring most likely live apart from their  
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49 parents. Furthermore, we were able to adjust for several offspring characteristics that could  
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51 confound the parent-offspring associations of chronic spinal pain, such as age,[64] BMI,[57]  
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3 leisure physical activity,[65] smoking,[64] depression[64] and education.[10, 66] However, we  
4 cannot exclude the possible residual confounding attributable to unknown or unmeasured factors.  
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10 There are some limitations that should be taken into account. First, information on chronic spinal  
11 pain was only reported at baseline and at follow-up 10-11 years later, with no information on  
12 possible changes in the status of chronic spinal pain during the follow-up period. Consequently, a  
13 person could have recovered from spinal pain at some time-point between the surveys, but still  
14 report pain at follow-up. However, if parental pain reflects an underlying heritable frailty, this  
15 may have an impact also on long-term recurrence and recovery from pain. Likewise, information  
16 on leisure time physical activity and BMI was only assessed at baseline, with no information on  
17 possible changes during the follow-up period. Second, although the questions about leisure time  
18 physical activity used in this study have been reported to have good reliability and provide useful  
19 measures of leisure physical activity,[67] subjective interpretations of the activity questions  
20 could have influenced the results. Besides, it is well known that self-reports may lead to under or  
21 overestimation of the variables of interest.[68] Third, a premise for inclusion into this study was  
22 that the mother, father and offspring all had to participate in the health survey. To some extent,  
23 this may have resulted in a selected and more health conscious sample than the general  
24 population. Nevertheless, it is questionable whether representativeness is a prerequisite for  
25 making valid risk assessments in epidemiological studies.[57] Fourth, although the Norwegian  
26 Family registry was used to identify family relations between parents and offspring,  
27 misclassification of biological family relations in the registry due to adoptions and non-paternity  
28 is possible. Although the influence on our results is likely to be small, such misclassification  
29 could give attenuated parent-offspring associations. Moreover, we had no information on  
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3 whether the offspring shared environment with none, one or both of their biological parents  
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5 during childhood. Finally, residual confounding due to unmeasured or unknown factors cannot  
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7 be ruled out.  
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## 11 12 **CONCLUSION**

13  
14 Offspring with chronic spinal pain are less likely to recover if they have parents with chronic  
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16 spinal pain compared to offspring without parental chronic spinal pain. This association is  
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18 stronger when the offspring present pain that interferes with their usual work and leisure  
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20 activities (activity limiting spinal pain). The inverse association between parental chronic spinal  
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22 pain on recovery was somewhat stronger among offspring who were overweight or obese. The  
23  
24 association between parental chronic spinal pain and the prognosis of chronic spinal pain in the  
25  
26 adult offspring underlines the importance of identifying those at high risk of non-recovery since  
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28 they account for significant social and individual financial burden. Therefore, clinicians should  
29  
30 consider family history of spinal pain when implementing strategies to improve recovery from  
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32 chronic spinal pain, chronic spinal pain. For instance, the assessment of the potential risks of  
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34 physical activity and education about the range of benefits, as well as highlights the importance  
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36 of maintenance of a normal body weight.  
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### 31 **Author Contributions**

32  
33 All authors critically revised the manuscript for important intellectual content and approved the  
34  
35 final manuscript. Please find below a detailed description of the role of each author:  
36  
37

- 38  
39 - Anita B Amorim: conception and design, analysis and interpretation of data, drafting and  
40  
41 revision of the manuscript, and final approval of the version to be published.  
42
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50 final approval of the version to be published.  
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# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5



1		#6b	For matched studies, give matching criteria and number of	6
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5	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	6, 7 and
6			confounders, and effect modifiers. Give diagnostic criteria, if	8
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11	measurement		methods of assessment (measurement). Describe	1
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	8
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21	Study size	#10	Explain how the study size was arrived at	6
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24	variables		analyses. If applicable, describe which groupings were chosen,	
25			and why	
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28	Statistical	#12a	Describe all statistical methods, including those used to control	8 and 9
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33			interactions	
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36		#12c	Explain how missing data were addressed	8 and 9
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38		#12d	If applicable, explain how loss to follow-up was addressed	8 and 9
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41		#12e	Describe any sensitivity analyses	8 and 9
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43	Participants	#13a	Report numbers of individuals at each stage of study—eg	9 and 10
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	9 and 10
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54		#13c	Consider use of a flow diagram	n/a
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56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	9 and 10
57			clinical, social) and information on exposures and potential	
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1		confounders. Give information separately for exposed and	
2		unexposed groups if applicable.	
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4		#14b Indicate number of participants with missing data for each	n/a
5		variable of interest	
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8		#14c Summarise follow-up time (eg, average and total amount)	9 and 10
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10	Outcome data	#15 Report numbers of outcome events or summary measures	10 and
11		over time. Give information separately for exposed and	11
12		unexposed groups if applicable.	
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15	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	10 and
16		adjusted estimates and their precision (eg, 95% confidence	11
17		interval). Make clear which confounders were adjusted for and	
18		why they were included	
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22		#16b Report category boundaries when continuous variables were	10 and
23		categorized	11
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26		#16c If relevant, consider translating estimates of relative risk into	n/a
27		absolute risk for a meaningful time period	
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30	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	10 and
31		interactions, and sensitivity analyses	11
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34	Key results	#18 Summarise key results with reference to study objectives	11 and
35			12
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38	Limitations	#19 Discuss limitations of the study, taking into account sources of	13
39		potential bias or imprecision. Discuss both direction and	
40		magnitude of any potential bias.	
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43	Interpretation	#20 Give a cautious overall interpretation considering objectives,	13 and
44		limitations, multiplicity of analyses, results from similar studies,	14
45		and other relevant evidence.	
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48	Generalisability	#21 Discuss the generalisability (external validity) of the study	13 and
49		results	14
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52	Funding	#22 Give the source of funding and the role of the funders for the	15 and
53		present study and, if applicable, for the original study on which	16
54		the present article is based	
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## Author notes

1. 6, 7 and 8

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# BMJ Open

## The influence of family history on prognosis of spinal pain and the role of leisure time physical activity and body mass index: a prospective study using family-linkage data from the Norwegian HUNT Study.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022785.R2
Article Type:	Research
Date Submitted by the Author:	28-Aug-2018
Complete List of Authors:	Amorim, Anita; The University of Sydney, Faculty of Health Sciences Ferreira, Paulo; University of Sydney, Faculty of Health Science Ferreira, Manuela; University of Sydney Institute of Bone and Joint Research, Lier, Ragnhild; NTNU Det Medisinske Fakultet DMF, Department of Public Health and General Practice Simic, Milena; The University of Sydney, Physiotherapy Pappas, Evangelos; University of Sydney, Discipline of Physiotherapy, Faculty of Health Sciences; University of Sydney Zadro, Joshua; University of Sydney, Faculty of Health Science Mork, Paul Jarle; Norges teknisk-naturvitenskapelige universitet, Department of Public Health and Nursing; Norwegian University of Science and Technology Nilsen, Tom; NTNU Det Medisinske Fakultet DMF, Department of Public Health and General Practice
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Genetics and genomics, Epidemiology, Public health
Keywords:	Low back pain, neck pain, chronic pain, obesity, family study, physical activity

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3 **The influence of family history on prognosis of spinal pain and the role of leisure time**  
4 **physical activity and body mass index: a prospective study using family-linkage data from**  
5 **the Norwegian HUNT Study.**  
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12 Anita B. Amorim<sup>1</sup>; Paulo H. Ferreira<sup>1</sup>; Manuela L. Ferreira<sup>2</sup>; Ragnhild Lier<sup>3</sup>; Milena Simic<sup>1</sup>;  
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14 Evangelos Pappas<sup>1</sup>; Joshua R. Zadro<sup>1</sup>; Paul Jarle Mork<sup>3</sup>; Tom Ivar Lund Nilsen<sup>3,4\*</sup>  
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## ABSTRACT

**Objectives:** To investigate the influence of parental chronic spinal pain on prognosis of chronic spinal pain in adult offspring, and whether offspring physical activity level and body mass index (BMI) modified this association.

**Design:** Prospective cohort study.

**Setting:** We used family linked longitudinal data from the Norwegian HUNT study collected in HUNT2 (1995-97) and HUNT3 (2006-08).

**Participants:** A total of 1,529 offspring who reported spinal pain in HUNT2 were linked with parental data and followed-up in HUNT3.

**Outcomes:** We estimated relative risk (RR) with 95% confidence intervals (CIs) for recovery from chronic spinal pain, and also from activity limiting spinal pain, in offspring related to chronic spinal pain in parents. We also investigated whether offspring leisure time physical activity and BMI modified these intergenerational associations in spinal pain.

**Results:** A total of 540 (35%) offspring were defined as recovered after approximately 11 years of follow-up. Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR: 0.83, 95% CI: 0.69, 0.99) and activity limiting spinal pain (RR: 0.71, 95% CI: 0.54, 0.94), compared to offspring of parents without chronic spinal pain.

Analyses stratified by BMI and physical activity showed no strong evidence of effect modification on these associations. However, offspring who were overweight/obese and with both parents reporting chronic spinal pain had particularly low probability of recovery from activity limiting spinal pain, compared to those who were normal weight and had parents without chronic spinal pain (RR: 0.57, 95% CI: 0.39-0.84).

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3 **Conclusion:** Offspring with chronic spinal pain are less likely to recover if they have parents  
4 with chronic spinal pain, particularly if offspring are overweight/obese.  
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10 **Key words:** Low back pain, neck pain, chronic pain, obesity, family study, physical activity.  
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### 15 **Strengths and limitations of this study**

- 16 • The HUNT Study is a large population-based health study with longitudinal data that  
17 allows prospective analysis on the prognosis of chronic spinal pain.  
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- 19 • Chronic spinal pain was independently reported in parents and offspring; family relations  
20 was informed by a linkage with a national registry; and the data allowed us to control for  
21 a wide range of potential confounders.  
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- 23 • Information on pain status, physical activity, and body mass index was not updated  
24 throughout the follow-up period.  
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## INTRODUCTION

Spinal pain that includes low back and neck pain is highly prevalent and a common cause of disability worldwide.[1] The natural history of spinal pain is extremely variable and may last a few days or persist for many years.[2] A substantial proportion of patients recover within the first three months of a spinal pain episode, but around three quarters of the remaining patients are likely to experience pain one year after onset.[3, 4] People who fail to recover in the first few months following an acute episode are at greater risk of poor prognosis.[5] Spinal pain, especially in its chronic and disabling form, could be a significant personal and financial burden,[6] and may also influence families and society.[1] It is therefore vital to identify factors that influence prognosis of spinal pain, which in turn can inform preventive interventions to reduce chronicity.

Family studies have suggested that chronic pain aggregate in families,[7, 8] with the parent-offspring transmission of chronic pain explained by genetic heritability[9, 10] and shared environment factors.[11-14] The mean heritability of chronic low back pain is 67%,[10, 15] suggesting that a substantial proportion of the risk of developing chronic spinal pain is driven by genetics. However, families also share similar lifestyles and express similar health behaviours and beliefs. This suggests shared environmental factors[8, 16] could also have an important influence on the prognosis of spinal pain.[17, 18]

Parental pain is strongly associated with the increased risk of chronic musculoskeletal pain in offspring, both during adolescence,[7] and in later adulthood.[19] Furthermore, there is preliminary evidence that treatment response in patients with chronic low back pain is influenced by genetic factors.[20] It is, therefore, possible that parental history of spinal pain influences the



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3 prognosis of spinal pain in offspring. Conversely, several studies have shown that engagement in  
4 moderate to vigorous-intensity leisure time physical activity and maintenance of a normal body  
5 mass index (BMI) are associated with better prognosis of spinal pain.[21-25] Thus, a healthy  
6 offspring lifestyle could modify a possible adverse effect of parental spinal pain on prognosis of  
7 offspring spinal pain. Currently, there is limited knowledge about the influence of parental spinal  
8 pain on prognosis of spinal pain in offspring and whether this association is modified by  
9 offspring lifestyle.  
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21 In this study, we have used population-based longitudinal data from the Norwegian HUNT Study  
22 to investigate the influence of parental spinal pain on the prognosis of chronic spinal pain  
23 regarding severity and activity limitation in the adult offspring. We have also investigated  
24 whether offspring leisure time physical activity and BMI modify any of these associations.  
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## 33 **METHODS**

### 34 **Study population**

35 The HUNT Study is a population-based health study conducted within the county of Nord-  
36 Trøndelag, Norway. The study was performed in three consecutive waves, first in 1984–1986  
37 (HUNT1), then in 1995–1997 (HUNT2), and last in 2006–2008 (HUNT3). In all three surveys,  
38 all residents 20 years of age and older were invited to participate, and information on lifestyle  
39 and health-related factors were collected by questionnaires and a clinical examination.  
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49 Information on musculoskeletal pain was not collected at HUNT1. Therefore, those who were  
50 eligible for inclusion in this study had participated at HUNT2 and HUNT3. At HUNT2, 93,898  
51 individuals were invited to participate, and 65,237 (65.5%) joined the study, while at HUNT3  
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3 93,860 were invited and 50,807 (54.1%) agreed to participate.[26, 27] Each participant signed  
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5 written consent, and the study was approved by the Regional Committee for Medical and Health  
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7 Research Ethics Central Norway (ref. no. 2011/1455). Further information about selection  
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9 procedures, participation and questionnaires used in the HUNT study can be found at  
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11 <http://www.ntnu.edu/hunt>.  
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### 16 17 **Patient involvement**

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19 Since historical cohort data was used in this study, patients were not involved in the conduct and  
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21 design of the study.  
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### 26 27 **Record linkage**

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29 The unique 11-digit personal identification number held by all Norwegian citizens was used to  
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31 link each participant's record to information from the Family Registry at Statistics Norway, and  
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33 there by establish a link between parents and offspring who participated in one or both of  
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35 HUNT2 and HUNT3. The Family Registry provide data on persons registered as legal parents,  
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37 either as biological parents or through adoption. A total of 11,483 offspring reported spinal pain  
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39 at HUNT2, and of these, 6,662 could be followed-up on spinal pain status in HUNT3,  
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41 approximately 11 years later. To be able to study the association between parental spinal pain  
42  
43 and offspring prognosis of spinal pain, we selected all 1,529 parent-offspring trios (i.e., mother,  
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45 father and adult offspring) where both the mother and the father had information on spinal pain  
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47 from HUNT2.  
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### **Chronic spinal pain**

At HUNT2 and HUNT3, participants were asked to complete the Standardized Nordic Questionnaire which has acceptable reliability and validity.[28] The question regarding musculoskeletal pain was as follows: “In the last year, have you had pain and/or stiffness in muscles or joints that have lasted at least 3 consecutive months?” (response options: “no” and “yes”). Participants who answered “yes” were asked to indicate the affected body area(s). Offspring who reported chronic neck and/or low back pain (spinal pain) at HUNT2 were included in this study, and offspring who also reported spinal pain at HUNT3 were considered not recovered (outcome measure). Offspring reporting spinal pain at HUNT2 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”). 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 limiting spinal pain”. In secondary analyses, we used this information to investigate the prognosis of activity limiting spinal pain; i.e., recovery was defined as not reporting activity limiting spinal pain at HUNT3. Based on the same question as described above, we obtained information on parental chronic spinal pain. Further, we created a variable with four mutually exclusive categories for presence of parental chronic spinal pain at baseline (exposure measure): “none”, “mother”, “father” or “both parents”.

### **Leisure time physical activity**

Leisure time physical activity was assessed by the following question “How much of your leisure time have you been physically active during the last year? (Think of a weekly average for the

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3 year. Your commute to work counts as leisure time)". Participants reported the number of hours  
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5 of either light (no sweating or heavy breathing) or hard (sweating and heavy breathing) activity  
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7 using the response options "none", "less than 1 hour", "1–2 hours" and "3 or more hours" for  
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9 each type of activity. Based on this information, we constructed a variable with four categories  
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11 (combining information on light and hard activity): 1) "inactive" (no light or hard activity), 2)  
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13 "low activity" (<3 hours light and no hard activity), 3) "moderate activity" ( $\geq 3$  hours light and/or  
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15 <1 hour hard activity), and 4) "high activity" (any light and  $\geq 1$  hour hard activity). In the  
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17 combined analyses of parental chronic spinal pain and offspring leisure time physical activity the  
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19 categories "inactive" and "low activity" were collapsed into one category labelled "Physically  
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21 inactive" and the categories "moderate activity" and "high activity" were collapsed into one  
22  
23 category labelled "Physically active". This categorization has been used previously in other  
24  
25 studies based in data from HUNT.[29, 30] We did not conduct analyses stratified by physical  
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27 activity status on the outcome "activity limiting spinal pain", since people with activity limiting  
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29 spinal pain are likely to have limited engagement in leisure and work activities.  
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### 38 **Body mass index**

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40 Standardized measurements of body height (to the nearest centimetre) and body weight (to the  
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42 nearest half kilogram) were obtained at clinical examination. BMI was calculated as weight  
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44 divided by the square of height ( $\text{kg/m}^2$ ), and classified into four BMI groups according to the  
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46 cut-off points suggested by the World Health Organization:[31] underweight ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ),  
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48 normal weight ( $\text{BMI} 18.5\text{--}24.9 \text{ kg/m}^2$ ), overweight ( $\text{BMI} 25.0\text{--}29.9 \text{ kg/m}^2$ ) and obese ( $\text{BMI}$   
49  
50  $\geq 30.0 \text{ kg/m}^2$ ). Only 27 participants (1 %) were classified as "underweight", and the combined  
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52 analysis of parental chronic spinal pain and offspring BMI, the categories "underweight" and  
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3 “normal weight” were collapsed into one category labelled “normal weight”. The categories  
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5 “overweight” and “obese” were collapsed into one category labelled “overweight/obese”.  
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## 10 **Statistical analysis**

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12 We used a Poisson regression model[32-35] to estimate relative risk (RR) of chronic spinal pain  
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14 and activity limiting spinal pain in offspring whose parents reported chronic spinal pain, using  
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16 parents with no chronic spinal pain as the reference category. Precision of estimates was assessed  
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18 by a 95% confidence interval (CI). All standard errors were adjusted for within-family clustering  
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20 (i.e., siblings) using the vce (cluster) option in Stata, treating observations between families as  
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22 independent and within families as dependent, and thus avoiding inflated precision of the  
23  
24 estimated associations.[36]  
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31 Possible effect modification by offspring leisure time physical activity or offspring BMI was  
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33 assessed by stratified analyses (i.e., physically active vs physically inactive and normal weight vs  
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35 overweight/obese) as well as by tests of the estimated relative excess risk due to interaction  
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37 (RERI) (i.e., departure from additive effects). We calculated RERI estimates with 95% CIs from  
38  
39 the following equation:  $RERI = RR_{\text{parental pain \& physically active/overweight and/or obese}} - RR_{\text{noparental pain \&}}$   
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41  $RR_{\text{physically activity/ overweight and/or obese}} - RR_{\text{parental pain \& physically inactivity/normal weight}} + 1$ , [37] i.e.,  $RERI > 0$   
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43 indicate a synergistic effect beyond an additive effect. Statistical interaction was also evaluated  
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45 on a multiplicative scale by a likelihood ratio test of a product term in the model (these  
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47 likelihood ratio tests had to be run without cluster-adjusted standard errors to avoid  
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49 misspecification of the model).  
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3 The main analyses (parental influence on risk of poor prognosis) were adjusted for possible  
4 confounding by offspring sex (male, female), age (continuous), BMI (“underweight”, “normal  
5 weight”, “overweight”, “obese” or “unknown”), leisure time physical activity (“physically  
6 inactive”, “physically active” or “unknown”), education (“<10 years”, “10–12 years”, “>13  
7 years” or “unknown”), and depression (“depressed”, “not depressed” or “unknown”). Depression  
8 was assessed using the depression subscale of the Hospital Anxiety and Depression Scale  
9 (HADs) using a score of 8 as a cut-off for a dichotomised variable.[38-40]  
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21 All statistical tests were two-sided, and all analyses were conducted using Stata statistical  
22 software (version 13.0, STATA Corp., College Station, TX, USA).  
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## 28 **RESULTS**

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30 In this prospective study of 1,529 offspring with chronic spinal pain at baseline, a total of 540  
31 (35%) offspring were defined as recovered after approximately 11 years of follow-up.  
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34 Additionally, among 775 offspring with activity limiting spinal pain, 244 were defined as  
35 recovered at follow-up. Descriptive statistics of offspring, mothers and fathers are shown in  
36 Table 1. The mean age at baseline was 32.8 (8.6) years among offspring. Most offspring were  
37 physically active (63.9%), and nearly half of the offspring (42.3%) were classified as overweight  
38 or obese. About one third (33.1%) of the offspring were current smokers, and just a small portion  
39 of offspring (20.7%) reported having a higher education degree. A small proportion (10.4%) of  
40 offspring had symptoms of depression according to the Hospital Anxiety and Depression Scale.  
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Table 1. Baseline characteristics of the study population at HUNT2

Variables	Offspring	Mothers	Fathers
Participants, no.	1,529	1,529	1,529
Age, mean (SD)	32.8 (8.6)	63.8 (9.4)	67.2 (9.5)
Body mass index, mean (SD)	25.9 (5.2)	28.3(7.3)	27.6 (6.9)
Overweight/obese, % (n)	42.3 (799)	70.6 (1,080)	72.2 (1,104)
Physically active <sup>a</sup> , % (n)	63.9 (977)	43.0 (510)	57.7 (716)
Current smoker, % (n)*	33.1 (506)	26.3 (400)	28.5 (434)
Higher education <sup>b</sup> , % (n)	20.7 (316)	4.5 (61)	6.0 (84)
Symptoms of depression <sup>c</sup> , %, (n)	10.4 (155)	17.0 (225)	16.5 (215)

SD, standard deviation

<sup>a</sup>Engagement in moderate ( $\geq 3$  hours light and/or  $< 1$  hour hard activity per week) or high leisure time physical activity (any light and  $\geq 1$  hour hard activity per week)

<sup>b</sup>University education or higher

<sup>c</sup>Score  $\geq 8$  on the Hospital Anxiety and Depression Scale

### Chronic spinal pain and activity limiting spinal pain

Offspring with both parents reporting chronic spinal pain were less likely to recover from chronic spinal pain (RR: 0.83, 95% CI: 0.69, 0.99) and activity limiting spinal pain (RR: 0.71, 95% CI: 0.54-0.94) compared to offspring with no parents with chronic spinal pain (Table 2).

These associations were weaker and less precise when chronic spinal pain was present in only one parent, with similar associations observed for maternal and paternal spinal pain.

Table 2. Relative risk (RR) of recovery from spinal pain and activity limiting spinal pain in adult offspring associated with parental spinal pain.

Parental spinal pain	Offspring spinal pain				Offspring activity limiting spinal pain			
	No. of persons	No. of cases	Crude RR	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Crude RR	Adjusted RR <sup>a</sup> (95% CI)
None	346	138	1.00	1.00 (Ref.)	163	66	1.00	1.00 (Ref.)
Mother	424	147	0.88	0.90 (0.75-1.07)	214	62	0.73	0.74 (0.56-0.98)
Father	272	97	0.90	0.91 (0.74-1.12)	127	40	0.77	0.78 (0.57-1.05)
Both	487	158	0.82	0.83 (0.69-0.99)	271	76	0.69	0.71 (0.54-0.94)

CI, confidence interval

<sup>a</sup>Adjusted for age, sex, BMI, smoking, leisure time physical activity, education and HADS score.

### Physical activity

In the stratified analysis for physical activity, there was no strong evidence of effect modification for either physically active offspring (RR: 0.78; 95% CI: 0.62, 0.98), or physically inactive offspring (RR: 0.98; 95% CI: 0.71, 1.36) (Table 3). Tests of statistical interaction indicate no departure from neither multiplicative ( $p = 0.11$ ) nor additive effects (RERI: 0.19; 95% CI: -0.17, 0.55), data not shown.



Table 3. Relative risk (RR) of recovery from spinal pain in adult offspring associated with parental spinal pain; analysis stratified by leisure time physical activity.

	Physically active			Physical inactive		
	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)
Parental spinal pain						
None	229	97	1.00 (Ref.)	111	40	1.00 (Ref.)
Mother or father	434	163	0.94 (0.77-1.14)	246	74	0.82 (0.60-1.11)
Both parents	314	100	0.78 (0.62-0.98)	166	58	0.98 (0.71-1.35)

CI: confidence interval

<sup>a</sup>Adjusted for age, sex, BMI, smoking, education and HADS score.

### Body mass index

In the stratified analysis for body mass index, there was no strong evidence of effect modification. However, offspring who were overweight or obese and with both parents reporting chronic spinal pain had the lowest probability of recovery from activity limiting spinal pain or chronic spinal pain (RR: 0.57; 95% CI: 0.39, 0.84 and RR: 0.79; 95% CI: 0.61, 1.03, respectively), compared to those who were normal weight and had parents without chronic spinal pain (Table 4). In addition, there was no clear evidence of statistical interaction neither on the additive (estimates of RERI for chronic spinal pain and activity limiting spinal pain were -0.04; 95% CI: -0.38, 0.30 and -0.34; 95% CI: -0.91, 0.23, respectively) nor on the multiplicative scale ( $p = 0.54$  and  $p = 0.20$ , respectively).

Table 4. Relative risk (RR) of recovery from spinal pain and activity limiting spinal pain in adult offspring associated with parental spinal pain; analysis stratified by BMI.

Variables	Normal weight			Overweight/obese		
	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)	No. of persons	No. of cases	Adjusted RR <sup>a</sup> (95% CI)
Offspring spinal pain						
Parental spinal pain						
None	168	68	1.00 (Ref.)	177	69	1.00 (Ref.)
Mother or father	316	111	0.88 (0.70-1.12)	380	133	0.89 (0.70-1.12)
Both parents	242	82	0.86 (0.66-1.11)	242	76	0.79 (0.61-1.03)
Offspring activity limiting spinal pain						
Parental spinal pain						
None	86	34	1.00 (Ref.)	130	50	1.00 (Ref.)
Mother or father	151	42	0.72 (0.49-1.04)	301	98	0.72 (0.51-0.99)
Both parents	129	41	0.84 (0.57-1.24)	188	52	0.57 (0.39-0.84)

CI: confidence interval.

<sup>a</sup>Adjusted for age, sex, leisure physical activity, smoking, education and depression.

## DISCUSSION

### Summary of findings

The findings of this large population-based prospective family-linkage study indicate that offspring with both parents reporting chronic spinal pain are less likely to recover from chronic spinal pain and activity limiting spinal pain compared with offspring with no parent with spinal pain. Overall, there was no strong evidence that physical activity or body mass index modified these associations, although the results suggest that the inverse association between parental spinal pain and recovery from activity limiting spinal pain was strongest among offspring with a high BMI. This study supports the evidence from twin studies that genetics potentially influences recovery from chronic spinal pain,[41] but these intergenerational associations incorporate shared environmental factors and shared beliefs that could influence recovery. For instance, there is evidence showing that negative beliefs about pain and negative expectations about recovery predict chronic and disabling spinal pain.[42-44] It seems clear that it is important to consider the family history of chronic spinal pain as well as lifestyle behaviours when identifying people at higher risk of non-recovery.

### Comparison of findings with previous research

A recent systematic review showed that offspring of parents with chronic pain have poorer outcomes regarding pain, general health, psychological, and family functioning as compared to offspring of parents without pain.[45] The inter-generational transmission of spinal pain could be explained by genetic heritability[9, 10] or a family shared environment.[11-14] Moreover, it has

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3 been suggested that the genetic influence is greater in more disabling pain conditions, such as  
4 chronic widespread pain and chronic activity limiting spinal pain, rather than in acute or sub-  
5 acute non-debilitating pain.[9, 10] It is widely accepted that lifestyle factors, such as physical  
6 activity and body weight, also play a significant role in the prognosis of chronic musculoskeletal  
7 pain.[46]  
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17 Some studies have suggested that people with chronic back pain who regularly engage in leisure  
18 time physical activity have better prognosis measured in terms of pain, disability, and quality of  
19 life than those who are sedentary.[29, 47] However, there remains conflicting evidence regarding  
20 how physical activity influences the prognosis of spinal pain,[48] with studies demonstrating that  
21 both low and high levels of physical activity can negatively influence the prognosis of spinal  
22 pain.[49, 50] For instance, a study found that high leisure time physical activity was related to  
23 decreased prevalence of low back pain.[51] Whereas another study found that either high or low  
24 levels of leisure time physical activity was related to increased prevalence of low back pain.[49]  
25 In contrast, a prospective study did not find any significant association between moderate/high  
26 levels of leisure physical activity and low back pain in young adults.[52] Another follow-up  
27 study found that regular habits of leisure physical activity have no effect on recovery from low  
28 back pain.[53] The inconsistency in the literature is possibly attributed to the diverse definitions  
29 and classifications of levels of physical activity. If such divergent associations with leisure time  
30 physical activity exist this could mask a possible modifying effect of physical activity in our  
31 analyses.  
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3 The literature has provided evidence that obesity is associated with poor outcomes in people with  
4 chronic widespread pain,[54, 55] as well as chronic spinal pain[29, 56, 57] and also decreases the  
5 probability of recovery from chronic spinal pain regardless of the care they receive,[25]  
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8 however, whether BMI could modify[30] the relationship between parental spinal pain on  
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10 offspring recovery from chronic spinal pain has not been investigated before. Our results suggest  
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12 that offspring BMI may modify on the parent-offspring association of spinal pain, with  
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14 somewhat stronger associations among offspring who were classified as overweight or obese  
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16 than those who were underweight or normal weight. Research has shown that inter-individual  
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18 differences in pain sensitivity and endogenous pain-inhibitory capacity could reflect variations in  
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20 the inherent susceptibility for chronic pain,[58, 59] but that a triggering exposure is required for  
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22 the development of chronic pain.[60, 61] This could suggest that a possible genetic susceptibility  
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24 for poor recovery from chronic pain[62, 63] as a higher penetrance between offspring who are  
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26 overweight or obese.  
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### 35 **Strengths and limitations**

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37 This study has several strengths including the prospective design utilising a large population-  
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39 based sample with a long follow-up period. In addition, the registry based information on family  
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41 relations allowed us to include information on chronic spinal pain obtained from parents and  
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43 offspring independently and at different time points. An important aspect is that the offspring  
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45 were adults at the time of data collection, indicating that the parent-to-offspring association of  
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47 chronic spinal pain persists into adulthood when the offspring most likely live apart from their  
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49 parents. Furthermore, we were able to adjust for several offspring characteristics that could  
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51 confound the parent-offspring associations of chronic spinal pain, such as age,[64] BMI,[57]  
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3 leisure physical activity,[65] smoking,[64] depression[64] and education.[10, 66] However, we  
4 cannot exclude the possible residual confounding attributable to unknown or unmeasured factors.  
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10 There are some limitations that should be taken into account. First, information on chronic spinal  
11 pain was only reported at baseline and at follow-up 10-11 years later, with no information on  
12 possible changes in the status of chronic spinal pain during the follow-up period. Consequently, a  
13 person could have recovered from spinal pain at some time-point between the surveys, but still  
14 report pain at follow-up. However, if parental pain reflects an underlying heritable frailty, this  
15 may have an impact also on long-term recurrence and recovery from pain. Likewise, information  
16 on leisure time physical activity and BMI was only assessed at baseline, with no information on  
17 possible changes during the follow-up period. Second, although the questions about leisure time  
18 physical activity used in this study have been reported to have good reliability and provide useful  
19 measures of leisure physical activity,[67] subjective interpretations of the activity questions  
20 could have influenced the results. Besides, it is well known that self-reports may lead to under or  
21 overestimation of the variables of interest.[68] Third, a premise for inclusion into this study was  
22 that the mother, father and offspring all had to participate in the health survey. To some extent,  
23 this may have resulted in a selected and more health conscious sample than the general  
24 population. Nevertheless, it is questionable whether representativeness is a prerequisite for  
25 making valid risk assessments in epidemiological studies.[57] Fourth, although the Norwegian  
26 Family registry was used to identify family relations between parents and offspring,  
27 misclassification of biological family relations in the registry due to adoptions and non-paternity  
28 is possible. Although the influence on our results is likely to be small, such misclassification  
29 could give attenuated parent-offspring associations. Moreover, we had no information on  
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3 whether the offspring shared environment with none, one or both of their biological parents  
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5 during childhood. Finally, residual confounding due to unmeasured or unknown factors cannot  
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7 be ruled out.  
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## 11 12 **CONCLUSION**

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14 Offspring with chronic spinal pain are less likely to recover if they have parents with chronic  
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16 spinal pain compared to offspring without parental chronic spinal pain. This association is  
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18 stronger when the offspring present pain that interferes with their usual work and leisure  
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20 activities (activity limiting spinal pain). The inverse association between parental chronic spinal  
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22 pain on recovery was somewhat stronger among offspring who were overweight or obese. The  
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24 association between parental chronic spinal pain and the prognosis of chronic spinal pain in the  
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26 adult offspring underlines the importance of identifying those at high risk of non-recovery since  
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28 they account for significant social and individual financial burden. Therefore, clinicians should  
29  
30 consider family history of spinal pain when implementing strategies to improve recovery from  
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32 chronic spinal pain, chronic spinal pain. For instance, the assessment of the potential risks of  
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34 physical activity and education about the range of benefits, as well as highlights the importance  
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36 of maintenance of a normal body weight.  
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### 31 **Author Contributions**

32  
33 All authors critically revised the manuscript for important intellectual content and approved the  
34  
35 final manuscript. Please find below a detailed description of the role of each author:  
36  
37

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39 - Anita B Amorim: conception and design, analysis and interpretation of data, drafting and  
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41 revision of the manuscript, and final approval of the version to be published.  
42
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# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5

1		#6b	For matched studies, give matching criteria and number of	6
2			exposed and unexposed	
3				
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5	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	6, 7 and
6			confounders, and effect modifiers. Give diagnostic criteria, if	8
7			applicable	
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9				
10	Data sources /	#8	For each variable of interest give sources of data and details of	See note
11	measurement		methods of assessment (measurement). Describe	1
12			comparability of assessment methods if there is more than one	
13			group. Give information separately for for exposed and	
14			unexposed groups if applicable.	
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18	Bias	#9	Describe any efforts to address potential sources of bias	8
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21	Study size	#10	Explain how the study size was arrived at	6
22				
23	Quantitative	#11	Explain how quantitative variables were handled in the	8
24	variables		analyses. If applicable, describe which groupings were chosen,	
25			and why	
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28	Statistical	#12a	Describe all statistical methods, including those used to control	8 and 9
29	methods		for confounding	
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32		#12b	Describe any methods used to examine subgroups and	8 and 9
33			interactions	
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36		#12c	Explain how missing data were addressed	8 and 9
37				
38		#12d	If applicable, explain how loss to follow-up was addressed	8 and 9
39				
40				
41		#12e	Describe any sensitivity analyses	8 and 9
42				
43	Participants	#13a	Report numbers of individuals at each stage of study—eg	9 and 10
44			numbers potentially eligible, examined for eligibility, confirmed	
45			eligible, included in the study, completing follow-up, and	
46			analysed. Give information separately for for exposed and	
47			unexposed groups if applicable.	
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51		#13b	Give reasons for non-participation at each stage	9 and 10
52				
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54		#13c	Consider use of a flow diagram	n/a
55				
56	Descriptive data	#14a	Give characteristics of study participants (eg demographic,	9 and 10
57			clinical, social) and information on exposures and potential	
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1		confounders. Give information separately for exposed and	
2		unexposed groups if applicable.	
3			
4		#14b Indicate number of participants with missing data for each	n/a
5		variable of interest	
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7			
8		#14c Summarise follow-up time (eg, average and total amount)	9 and 10
9			
10	Outcome data	#15 Report numbers of outcome events or summary measures	10 and
11		over time. Give information separately for exposed and	11
12		unexposed groups if applicable.	
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14			
15	Main results	#16a Give unadjusted estimates and, if applicable, confounder-	10 and
16		adjusted estimates and their precision (eg, 95% confidence	11
17		interval). Make clear which confounders were adjusted for and	
18		why they were included	
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22		#16b Report category boundaries when continuous variables were	10 and
23		categorized	11
24			
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26		#16c If relevant, consider translating estimates of relative risk into	n/a
27		absolute risk for a meaningful time period	
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30	Other analyses	#17 Report other analyses done—e.g., analyses of subgroups and	10 and
31		interactions, and sensitivity analyses	11
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34	Key results	#18 Summarise key results with reference to study objectives	11 and
35			12
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38	Limitations	#19 Discuss limitations of the study, taking into account sources of	13
39		potential bias or imprecision. Discuss both direction and	
40		magnitude of any potential bias.	
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43	Interpretation	#20 Give a cautious overall interpretation considering objectives,	13 and
44		limitations, multiplicity of analyses, results from similar studies,	14
45		and other relevant evidence.	
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48	Generalisability	#21 Discuss the generalisability (external validity) of the study	13 and
49		results	14
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52	Funding	#22 Give the source of funding and the role of the funders for the	15 and
53		present study and, if applicable, for the original study on which	16
54		the present article is based	
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## Author notes

1. 6, 7 and 8

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