Long-term changes in musculoskeletal pain sites in the general population: The HUNT study

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Abstract

In a Norwegian prospective population-based cohort study, we examined whether the number of chronic musculoskeletal pain sites changed over an 11-year period, and if the number of pain sites at follow-up was associated with health-related and lifestyle factors at baseline. The study included data on 78,973 adults participating in the Nord-Trøndelag Health Study (HUNT) in 1995–1997 (HUNT2) and 2006–2008 (HUNT3). Based on three categories of baseline pain sites, associations between baseline health-related, lifestyle, and demographic factors and number of pain sites at follow-up were analysed with linear regression models adjusted for age, sex, marital status, physical activity, education, and other chronic diseases. We also estimated within-subject associations. Regardless of pain extent at baseline, anxiety and/or depression, sleeping problems, smoking, and obesity were positively associated with number of pain sites at follow-up, while education and physical activity were inversely associated with number of pain sites. The within-subject analyses showed largely similar associations for the health-related factors, whereas associations of lifestyle factors were attenuated. The mean number of pain sites remained unchanged between the two surveys.
Overall, our study revealed prospective associations between several factors and pain sites 11 years later, regardless of the number of pain sites at baseline.

Perspective

This prospective study examines the association between development of pain and risk factors in the general population, on the basis of three categories of baseline pain sites. It also examines how these factors influence possible long-term changes in pain within individuals. We demonstrate that having no or few baseline pain sites may not differ in its risk factors compared with having multiple pain sites. This article provides an important contribution to the ongoing debate regarding the association between lifestyle, demographic, and

psychosocial risk factors, versus the course of multisite chronic pain. Additionally, we provide discussion on potential directions for clinical relevance and further research in this field.

Keywords

Chronic musculoskeletal pain; Pain; Risk factors; General population; Prospective epidemiologic study

Introduction

The more pain sites an individual reports, the more severe are the functional, physical, psychological, neurocognitive, and social consequences experienced, regardless of pain location.[1, 23, 35, 39] Recent research also suggests that there are important differences in the risk factors for single-site pain and widespread pain, and that the overall consequences are highly dependent on number of pain sites.[8, 24] Indeed, chronic pain can be classified as regional or widespread, depending on the number of pain sites affected.[2, 7, 23] Regional pain appears as single pain sites in, e.g., lower back, shoulder, or neck, with lower back and neck pain as the most frequently reported sites, [11, 24] whereas widespread pain has commonly been categorized as pain in the trunk, in upper and lower limbs, and on both sides of the body.[52]

There is equivocal evidence regarding population-level changes in the prevalence of musculoskeletal pain over time. A UK study indicated a substantial increase in the prevalence of musculoskeletal pain between two cross-sectional surveys conducted over 40 years apart.[22]

However, other studies have indicated small changes over time.[18, 20, 37] It is difficult to assess differences in prevalence between cross-sectional studies. Differences can be sensitive to changes in survey methods and representativeness. Taking advantage of repeated measures of pain within individuals could be one possible way to overcome such analytical problems.[47, 54]

At the individual level, chronic musculoskeletal pain might spread between body regions.[1] However, a Norwegian study suggested a highly stable number of pain sites over time, and that previous multisite pain appeared as a strong predictor of future multisite pain, independent of sex, age, sleep quality, and education.[23] A multinational cross-sectional study reported progressively stronger associations between physical and psychosocial risk factors and an increasing number of pain sites.[8] Female sex, anxiety and depression, sleeping problems, smoking, overweight/obesity, and family history of pain are also known risk factors for chronic widespread pain (CWP).[3, 32, 45]

Chronic musculoskeletal pain is complex and determined by multiple causal pathways involving biological, psychological, and social influences that can interact with each other.[13, 17, 34] Yet the full aetiology is unclear.[49] In addition, the classification of multisite pain is not clearly defined, usually taken to be two or more sites,[7] which challenges comparability. It is not clear how the number of pain sites change over time and if there are factors that influence these changes from the extent of baseline pain.

This large population-based prospective study aims to (1) study long-term changes in the mean number of musculoskeletal pain sites, relative to the influence of demographic, lifestyle, and morbidity variables, and (2) examine the development of musculoskeletal pain in terms of number of pain sites within individuals over an 11-year period according to the same risk

factors. Examining these associations over time within individuals prevents confounding related to factors that remain stable within individuals (such as sex, occupation, genetic make-up, presence of chronic disease) because each individual serves as her/his own control.

Methods

Study population

The HUNT study ("*Helseundersøkelsen i Nord-Trøndelag*") was designed as a longitudinal cohort study consisting of three health surveys carried out at 11-year intervals in which all residents aged 20 years and older in Norway's Nord-Trøndelag County were invited to participate.[28] Since the first survey (HUNT1, 1984–86) did not collect information on musculoskeletal pain, it is not included in the current analysis. The present study was based on data from the second (HUNT2, 1995–1997) and third (HUNT3, 2006–2008) surveys. Data in all HUNT surveys were collected through interviews, self-administrated questionnaires, and clinical examinations with measures of weight, height, waist and hip circumference, blood pressure, and heart rate.[21, 29]

Participation in HUNT2 and HUNT3 was defined as having completed questionnaire 1 (Q1) and having provided written consent regarding the screening, subsequent follow-up, and data linkages to other registers. The study population comprised 78,973 individuals who participated in either HUNT2 or HUNT3, or in both surveys. More specifically, 65,237 (69.5% of those invited) participated in HUNT2, and 50,807 (54.1%) participated in HUNT3. A total of 37,071 individuals participated in both surveys. Of those, 26,875 participants had complete information. The distribution of the eligible participants and the inclusion process is illustrated in Figure 1.

Figure 1

Study variables

In both HUNT2 and HUNT3, information on chronic musculoskeletal pain was obtained from the Standardized Nordic Questionnaire (SNQ).[30] The SNQ has been considered a reliable and sensitive screening instrument for investigating musculoskeletal symptoms, having excellent sensitivity and moderate specificity when assessing the agreement between questionnaires and clinical examination, and with high utility and generalizability in the screening context in epidemiological surveys and surveillance.[10, 18, 46] If a participant confirmed the introductory question, "During the last year, have you had pain and/or stiffness in your muscles and limbs that has lasted for at least three consecutive months?", they were then asked to specify whether pain was present in any of the nine different body regions: neck, shoulder, elbow, hand/wrist, upper back, lower back, hip, knee, and ankle/foot. If the participants responded only to the introductory pain question, without specifying their pain locations, they were defined as missing observations. Based on the introductory pain question in HUNT2 and HUNT3, we defined chronic pain as "having pain that has lasted for at least three consecutive months during the last year". The number of pain sites was classified as "no pain", "1–2 pain sites", and "3 or more pain sites", to examine whether the level of baseline pain sites is of importance for prospective associations. The categorization of pain sites into three pain categories reached a balance between categorization and power. The choice was determined by the number of pain sites, not by the pain localizations. The categorization of pain sites has been motivated by Coggon et al.'s classification of pain.[8] Having 1–2 pain sites at baseline represents limited pain, whilst 3 or more pain sites will include, but not be limited to, those with pain consistent with American College of Rheumatology (ACR) criteria of CWP.[52]

Lifestyle and health-related factors

Information on age and marital status was obtained from the National Population Registry. Marital status was categorized as "single/divorced/separated/widower" and "married/cohabitant/partnership".

Information on mood was collected from the Hospital Anxiety and Depression Scale (HADS), which comprises seven items for depression (HADS-D) and seven items for anxiety (HADS-A).[58] According to a HADS validity study [4], the best balance between sensitivity (0.80) and specificity (0.80) was achieved when setting the cut-off score at ≥ 8, which marks a borderline case of anxiety or depression on the sub-scales. A score of ≥8 on each subscale indicates clinically relevant symptoms consistent with depression (HADS-D) or anxiety (HADS-A).[57] In this study, we wanted to examine the co-occurrence of clinically relevant anxiety and/or depression symptoms alongside chronic musculoskeletal pain. Based on this recommended cut-off score of ≥ 8 for each subscale,[4] we categorized anxiety and depression into four groups: 1) neither anxiety nor depression, 2) depression only, 3) anxiety only, and 4) both depression and anxiety. We also utilized the continuous scores of the HADS-subscales. As a sensitivity analysis, we also investigated the associations between different levels of anxiety and depression symptoms and number of pain sites. Ordinal variables for anxiety and depression symptom load were computed as reference (0–4), sub-symptom load, (5–7) mild symptom load (8–10), moderate symptom load (11–14), and severe symptom load (15–21).[4, 27] Sleeping problems were identified by two questions: "Have you had difficulty falling asleep in the last month?" and "During the last month, have you woken too early and not been able to get back to sleep?". Response options were "almost every night", "often", "now and

again", and "never". People reporting "almost every night" and "often" on either of these questions were classified as having sleeping problems. Long-term illnesses (other chronic diseases) were detected by the question: "Do you suffer from any long-term illness or injury of a physical or psychological nature that impairs your functioning in everyday life?".

Alcohol use was measured by the two questions: "Concerning alcohol, are you a non-drinker?" and "How many times a month do you normally drink alcohol?". Responses were classified as 1) zero times/ month, 2) 1–7 times/ month, 3) ≥ 8 times/ month, and 4) abstainers. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m) and classified according to *the World Health Organization's recommendations:*[55] underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥ 30 kg/m^2).[51] Additionally, BMI was analysed as a continuous variable. Smoking was categorized into three groups: 1) "never smoking", 2) "former smoking", and 3) "current smoker". Education was classified as 1) primary school, 2) high school, and 3) university/college. Leisure-time physical activity was identified by the question: "Think of a weekly average for the year. How has your leisure-time physical activity been the last year?". This question sought to discern between light activity (no sweating or being out of breath) per week, versus hard physical activity (sweating/out of breath), according to the average number of hours of exercise per week. The response options were "never", "less than 1", "1–2", and "3 hours or more per week". The level of physical activity was merged into a summary variable and computed as the average hours of low and hard physical activity per week during the last year, and classified into two groups: 1) "inactive" and 2) "active" *(at least 30 minutes per day).*[31]

Statistical analysis

First, we presented a descriptive analysis of the change in number of pain sites, from 0 (no pain) to 9 pain sites for those who participated in both HUNT2 and HUNT3. We then performed a linear regression analysis and finally a multilevel linear regression analysis to investigate the mean difference in number of pain sites between HUNT2 and HUNT3 according to different risk factors reported in HUNT2 and taking into account those participants with repeated measures between surveys. As a measure of within-person stability, we calculated the degree of clustering for number of pain sites among individuals, using the intra-class correlation coefficient (ICC), which reflected the proportion of pain site variance attributable to stability within individuals.[47] In an extreme situation where there is no concordance in number of pain sites within individuals, the ICC would be zero, whereas if all individuals participating in the two surveys had the same value at each time point, then the ICC would equal one.

In the next step of the analyses, we used a linear regression analysis to examine possible differences in risk factors for different numbers of baseline pain sites. These analyses were conditioned on 0, 1–2, or 3 or more reported pain sites in HUNT2. The levels of adjustment were carried out to assess the importance of potential confounders. In the first model (data not shown), each variable was adjusted for age and sex. In a fully adjusted model, we controlled for marital status, education, physical activity, and chronic disease in HUNT2, in addition to age and sex. Age and sex are considered potential confounding variables since they are associated with both the risk of developing chronic pain (higher prevalence with age and in females) and the exposure variables (e.g. sex differences in prevalence of anxiety and

depression symptoms, and increasing symptom load with age). Smoking and physical inactivity might also be a part of the same lifestyle leading to the risk of developing chronic musculoskeletal pain, and the same holds true for obesity and physical activity. Socioeconomic status (education) might be related to lifestyle and the incidence of chronic pain. Also, baseline chronic pain might account for the symptom load in, for instance, anxiety and depression, and in sleeping problems. Only complete cases were included in the regression analyses, as some participants did not report information on some of the included variables. Our outcome measure – i.e. number of pain sites – did not meet the formal assumption for linear regression analysis. As a sensitivity analysis, we also ran an ordered logistic regression model (Web table 2).

Subsequently, we performed a within-individual linear fixed effect regression analysis of the mean change in number of pain sites in HUNT2 and HUNT3 according to change in different risk factors. The within-individual fixed effect linear regression analysis was adjusted for exercise and chronic disease, making it possible to control for all stable characteristics among the individuals (observed and unobserved). These models used a within-subject variation of the 26,875 participants with data from both time points,[47] reflecting that the individuals were serving as their own control, and also used information on individuals discordant on exposure and outcome in the models. *The central idea for employing a fixed effect model is to use each individual as his/her own control in order to eliminate between-individual differences that may be present in ordinary population analyses (between-subjects variation) in population analyses.*

All statistical analyses were performed with the statistical package Stata version 13.1 (StataCorp, College Station, Texas, USA).

Ethics

This study was approved by the Regional Norwegian Committee for Medical and Health Research Ethics and the National Data Inspectorate.

Results

Demographic data and characteristics of the two surveys (HUNT2 and HUNT3) are presented in Table 1. In the HUNT2 cohort (n=34,662, 53% female), 48% (n=30,976) of participants reported chronic musculoskeletal pain ranging from 1 to 9 pain sites, measured by the SNQ map, of which 57% (n=17,734) were female. In HUNT2, 43% of those with chronic musculoskeletal pain reported 1 to 2 pain sites, and approximately 56% reported 3 or more pain sites (Table 1). Only 0.5 % of those reporting chronic musculoskeletal pain in HUNT2 or in HUNT3 did not specify their pain location and were thus excluded from the analyses. Chronic musculoskeletal pain was most prevalent in those aged 40–49 (21%).

Table 1

Long-term course of chronic musculoskeletal pain sites

Of those reporting no chronic pain in HUNT2, 62% (n=9,686) remained free of chronic pain in HUNT3 (Table 2). Of those reporting 1 to 2 sites of pain in HUNT2, 32% reported the same number of pain sites at follow-up, and the corresponding figure among those with ≥ 3 sites in HUNT3 was 30%. Although the majority reported less pain at follow-up, the proportion who reported that all of their pain had resolved (i.e. zero pain sites) was small, and

this proportion decreased as the number of pain sites from HUNT2 increased. Of those who reported ≥ 3 sites in HUNT2, 63% continued to report ≥ 3 pain sites in HUNT3, with the remainder reporting less pain (16% reporting zero pain sites). Based on the results from a multilevel regression analysis, a total of 53% of the variability in pain sites could be attributed to stability within individuals (ICC=0.53, p<0.001), indicating a substantial stability in the number of pain sites within individuals over the 11-year period.

Table 2

Table 3 summarizes the fully adjusted 11-year prospective associations of subsequent number of pain sites conditional on number of pain sites reported at baseline. For those without baseline pain, anxiety and depression symptoms were associated with 0.54 (95% confidence interval (CI): 0.38 to 0.70) more pain sites in HUNT3, compared to the absence of these symptoms. A largely similar association was observed for people with only anxiety, whereas the association was weaker for those with only depression symptoms. These associations did not deviate substantially when based on number of pain sites in HUNT2. For continuous scores of HADS- subscales, one point change in depression was associated with 0.04 more pain sites for those without baseline pain (95% CI: 0.03 to 0.06). Similar associations were found in those reporting 1-2 or 3 or more pain sites in HUNT3. In addition, the anxiety HADS-subscale and the total HADS-scale showed largely similar associations. The results from supplementary sensitivity analysis based on categories of anxiety and depression symptoms, rather than a binary variable using multivariable linear regression, are largely in line with the results presented above, except that the increasing levels of depression symptoms in those reporting no baseline pain were associated with an increase in the number of pain sites (from 0.30 (95% CI: 0.18 to 0.43) among those with mild symptoms of

depression, and up to 1.03 (95% CI: 0.36 to 1.70)) among those with severe symptoms, compared to those with no depression symptoms (data not shown).

Among people without baseline pain, problems with initiating or maintaining sleep were associated with 0.38 (95% CI: 0.27 to 0,49) more pain sites in HUNT3 compared with no sleep problems. For those reporting 1–2 or 3 or more pain sites, sleep problems were associated with a 0.34 (95% CI: 0.18 to 0.50) and 0.56 (95% CI: 0.41 to 0.71) increase in the number of pain sites, respectively.

Among people without baseline pain, the frequency of alcohol consumption was not associated with number of pain sites at follow-up. However, for those reporting 3 or more pain sites, drinking alcohol ≥ 8 times a month was associated with 0.29 (95% CI: -0.56 to -0.01) fewer pain sites in HUNT3, versus those drinking zero times a month. Analyses of BMI showed that among people without pain at baseline, obesity was associated with 0.30 (95% CI: 0.21 to 0.38) more pain sites in HUNT3, compared to those of normal weight, and this relationship was stronger among those with 3 or more pain sites (0.44, 95% CI: 0.28 to 0.61). For continuous scores of BMI, one point change in BMI was associated with 0.03 more pain sites (95% CI: 0.02 to 0.03) in those without baseline pain, while among those reporting 1-2, and 3 or more baseline pain sites, one point change in BMI was associated with 0.02 (95% CI: 0.01 to 0.04), and 0.04 (95% CI: 0.02 to 0.06) more pain sites at follow-up, respectively.

Compared with never smoking, daily smoking was associated with 0.26 (95% CI: 0.20 to 0.33) more pain sites at follow-up among people reporting no baseline pain, whereas the association was attenuated among those reporting ≥ 3 pain sites (0.13, 95% CI: -0.02 to 0.27). Physical activity was not associated with number of pain sites at follow-up among those free

of chronic pain at baseline. Yet it was inversely associated with number of pain sites among those reporting 1–2 pain sites (-0.15, 95% CI: -0.25 to -0.05) and (-0.12, 95% CI: -0.24 to -0.00) among those reporting ≥ 3 pain sites, compared with those who reported being inactive. Among people without baseline pain, education (comparing university/college education with primary school) was inversely associated with number of pain sites at follow-up (-0.30, 95% CI: -0.38 to -0.22). The strength of this association increased with an increase in the number of pain sites at baseline (-0.41 (95% CI: -0.56 to -0.27) for those with 1–2 pain sites, and -0.61 (95% CI: -0.79 to -0.44) for those with ≥ 3 pain sites at baseline). As presented in Web table 1, results from the age- and sex-adjusted linear regression analyses do not differ distinctly from the fully adjusted analyses. The results from supplementary analyses using ordered logit regression are in line with the results presented above (see Web table 2).

Table 3

The fixed effect within-subject analysis (Table 4) comprised 26,875 individuals with 48,669 observations and gave largely similar results for anxiety and depression symptoms, problems initiating or maintaining sleep, and exercise as those presented in Table 3. However, the within-subject analysis showed weaker associations for changes in alcohol frequency, smoking, and BMI than those reported for the total sample. The number of pain sites in the within-subject analysis remained relatively unchanged over 11 years, with a decrease of -0.07 (95%: CI -0.11 to -0.04) pain sites.

Table 4

Discussion

This study showed that regardless of pain extent at baseline, symptoms of anxiety and/or depression, sleeping problems, smoking, and obesity were associated with an increase in the number of pain sites at follow-up, whereas education was associated with a decrease in the number of pain sites. Physical activity showed a weak inverse association with number of pain sites, but only among people reporting baseline pain. Except for anxiety and depression symptoms, and sleeping problems, these associations were attenuated in the within-subject analysis. On average, the number of pain sites reported by participants remained unchanged over 11 years.

Relevance to other studies

Using data from the HUNT study, previous studies have examined prevalence of pain and potential associations between number of pain sites, body pain locations, or CWP, versus physical and psychosocial risk factors.[18, 40, 42, 44] However, we have not found comparable studies that have examined the association between pain development and these risk factors on the basis of different levels of reported baseline pain sites, or examined how these factors influence possible long-term changes in pain sites within individuals.

Our study indicated no substantial change in number of pain sites between the two surveys performed in the mid-1990s and 2000s. A UK study[22] suggested an increased prevalence of musculoskeletal pain in the general population, based on results from two surveys conducted over 40 years apart. Other studies over shorter time spans reported results more similar to our own.[25] The minor differences in number of pain sites between the two surveys is also in line with the results from a Norwegian study[18] based on the same material as the present study, which indicated a small but statistically significant increase in the prevalence of chronic musculoskeletal complaints in HUNT2 compared to HUNT3. The differences between the

conclusions may be due to different designs and methodological approaches, i.e. cross-sectional prevalence study against our prospective study examining possible changes in pain sites using multilevel within-subject regression analyses. In population studies, chronic pain might not occur among the same people at each time point. Thus, within-subject analysis is less biased and gives a stronger indication of the relationship.

Others have examined a classification for multisite pain patterns, demonstrating that pain involving 6–10 body sites yielded a stronger association with physical and psychosocial risk factors than having 1–3 pain sites or CWP.[8] In this study, we examined potential associations between risk factors and change in pain on the basis of three baseline pain categories: no pain, 1–2 pain sites, and 3 or more pain sites. Thus we could include but not limit the study to those with pain consistent with CWP according to the ACR criteria.[53]

The present study demonstrates that having anxiety or both anxiety and depression were strongly associated with increased pain regardless of pain at baseline, although this was particularly evident in those with no chronic pain at baseline. Chronic pain is a complex perceptual experience, often comorbid with anxiety and depression and determined by sensory and social influences.[13,26] Emotional distress is commonly observed in people with chronic pain, and it may also predispose an individual to experience pain.[13] A prospective Dutch study examined the impact of pain on depression and anxiety onset and found that only joint pain and increasing number of pain locations (but not pain duration) were associated with depression and anxiety onset.[14] Notwithstanding the co-occurrence of chronic pain and psychological symptoms, the onset of pain and mild psychological symptoms do not typically coincide, and could be mutually independent.[9] We also found that baseline sleeping problems were most positively associated with the number of pain sites at follow-up among those

reporting 3 or more pain sites, which is consistent with previous studies reporting sleep problems as a risk factor for CWP persistence and development [43, 45]

Regarding the frequency of alcohol use, our results suggest a modest preventive effect of moderate alcohol use on number of pain sites at follow-up among those with baseline pain, compared to alcohol abstinence. This is consistent with other studies examining risk factors for CWP development,[3, 45] and may be explained by possible biological[3] or confounding effects of other health and lifestyle concerns. Consistent with previous studies,[43, 45] we found that obesity was associated with both the development and persistence of chronic pain. Similarly, several prospective studies have found some evidence that being overweight and obese are risk factors for chronic pain because weight gains increase strains, especially in joints.[22, 50] Former and current smoking are also associated with a prospective increased pain among those with no pain or 1–2 pain sites at baseline. However, this relationship is denoted as complex because of possible mediating factors between smoking and pain, such as depression symptoms.[15,16] In those with baseline pain, physical activity was weakly associated with a subsequent decrease in pain. Current public health recommendations are an average of 30 minutes of moderate to intense daily physical activity, which is supposed to provide substantial benefits across a wide range of health outcomes.[5] Others have also found evidence of a robust relationship between exercise and pain.[34]

Our study showed that education at the university/college level was inversely associated with number of pain sites at follow-up, and particularly among those with 3 or more pain sites. Education has been considered as the best indicator of socioeconomic status (SES),[19] and low SES has been associated with increased mortality and morbidity.[38] However, the association between chronic pain and educational level may be merely a part of a more complex picture.[6]

Because we did not examine occupation or other corresponding social factors, we may not have fully grasped the nature of this relationship.

The within-subject associations between the number of pain site changes and measures of anxiety or depression were attenuated, while the associations with lifestyle factors dissolved compared with the population analyses. Even though high BMI and previous smoking have been associated with risk of chronic pain,[22, 32, 45, 56] our results indicate that these risk factors could be influenced by time-lagged effects, i.e. they must have been present for some time in order to result in a change in the number of pain sites. The results may also be explained from the fixed-effect analyses, where each person is her/his own control and where bias caused by unmeasured time-invariant confounding effects, such as individual personality traits, ability, SES, and genetics, can be avoided.[17] With repeated measures of both the exposure and outcome, only within-individual changes over time were analysed, eliminating between-individual differences that may be present in the population analyses.

Strengths and limitations

Major strengths of this study are the large population base and sample size, *and the 11-year span between HUNT2 and the follow-up in HUNT3.* The prospective design and length of follow-up are useful for determining possible causal directions of health-related and lifestyle factors and the association with prospective changes in pain sites. *Complete baseline and follow-up data from this large sample also indicates high validity. Using standardized and comparable questions to collect pain data at two time points also ensures the comparability of results across different studies.*

While approximately 70% of those invited to HUNT2 participated, 54% of those invited to HUNT3 participated, representing an attrition of 15%. The lower response rate in HUNT3 may have affected the prevalence estimates of chronic pain at follow-up and thus implied a loss of accuracy in population estimates and threatened external validity.[33, 48] Non-participants in HUNT3 had a lower socioeconomic status and higher mortality, along with higher rates of smoking and physical inactivity, and a higher prevalence of several chronic diseases.[36] For those who participated, different patterns were found for problems like musculoskeletal pain, urine incontinence, and headache, which might have affected the prevalence estimates of pain in HUNT3.[36] This might also indicate that pain is not an important cause of non-participation. However, low participation rates do not necessarily indicate a high level of bias inherent in a study.[12, 36, 41]

Conclusions and implications

This large 11-year follow-up study demonstrates that risk factors for change in the number of pain sites over time are not exclusively dependent on pain extent at baseline. However, having anxiety and depression symptoms, sleeping problems, and being obese, were the most important predictors of an increase in number of pain sites reported over time. To better understand risk factors for worsening pain or indeed factors for reducing pain over time, socioeconomic, lifestyle, and health-related factors should be studied more extensively within individuals. A standardised approach to counting and classifying number of pain sites would allow for further comparison between studies and an ability to pool study data for a more powerful analysis. For a population approach, there is a need for perspectives expressed in terms of risk and probability. To improve clinical pain management, pain should be examined from prospectively collected data both among adolescence and adults in clinical and population-based samples, and in association with how pain interferes with daily function.

Conflict of interest statement

The authors declare no conflicts of interest.

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References

1. Andersen LL, Clausen T, Carneiro IG, Holtermann A. Spreading of chronic pain between body regions: prospective cohort study among health care workers. *Eur J Pain.* 16:1437-1443, 2012

2. Andersson HI. The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. *European journal of pain (London, England).* 8:47-53, 2004

3. Bergman S, Herrstrom P, Jacobsson LT, Petersson IF. Chronic widespread pain: a three year followup of pain distribution and risk factors. *J. Rheumatol.* 29:818-825, 2002

4. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J. Psychosom. Res.* 52:69-77, 2002

5. Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical activity recommendations: how much is enough? *Am. J. Clin. Nutr.* 79:913s-920s, 2004

6. Bonathan C, Hearn L, Williams AC. Socioeconomic status and the course and consequences of chronic pain. *Pain management.* 3:159-162, 2013

7. Carnes D, Parsons S, Ashby D, Breen A, Foster NE, Pincus T, Vogel S, Underwood M. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. *Rheumatology (Oxford).* 46:1168-1170, 2007

8. Coggon D, Ntani G, Palmer KT, Felli VE, Harari R, Barrero LH, Felknor SA, Gimeno D, Cattrell A, Vargas-Prada S, Bonzini M, Solidaki E, Merisalu E, Habib RR, Sadeghian F, Masood Kadir M, Warnakulasuriya SS, Matsudaira K, Nyantumbu B, Sim MR, Harcombe H, Cox K, Marziale MH, Sarquis LM, Harari F, Freire R, Harari N, Monroy MV, Quintana LA, Rojas M, Salazar Vega EJ, Harris EC, Serra C, Martinez JM, Delclos G, Benavides FG, Carugno M, Ferrario MM, Pesatori AC, Chatzi L, Bitsios P, Kogevinas M, Oha K, Sirk T, Sadeghian A, Peiris-John RJ,

Sathiakumar N, Wickremasinghe AR, Yoshimura N, Kelsall HL, Hoe VC, Urquhart DM, Derrett S, McBride D, Herbison P, Gray A. Patterns of multisite pain and associations with risk factors. *Pain.* 154:1769-1777, 2013

9. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. *Psychosom. Med.* 64:773-786, 2002

10. Descatha A, Roquelaure Y, Chastang JF, Evanoff B, Melchior M, Mariot C, Ha C, Imbernon E, Goldberg M, Leclerc A. Validity of Nordic-style questionnaires in the surveillance of upper-limb work-related musculoskeletal disorders. *Scand. J. Work. Environ. Health.* 33:58-65, 2007

11. Ferrari R, Russell AS. Regional musculoskeletal conditions: neck pain. *Best practice & research. Clinical rheumatology.* 17:57-70, 2003

12. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann. Epidemiol.* 17:643-653, 2007

13. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol. Bull.* 133:581-624, 2007

14. Gerrits MM, van Oppen P, van Marwijk HW, Penninx BW, van der Horst HE. Pain and the onset of depressive and anxiety disorders. *Pain.* 155:53-59, 2014

15. Goesling J, Brummett CM, Hassett AL. Cigarette smoking and pain: depressive symptoms mediate smoking-related pain symptoms. *Pain.* 153:1749-1754, 2012

16. Goesling J, Brummett CM, Meraj TS, Moser SE, Hassett AL, Ditre JW. Associations Between Pain, Current Tobacco Smoking, Depression, and Fibromyalgia Status Among Treatment-Seeking Chronic Pain Patients. *Pain medicine (Malden, Mass.).* 16:1433-1442, 2015

17. Gunasekara FI, Richardson K, Carter K, Blakely T. Fixed effects analysis of repeated measures data. *Int J Epidemiol.* 43:264-269, 2014

18. Hagen K, Linde M, Heuch I, Stovner LJ, Zwart JA. Increasing prevalence of chronic musculoskeletal complaints. A large 11-year follow-up in the general population (HUNT 2 and 3). *Pain Med.* 12:1657-1666, 2011

19. Hagen KB, Tambs K, Bjerkedal T. What mediates the inverse association between education and occupational disability from back pain?--A prospective cohort study from the Nord-Trondelag health study in Norway. *Soc. Sci. Med.* 63:1267-1275, 2006

20. Heistaro S, Vartiainen E, Heliovaara M, Puska P. Trends of back pain in eastern Finland, 1972-1992, in relation to socioeconomic status and behavioral risk factors. *Am. J. Epidemiol.* 148:671-682, 1998

21. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, Vatten L, Lund-Larsen PG. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi 2003; 13 (1): 19-33. 2003

22. Janke EA, Collins A, Kozak AT. Overview of the relationship between pain and obesity: What do we know? Where do we go next? *J. Rehabil. Res. Dev.* 44:245-262, 2007

23. Kamaleri Y, Natvig B, Ihlebaek CM, Benth JS, Bruusgaard D. Change in the number of musculoskeletal pain sites: A 14-year prospective study. *Pain.* 141:25-30, 2009

24. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. Localized or widespread musculoskeletal pain: does it matter? *Pain.* 138:41-46, 2008

25. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. Does the number of musculoskeletal pain sites predict work disability? A 14-year prospective study. *Eur J Pain.* 13:426-430, 2009

26. Katz J, Rosenbloom BN, Fashler S. Chronic Pain, Psychopathology, and DSM-5 Somatic Symptom Disorder. *Canadian journal of psychiatry. Revue canadienne de psychiatrie.* 60:160-167, 2015

27. Knudsen AK, Overland S, Aakvaag HF, Harvey SB, Hotopf M, Mykletun A. Common mental disorders and disability pension award: seven year follow-up of the HUSK study. *J. Psychosom. Res.* 69:59-67, 2010

28. Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, Stene T, Bratberg G, Heggland J, Holmen J. Cohort Profile: The HUNT Study, Norway. *Int. J. Epidemiol.*, 2012

29. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort Profile: the HUNT Study, Norway. *Int J Epidemiol.* 42:968-977, 2013

30. Kuorinka I, Jonsson B, Kilbom A, Vinterberg H, Biering-Sorensen F, Andersson G, Jorgensen K. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl. Ergon.* 18:233-237, 1987

31. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trondelag Health Study (HUNT 2). *Eur. J. Epidemiol.* 22:379-387, 2007

32. Kvalheim S, Sandven I, Hagen K, Zwart JA. Smoking as a risk factor for chronic musculoskeletal complaints is influenced by age. The HUNT study. *Pain.* 154:1073-1079, 2013

33. Lahaut VM, Jansen HA, van de Mheen D, Garretsen HF. Non-response bias in a sample survey on alcohol consumption. *Alcohol Alcohol.* 37:256-260, 2002

34. Landmark T, Romundstad PR, Borchgrevink PC, Kaasa S, Dale O. Longitudinal associations between exercise and pain in the general population--the HUNT pain study. *PLoS One.* 8:e65279, 2013

35. Landro NI, Fors EA, Vapenstad LL, Holthe O, Stiles TC, Borchgrevink PC. The extent of neurocognitive dysfunction in a multidisciplinary pain centre population. Is there a relation between reported and tested neuropsychological functioning? *Pain.* 154:972-977, 2013

36. Langhammer A, Krokstad S, Romundstad P, Heggland J, Holmen J. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC medical research methodology.* 12:143, 2012

37. Leino PI, Berg MA, Puska P. Is back pain increasing? Results from national surveys in Finland during 1978/9-1992. *Scand. J. Rheumatol.* 23:269-276, 1994

38. Mackenbach JP, Kunst AE, Cavelaars AE, Groenhof F, Geurts JJ. Socioeconomic inequalities in morbidity and mortality in western Europe. The EU Working Group on Socioeconomic Inequalities in Health. *Lancet.* 349:1655-1659, 1997

39. Miranda H, Kaila-Kangas L, Heliovaara M, Leino-Arjas P, Haukka E, Liira J, Viikari-Juntura E. Musculoskeletal pain at multiple sites and its effects on work ability in a general working population. *Occup Environ Med.* 67:449-455, 2010

40. Mork PJ, Vik KL, Moe B, Lier R, Bardal EM, Nilsen TI. Sleep problems, exercise and obesity and risk of chronic musculoskeletal pain: the Norwegian HUNT study. *Eur J Public Health.* 24:924-929, 2014

41. Morton SM, Bandara DK, Robinson EM, Carr PE. In the 21st Century, what is an acceptable response rate? *Aust. N. Z. J. Public Health.* 36:106-108, 2012

42. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: the HUNT study. *BMC Musculoskelet Disord.* 15:213, 2014

43. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: the HUNT study. *BMC musculoskeletal disorders.* 15:213, 2014

44. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Psychosocial factors and risk of chronic widespread pain: an 11-year follow-up study--the HUNT study. *Pain.* 155:1555-1561, 2014

45. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Psychosocial factors and risk of chronic widespread pain: An 11-year follow-up study-The HUNT study. *Pain.* 2014

46. Palmer K, Smith G, Kellingray S, Cooper C. Repeatability and validity of an upper limb and neck discomfort questionnaire: the utility of the standardized Nordic questionnaire. *Occupational medicine (Oxford, England).* 49:171-175, 1999

47. Rabe-Hesketh S, Skrondal A: Multilevel and Longitudinal Modeling Using Stata. Second Editio edition, Stata Press, Texas, 2008.

48. Tolonen H, Dobson A, Kulathinal S, Project WM. Effect on trend estimates of the difference between survey respondents and non-respondents: results from 27 populations in the WHO MONICA Project. *Eur J Epidemiol.* 20:887-898, 2005

49. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JW, Wang SJ. A classification of chronic pain for ICD-11. *Pain.* 156:1003-1007, 2015

50. Tukker A, Visscher TL, Picavet HS. Overweight and health problems of the lower extremities: osteoarthritis, pain and disability. *Public Health Nutr.* 12:359-368, 2009

51. WHO: World Health Organization global database on body mass index (BMI): An interactive surveillance tool for monitoring nutrition transition2006.

52. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 33:160-172, 1990

53. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin M, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, Mccain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 33:160-172, 1990

54. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clinical trials (London, England).* 1:368-376, 2004

55. World Health O. Global database on body mass index (BMI): An interactive surveillance tool for monitoring nutrition transition. 2006

56. Yunus MB, Arslan S, Aldag JC. Relationship between body mass index and fibromyalgia features. *Scand. J. Rheumatol.* 31:27-31, 2002
57. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica.* 67:361-370, 1983
58. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67:361-370, 1983

Figure and tables legends

Figure 1: Flowchart of the inclusion process of participation in HUNT2 and HUNT3 studies

Tables

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Supplementary material/WEB appendix

Web table 1: Mean differences in number of pain sites in HUNT3 according to different risk factors reported in HUNT2, conditional on baseline number of pain sites (age and sex adjusted)

Web table 2: Ordered logit model, conditional on 0, 1–2, or 3 or more reported pain sites in HUNT2

Table 1: Sample characteristics[a] of HUNT2 (1995-1997) and HUNT3 (2006-2008) cohort

	HUNT2 n=65.237	HUNT3 n=50.807
Sex Female (%)	34,662 (53)	27,758 (55)
Males (%)	30,575 (47)	23,049 (45)
HADS score (%)		
No anxiety or depression	48.811 (80)	32.822 (81)
Depression, not anxiety	3.032 (5)	1.907 (5)
Anxiety, not depression	5.864 (10)	3.789 (9)
Anxiety and depression	3.639 (6)	2.000 (5)
Sleeping difficulties (%)		
No sleep problems	46.497 (86)	33.031 (82)
Sleep problems	7.883 (14)	7.383 (18)
Alcohol use (%)		
0 times/month	16.970 (28)	11.852 (24)
1-7 times/month	33.013 (54)	28.092 (57)
≥8 times/month	3.420 (6)	7.547 (15)
Abstainers	8.100 (8)	2.051 (4)
Body mass index (%)		
Underweight	458 (0.7)	312 (0.6)
Normal	25.308 (39)	16.169 (32)
Overweight	27.973 (43)	22.358 (44)
Obesity	10.722 (17)	11.575 (23)
Smoking status (%)		
Never smoker	27.761 (44)	21.053 (43)
Former smoker	17.489 (27)	11.116 (33)
Current smoker	18.535 (29)	12.209 (25)
Physical activity (%)		
Inactive	35.408 (61)	17.984 (45)
Active	22.851 (39)	21.606 (55)
Marital status (%)		
Not married	28.920 (41)	29.174 (44)
Married/cohabitant	41.203 (59)	36.900 (56)
Education (%)		
Primary school	22.687 (37)	N/A
High school	26.772 (43)	N/A
College/university	12.311 (20)	N/A
Chronic disease (%)		
No	44.717 (74)	32.368 (66)
Yes	15.851 (26)	16.760 (34)
Number of pain sites (%)		
0	33.997 (52)	19.105 (48)
1	6.470 (10)	4.445 (11)
2	6.931 (11)	4.667 (12)
3	5.328 (8)	3.887 (10)
4	4.092 (6)	2.955 (7)
5	2.746 (4)	1.865 (5)
6	1.840 (3)	1.201 (3)
7	1.354 (2)	808 (2)
8	971 (1.5)	514 (1.3)
9	1.244 (2)	680 (2)

Abbreviations: N/A = not available

[a]Given as number and percentage (%)

Because of rounding errors, percentages do not sum to 100

Table 2. Stability[a] in number of pain sites from HUNT2 (1995-1997) to HUNT3 (2006-2008)

Number of pain sites in HUNT2 (1995-1997)	Number of pain-sites (%) in HUNT3 (2006-2008)		
	0	1-2	≥3
0	9,686 (62)	3,526 (22)	2,479 (16)
1-2	2,392(39)	1,926 (32)	1,837 (30)
≥3	1,557(19)	1,546 (18)	5,313 (63)

[a]Given as number and percentage (%)

Because of rounding errors, percentages do not sum to 100

Table 3: Mean differences in number of pain sites in HUNT3 (2006-08) according to different risk factors reported in HUNT2 (1995-97), conditional on baseline number of pain sites

Risk factors	No pain		1-2 pain sites		3+ pain sites	
	Mean difference[a]	95% CI	Mean difference[a]	95% CI	Mean difference[a]	95% CI
HADS score						
No anxiety or depression, cut-off score <8	0.00	Reference	0.00	Reference	0.00	Reference
Depression, not anxiety, cut-off score ≥8	0.15	-0.01 to 0.31	0.22	-0.04 to 0.48	0.17	-0.09 to 0.43
Depression, dimensional variable	0.04	0.03 to 0.06	0.04	0.02 to 0.06	0.03	0.01 to 0.06
Anxiety, not depression, cut-off score ≥8	0.40	0.30 to 0.50	0.21	0.04 to 0.38	0.45	0.28 to 0.62
Anxiety, dimensional	0.06	0.05 to 0.07	0.05	0.04 to 0.07	0.05	0.03 to 0.07
Anxiety and depression ,cut-off score ≥8	0.54	0.38 to 0.70	0.33	0.09 to 0.56	0.44	0.24 to 0.64
HADS total score, dimensional variable	0.03	0.03 to 0.04	0.03	0.02 to 0.04	0.03	0.01 to 0.04
Sleeping difficulties						
No sleep problems	0.00	Reference	0.00	Reference	0.00	Reference
Sleep problems	0.38	0.27 to 0.49	0.34	0.18 to 0.50	0.56	0.41 to 0.71
Alcohol use						
0 times/month	0.00	Reference	0.00	Reference	0.00	Reference
1-7 times/month	-0.04	-0.11 to 0.02	-0.13	-0.26 to -0.01	-0.11	-0.25 to 0.03
≥8 times/month	-0-04	-0.16 to 0.08	-0.24	-0.46 to -0.02	-0.29	-0.56 to -0.01
Abstainers	-0.07	-0.18 to 0.04	-0.06	-0.26 to 0.15	0.07	-0.15 to 0.30
Body mass index						
Normal weight, 18.5 to 24.9 kg/m^2	0.00	Reference	0.00	Reference	0.00	Reference
Underweight, <18.5 kg/m^2	0.14	-0.20 to 0.47	0.42	-0.29 to 1.13	-0.10	-0.93 to 0.72
Overweight, 25 to 29.9 kg/m^2	0.14	0.08 to 0.20	0.12	0.02 to 0.23	0.12	-0.01 to 0.25
Obesity, ≥30 kg/m^2	0.30	0.21 to 0.38	0.18	0.02 to 0.34	0.44	0.28 to 0.61
Body mass index, dimensional variable	0.03	0.02 to 0.03	0.02	0.01 to 0.04	0.04	0.02 to 0.06
Smoking status						
Never smoker	0.00	Reference	0.00	Reference	0.00	Reference
Former smoker	0.20	0.13 to 0.26	0.21	0.09 to 0.33	0.19	0.05 to 0.33
Current smoker	0.26	0.20 to 0.33	0.32	0.19 to 0.45	0.13	-0.02 to 0.27
Physical activity						
Inactive	0.00	Reference	0.00	Reference	0.00	Reference
Active	-0.05	-0.12 to 0.02	-0.15	-0.25 to -0.05	-0.12	-0.24 to – 0.00
Education						
Primary school	0.00	Reference	0.00	Reference	0.00	Reference
High school	-0.05	-0.12 to 0.02	-0.01	-0.14 to 0.11	-0.10	-0.23 to 0.03
College/university	-0.30	-0.38 to -0.22	-0.41	-0.56 to -0.27	-0.61	-0.79 to -0.44

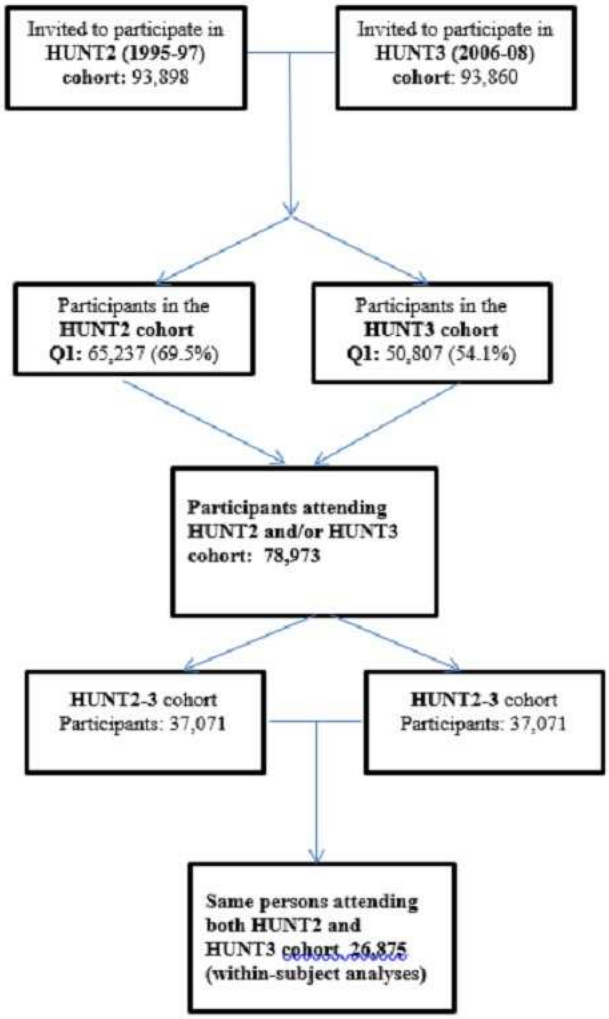
[a]Adjusted for age, sex, chronic disease, marital status, as well as education and physical activity in analyses where these variables are not the main variable of interest

Table 4. Mean change in number of pain sites in HUNT2 (1995-97) and HUNT3 (2006-08) according to change in different risk factors. Within individual fixed effect linear regression analyses.

Risk factors	Within-subjects N=26,875 individuals in 48,669 observations	
	Mean change[a]	95% CI
HADS score		
No anxiety or depression	Ref.	
Depression, not anxiety	0.17	0.06 to 0.28
Anxiety, not depression	0.23	0.15 to 0.32
Anxiety and depression	0.46	0.34 to 0.57
Sleeping difficulties		
No sleep problems	Ref.	
Sleep problems	0.31	0.25 to 0.38
Smoke status, never smoking	Ref.	
ex. smoker	0.11	-0.04 to 0.26
current daily smoker	0.11	-0.05 to 0.26
BMI normal 18.5-24.9 kg/m^2	Ref.	
underweight <18.5 kg/m^2	-0.09	-0.45 to 0 .27
overweight 25-29.9 kg/m^2	0.08	0.01 to 0.14
obese ≥30 kg/m^2	0.14	0.04 to 0.25
Alcohol-monthly use, 0 time a month	Ref.	
1-7 times a month	0.05	-0.02 to 0.11
8 times or more a month	-0.04	-0.14 to 0.06
abstainers	-0.03	-0.16 to 0.10
Physical activity		
inactive	Ref.	
active	0.03	-0.08 to 0.01
Pain-sites from HUNT2 to HUNT3	-0.07	-0.11 to -0.04

[a] Adjusted for physical activity and chronic disease were these variables are not the main variable of interest

Figure 1 Flow chart of the inclusion process in HUNT2 (1995-1997) and HUNT3 (2006-2008)



Q1: questionnaire 1