BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015312
Article Type:	Research
Date Submitted by the Author:	29-Nov-2016
Complete List of Authors:	Nordstoga, Anne Lovise; Norwegian University of Science and Technology, Department of Public Health and General Practice Nilsen, Tom; Norwegian University of Science and Technology, Department of Public Health and General Practice Vasseljen, Ottar; Norwegian University of Science and Technology, Department of PublicHealth and General Practice Unsgaard-Tøndel, Monica; Norwegian University of Science and Technology, Department of Health Science Mork, Paul Jarle; Norwegian University of Science and Technology, Department of Public Health and General Practice
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Spine < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY

The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: Longitudinal data from the Norwegian HUNT Study

Running head: Comorbidities and prognosis of chronic low back pain

AL Nordstoga[1], TIL Nilsen[1], O Vasseljen[1], M Unsgaard-Tøndel[1,2], PJ Mork[1]

[1]Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Health Science, Faculty of Health and Social Science, Norwegian University of Science and Technology, Trondheim, Norway

Corresponding author:

Anne Lovise Nordstoga, Department of Public Health and General Practice, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway.

E-mail: anne.l.nordstoga@ntnu.no, Phone number : +4799268260

Word count: 2979

ABSTRACT

Objectives: This study aimed to investigate the prospective influence of multisite pain, depression, anxiety, self-rated health, and pain-related disability on recovery from chronic low back pain (LBP).

Setting: The data is derived from the second (1995-98) and third (2006-08) wave of the Nord-Trøndelag Health Study (HUNT) in Norway.

Participants: The study population comprises 4,484 women and 3,039 men in the Norwegian HUNT Study who reported chronic LBP at baseline in 1995-97.

Primary outcome measures: The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons indicating no pain and/or stiffness during the last year, for at least three consecutive months, were defined as recovered. A Poisson regression model was used to estimate adjusted risk ratios (RRs) with 95% confidence intervals (CIs).

Results: At follow-up, 1,822 (40.6%) women and 1,578 (51.9%) men reported recovery from chronic LBP. Recovery was inversely and dose-dependently associated with multisite pain in both women and men (P-trend<0.001). Compared to the reference category of 2-3 pain sites, RRs for recovery were 1.10 (95% CI, 0.98-1.22) in women and 1.10 (95% CI, 1.01-1.21) in men reporting one pain site and 0.58 (95% CI, 0.52-0.63) in women and 0.70 (95% CI, 0.63-0.79) in men reporting 6-9 pain sites. Poor/not so good self-rated general health was associated with reduced probability of recovery in both women (RR, 0.66 [95% CI, 0.61-0.71]) and men (RR, 0.72 [95% CI, 0.67-0.78]). Psychological symptoms and pain-related disability were more weakly associated with recovery. There was no statistical interaction between multisite pain and the other comorbidities (P≥0.24).

Conclusions: Number of chronic pain sites is inversely and dose-dependently associated with recovery from chronic LBP. Poor self-rated health reduces the probability of recovery,

whereas psychological symptoms and disability have weaker influence on prognosis of chronic LBP.

Strengths and limitations of this study

- The strengths of the current study are the large and unselected population of women and men with chronic LBP, the prospective design, and the possibility of adjusting for several potential confounding factors.
- A limitation is the lack of follow-up information about the course of LBP and the other variables between the HUNT2 and HUNT3 study.
- Furthermore, we cannot rule out that changes in lifestyle was differential between participants who experienced remission of symptoms versus those who did not, e.g., individuals with a high number of pain sites at baseline could be less prone to adopt a healthy lifestyle during the follow-up period because of pain-related disability.

INTRODUCTION

Low back pain (LBP) is a common cause of disability and is ranked as the most burdensome disease globally [1, 2]. LBP is the fourth most common diagnosis (after upper respiratory infection, hypertension, and coughing) seen in primary care [3] and approximately every fifth adult suffer from chronic LBP [4]. Thus, in addition to the suffering experienced by affected individuals, LBP represents a substantial economic burden to the society. This underscore the importance of increased knowledge about factors that can improve the prevention and management of chronic LBP.

Chronic LBP rarely exist as a separate entity and co-occurrence of multisite pain and other co-morbidities are common [5-9]. A large case-control study comprising more than 100,000 people showed that individuals with chronic low back had higher occurrence of other musculoskeletal conditions, depression, anxiety, and sleep disorders compared to controls without chronic LBP [10]. In particular, other chronic pain conditions are very prevalent among people with chronic LBP [5]. Number of pain sites by itself has been suggested to be dose-dependently related to reduced physical and mental function [11, 12] and there is also data to support the notion that generalized pain differs markedly from conditions with only one or a few pain sites with respect to other risk factors [13]. Currently, there is a lack of longitudinal studies addressing how the extent of multisite pain influences the prognosis of chronic LBP. Moreover, it is unclear to what extent multisite pain interacts with other comorbid factors such as poor self-rated general health, pain-related disability and poor mental health to influence the prognosis of chronic LBP.

The main objective of this study was therefore to prospectively investigate the influence of common somatic and psychological comorbidities on prognosis of chronic LBP. We hypothesized 1) that multi-site chronic pain, poor self-rated general health, pain-related disability, and poor psychological health are factors that are inversely and independently

related to the probability of relief from chronic LBP, and 2) that the possible association between number of pain sites and prognosis of LBP is modified by other somatic and psychological comorbidities.

METHOD

Study population

In Nord-Trøndelag County, Norway, all inhabitants aged 20 years or older were invited to participate in three health surveys (the Nord-Trøndelag Health Study [the HUNT Study]), the first in 1984-86 (HUNT1), the second in 1995-97 (HUNT2), and last in 2006-08 (HUNT3). The current study is based on data from HUNT2 and HUNT3. Of 93,898 eligible participants, 65,237 (65.5%) accepted the invitation to participate in HUNT2. In HUNT3, a total of 93,860 were invited, and 50,807 (54.1%) accepted the invitation. More detailed information about selection procedures, participation, and questionnaires used in the HUNT Study can be found at http://www.ntnu.edu/hunt.

Information on lifestyle and health related factors were collected by questionnaires and a clinical examination at both HUNT2 and HUNT3. For the purpose of this study, we included data from the 37,070 people who participated at both surveys. We excluded 15,062 women and 12,861 men who reported to be free from chronic LBP at HUNT2. Moreover, we excluded 1,557 persons with missing information on musculoskeletal pain at HUNT3 and 23 persons without complete values on body mass index (BMI) from the clinical examination. Further, 44 persons defined as underweight (BMI <18.5 kg/m^2) were additionally excluded from the analyses. Thus, the prospective analyses were based on 4,484 women and 3,039 men. Each participant signed a written consent, and the study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/2044 REK midt, Norway).

Chronic low back pain

The questions about musculoskeletal pain were adopted from the Standard Nordic Questionnaire [14]. The participants were asked “During the last year, have you had pain and/or stiffness in your muscles and joint that lasted for at least three consecutive months?”. Response options were “yes” and “no”. If answering “yes”, the participants were asked to indicate the affected body area(s), i.e., up to nine body areas (neck, shoulders/upper arms, upper back, elbows, low back, wrists/hands, hips, knees, and ankles/feet). Chronic LBP was in both surveys defined by “yes” to the first question and low back indicated as an affected body area by the second questions. Persons who responded “yes” to the first questions but did not indicate low back as an affected body area were considered to be free from chronic LBP. Number of chronic pain sites were estimated by adding together pain-afflicted body areas. The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons categorized with chronic LBP at HUNT2 responding "no" at HUNT3 to the question “During the last year, have you had pain and/or stiffness in your muscles and joint that lasted for at least three consecutive months?” were defined as recovered.

Other variables

The participants’ self-rated general health was evaluated using the question “How is your health at the moment?”, with response options “very good”, “good”, “not so good”, and “poor”. The answers were dichotomized into two groups: “very good/good” and “not so good/poor” in line with previous studies [15].

Pain-related disability was evaluated separately for work ability and leisure time activity. The question about work ability was: “Have the pain and/or stiffness reduced your ability to work during the last year?” with four possible responses: “no, not significantly”, “to some degree”, “significantly”, and “don’t know”. The first and last response options were

merged and categorized as "no disability", and the two middle categories as "work disability". For leisure time activity, the question was: “Have the pain/or stiffness reduced your leisure activity?” with possible responses: “yes” and “no”. The responses on disability due to musculoskeletal symptoms were then categorized into four groups; “no disability”, “work disability”, “leisure disability”, and “work and leisure disability”.

Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). HADS is a validated and well-established self-rating questionnaire including seven questions on anxiety and seven questions on depression [16]. As recommended, the cut-off score value was set to ≥8 on both anxiety and depression and were dichotomized as presence or no presence of anxiety and/or depression [16, 17]. Additionally, a mixed HADS variable were constructed consisting of four groups: “no depression or anxiety”, “only depression”, “only anxiety”, and “both depression and anxiety” [18]. Symptoms of only depression or only anxiety was defined by a HADS score ≥8 on the respective subscales, while symptoms of both depression and anxiety was defined by a HADS score ≥8 on both subscales.

Statistical analysis

We used a generalized linear model of the Poisson family to estimate the risk ratio (RR) with 95% confidence interval (CI) for recovery from chronic LBP. All estimated associations were adjusted for age (20-29, 30-39,…≥60 years), BMI (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, unknown), education (primary school, high school, college ≤4 years, college >4 years, unknown), smoking (never smoker, previous smoker, current smoker, unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, unknown). All main analyses were conducted separately for men and women.

Additionally, we conducted analyses combining number of pain sites (<4 vs. 4-9 sites) and comorbid conditions in relation to the probability of recovery from chronic LBP. Statistical interaction was evaluated by likelihood ratio tests of a product term of number of pain sites and each of the comorbid factors (self-reported health, pain-related disability and HADS). All statistical analyses were performed using Stata for Windows, version 13.1 (StataCorp LP, College Station, Texas).

RESULTS

Table 1 presents the baseline characteristics of the study population according to number of chronic pain sites. At baseline, 66.4% of the women and 47.2% of the men reported ≥4 pain sites. Of the 4,484 women and 3,039 men who reported chronic LBP at baseline (HUNT2), 1,822 (40.6%) women and 1,578 (51.9%) men were reported recovered from chronic LBP at the 11-year follow-up (HUNT3).

Table 2 shows the association between number of pain sites, pain-related disability, psychological symptoms, self-rated general health, and RRs for recovery from chronic LBP at follow-up. The probability of recovery was inversely and dose-dependently associated with number of pain sites (P-trend<0.001 in both women and men). In specific, women and men who reported 6-9 pain sites had RRs of 0.58 (95% CI, 0.52-0.63) and 0.70 (95% CI, 0.63-0.79), respectively, compared to women and men who reported 2-3 pain sites. Work or leisure disability alone was weakly associated with prognosis of chronic LBP while pain-related disability that influenced both work ability and leisure activity was associated with reduced probability of recovery in both women (RR, 0.68 [95% CI, 0.62-0.74]) and men (RR, 0.76 [95% CI, 0.70-0.83]). Symptoms of depression or anxiety alone was weakly associated with prognosis of LBP; however, a HADS score ≥8 on both subscales was associated with reduced probability of recovery in both women (RR, 0.77 [95% CI, 0.66-0.91]) and men (RR,

Table 1. Baseline characteristics of the study population stratified by gender and number of chronic pain sites.

	Women		Men	
	<4 pain sites	4-9 pain sites	<4 pain sites	4-9 pain sites
No. of persons (%)	1,506 (33.6)	2,978 (66.4)	1,605 (52.8)	1,434 (47.2)
Age (years), mean (SD)	47.9 (13.6)	50.7 (11.9)	48.4 (12.1)	51.8 (11.4)
Body mass index (kg/m^2), mean (SD)	26.1 (4.1)	27.0 (4.5)	26.5 (3.3)	27.0 (3.4)
Physically inactive, no. (%)	82 (5.4)	208 (7.0)	96 (6.0)	103 (7.2)
Education ≤13 years, no. (%)	1142 (75.8)	2470 (82.9)	1244 (77.5)	1220 (85.1)
Current smoker, no. (%)	427 (28.4)	1021 (34.3)	416 (25.9)	412 (28.7)
Poor/not so good self-rated health, no. (%)	443 (29.4)	1786 (60.0)	461 (28.7)	831 (57.9)
Pain-related disability, work and leisure, no. (%)	726 (48.2)	2034 (68.3)	784 (48.8)	970 (67.6)
HADS score depression >8, no. (%)	65 (4.3)	187 (6.3)	96 (6.0)	124 (8.6)
HADS score anxiety >8, no. (%)	149 (9.9)	425 (14.3)	110 (6.9)	147 (10.3)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation

Table 2. Risk ratio with 95% confidence interval for recovery from chronic low back pain at 11-years follow-up according to number of chronic pain sites, pain-related disability, the Hospital Anxiety and Depression Scale score, and self-rated general health.

	Women				Men			
	No. of persons	No. of cases	Age-adjusted[a] RR	Multi-adjusted[b] RR (95% CI)	No. of persons	No. of cases	Age-adjusted[a] RR	Multi-adjusted[b] RR (95% CI)
No. of pain sites								
1	326	189	1.12	1.10 (0.98-1.22)	454	284	1.12	1.10 (1.01-1.21)
2-3	1,180	608	1.00	1.00 (reference)	1,151	651	1.00	1.00 (reference)
4-5	1,330	557	0.81	0.83 (0.76-0.90)	873	422	0.85	0.86 (0.79-0.94)
6-9	1,648	468	0.55	0.58 (0.52-0.63)	561	221	0.69	0.70 (0.63-0.79)
Pain-related disability								
No disability	649	355	1.00	1.00 (reference)	487	304	1.00	1.00 (reference)
Work disability	591	271	0.84	0.87 (0.78-0.98)	430	249	0.92	0.94 (0.85-1.05)
Leisure disability	257	131	0.93	0.94 (0.82-1.08)	250	143	0.91	0.90 (0.79-1.02)
Work and leisure disability	2,760	964	0.64	0.68 (0.62-0.74)	1,754	818	0.73	0.76 (0.70-0.83)
HADS								
No depression or anxiety	2,572	1,103	1.00	1.00 (reference)	2,050	1,110	1.00	1.00 (reference)
Depression	252	90	0.86	0.90 (0.76-1.07)	220	101	0.84	0.85 (0.73-0.99)
Anxiety	574	215	0.87	0.88 (0.78-0.98)	257	120	0.87	0.88 (0.77-1.01)
Depression and anxiety	342	107	0.74	0.77 (0.66-0.91)	195	80	0.76	0.79 (0.67-0.94)
Self-rated general health								
Very good/good	2,208	1,099	1.00	1.00 (reference)	1,730	1,017	1.00	1.00 (reference)
Poor/not so good	2,229	704	0.64	0.66 (0.61-0.71)	1,292	551	0.70	0.72 (0.67-0.78)

Abbreviations: confidence interval, CI; Hospital Anxiety and Depression Scale, HADS; risk ratio, RR

[a]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60).

[b]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education > 4 years, and unknown), body mass index (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, and unknown), smoking (never smoker, previous smoker, current smoker, and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, and unknown).

Table 3. Risk ratio with 95% confidence interval for recovery from chronic low back pain at 11-years follow-up according to the combined effect of number of chronic pain sites and pain-related disability, score on the hospital anxiety and depression scale, and self-rated general health.

	1-3 pain sites			4-9 pain sites			
	No. of persons	No. of cases	Multi-adjusted[a] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[a] RR (95% CI)	P value[b]
Pain-related disability							
No disability	714	448	1.00 (reference)	422	211	0.84 (0.75-0.94)	0.002
Work disability	466	270	0.94 (0.85-1.03)	555	256	0.77 (0.69-0.86)	0.002
Leisure disability	271	172	0.98 (0.88-1.09)	236	102	0.71 (0.61-0.83)	<0.001
Work and leisure disability	1,510	756	0.81 (0.75-0.87)	3,004	1,026	0.59 (0.54-0.64)	<0.001
HADS							
No depression or anxiety	2,151	1,225	1.00 (reference)	2,471	988	0.75 (0.70-0.80)	<0.001
Depression	161	84	0.92 (0.79-1.07)	311	107	0.66 (0.56-0.77)	0.002
Anxiety	259	142	1.00 (0.89-1.12)	572	193	0.65 (0.58-0.73)	<0.001
Depression and anxiety	138	69	0.92 (0.77-1.09)	399	118	0.58 (0.49-0.68)	<0.001
Self-rated general health							
Very good/good	2,187	1,302	1.00 (reference)	2,617	838	0.57 (0.53-0.61)	<0.001
Not all good/poor	904	417	0.78 (0.72-0.85)	1,751	814	0.82 (0.77-0.87)	0.301

Abbreviations: confidence interval, CI; hospital anxiety and depression scale, HADS; risk ratio, RR.

[a]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education > 4 years, and unknown), body mass index (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, and unknown), gender, smoking (never smoker, previous smoker, current smoker, and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work and unknown).

[b]P-value from stratified analysis of number of pain sites by general health, physical function, and HADS score.

0.79 [95% CI, 0.67-0.94]). Persons reporting poor or not so good general health had a markedly reduced probability of recovery, both in women (RR, 0.66 [95% CI, 0.61-0.71]) and men (RR, 0.72 [95% CI, 0.67-0.78]), compared to those reporting good or very good general health.

Table 3 presents the combined effect of number of pain sites and pain-related disability, psychological symptoms, and self-rated general health. We did not observe any statistical interaction between number of pain sites and pain-related disability, psychological symptoms or self-rated health (P≥0.24 for all tests). However, stratified analysis within categories of the exposure variables showed that reporting of ≥4 pain sites was associated with lower probability of recovery independently of level of pain-related disability, and psychological symptoms. Within strata of pain-related disability, persons who reported ≥4 pain sites had 16% to 27% lower probability of remission compared to persons with 1-3 pain sites in the same pain-related disability categories. Likewise, within the different strata of psychological symptoms, persons with ≥4 pain sites had 25% to 35% lower probability of recovery compared to persons with 1-3 pain sites.

DISCUSSION

In this large population-based study we found that musculoskeletal comorbidity, reduced self-rated general health, and psychological symptoms were independently associated with reduced probability of recovery from chronic LBP at 11-year follow-up. The strongest predictors for poor prognosis were widespread chronic pain (6-9 pain sites) and poor or not so good self-rated general health. The strength of the associations between the various comorbidities and pain prognosis was fairly similar for women and men. Probability of relief from chronic LBP was inversely and dose-dependently associated with number of chronic pain sites. Although there was no interaction between number of chronic pain sites and other

comorbidities, we observed in the combined analysis that persons with four or more pain sites had consistently lower probability of recovery from chronic LBP within all strata of pain-related disability and symptoms of depression and/or anxiety. The current findings indicate that musculoskeletal comorbidity has a strong and independent influence on long-term prognosis of chronic LBP.

It is noteworthy that about 66% of the women and 47% of the men in this study reported four or more chronic pain sites at baseline. This supports the view that co-occurrence of musculoskeletal pain is very common in chronic LBP [5, 6]. To our knowledge, this is the first population-based study to investigate the prospective influence of graded musculoskeletal comorbidity on the prognosis of chronic LBP. The dose-dependent association between number of chronic pain sites and reduced probability of recovery from chronic LBP suggest that musculoskeletal comorbidity should be considered an important predictor in identifying target groups for public health secondary prevention. This was also supported by our combined analysis, showing that number of pain sites was the main driving factor for predicting persistence of chronic LBP.

More than 40% of the women and 50% of the men in the current study reported recovery from chronic LBP at 11-year follow-up. Interestingly, a previous study showed that the prevalence of chronic LBP was relatively stable from HUNT2 to HUNT3 with about 26% of women and 20% of men reporting chronic LBP at both surveys [19]. Thus, our results indicate that during an 11-year period a substantial proportion of the population shift from having chronic low back to remission, but that a substantial proportion also develops pain in the same period. Similar large fluctuations in reporting of chronic LBP at the individual level have also been observed by others [20, 21]. Thus, our findings lend further support to the notion that chronic LBP on the individual level may fluctuate substantially over time while the population prevalence remains relatively stable. The current study adds to this knowledge

by showing that individuals who shift from having chronic low back symptoms to remission of symptoms are more likely to have fewer chronic pain sites, less pain-related disability, better self-rated health, and no major symptoms of anxiety or depression.

Number of chronic pain sites were dose-dependently associated with probability of recovery with women and men who reported 6 or more pain sites having about 30-40% lower probability of recovery from chronic LBP compared to women and men with 2-3 pain sites. Number of pain sites have in previous cross-sectional studies been shown to be dose-dependently associated with a range of negative health outcomes such as psychological distress, poor sleep, poor self-rated health, reduced social and functional ability [11] as well as increased sickness absence and health care utilization [22]. The current prospective study extends this body of knowledge showing that number of chronic pain sites have a strong dose-dependent influence on prognosis of chronic LBP. Although we observed no interaction between number of chronic pain sites and other comorbid factors, the probability of relief from chronic LBP was consistently lower for the group with multisite pain within all strata of pain-related disability and psychological symptoms scores. These findings support the long-held view that it may be useful to classify patients with chronic LBP into "back pain alone" or "back pain plus other pain" to improve clinical decision-making [23].

Stratified care of patients with LBP have shown promising results [24, 25]. These studies used the Keele STarT Back Screening Tool, which was developed to identify patients with low, medium and high risk of persistent and disabling LBP [26, 27]. The current finding of a dose-dependent association between number of chronic pain sites and prognosis of chronic LBP may indicate that the extent of musculoskeletal comorbidity could provide additional complementary information to improve classification in stratified care approaches. The idea that assessment of multisite pain can assist clinical judgment of prognosis and improve targeted treatment has been proposed before [6] and the current data lend further

support to this idea. Furthermore, since number of chronic pain sites *per se* seem to be a strong prognostic factor in chronic LBP it may also be useful to consider this variable when recruiting subjects into research studies to facilitate baseline comparisons.

Although previous data indicate that psychological symptoms are more common in patients with LBP than in comparable controls [10], our results do not indicate that such symptoms strongly influence the prognosis of chronic LBP. However, another study of subjects with neck and/or LBP in HUNT 3 showed that symptoms of mental distress were significant determinants for seeking health care, which could have moderated the associations [28]. Our findings are in line with Dunn and colleagues [29] who found no significant association between depression, and only a modest association between anxiety, and the risk of disabling LBP at 12-months follow-up in patients presenting with LBP in general practice. In the same study it was observed that self-rated health had a relatively strong impact on prognosis of LBP with patients who rated their health as poor having more than twofold increased risk of disabling back pain. Very few individuals in our study population rated their health as poor and we were therefore not able to estimate probability for recovery among these individuals. However, we observed that women and men who rated their health as less than good (i.e., poor or not so good) had about 30% lower probability of recovery from chronic LBP compared to those who rated their health as good or very good.

The strengths of the current study are the large and unselected population of women and men with chronic LBP, the prospective design, and the possibility of adjusting for several potential confounding factors. The questions on chronic musculoskeletal pain used in HUNT2 have acceptable reliability and validity [14, 30, 31]. Likewise, the HADS scale has been shown to be at a valid indicator of possible depression and anxiety in clinical practice as well as in the general population [16, 17, 32]. A limitation is the lack of follow-up information about the course of LBP and the other variables between the HUNT2 and

HUNT3 study. Thus, any changes occurring during the follow-up period could not be taken into account in the analyses. For example, a healthy lifestyle has been associated with improved long-term outcome in individuals with recurrent LBP episodes [33]. Thus, it may be possible that individuals who changed their lifestyle during the follow-up period also altered their course of chronic LBP. Furthermore, we cannot rule out that such changes in lifestyle was differential between participants who experienced remission of symptoms versus those who did not, e.g., individuals with a high number of pain sites at baseline could be less prone to adopt a healthy lifestyle during the follow-up period because of pain-related disability.

In conclusion, the current study indicates that multisite chronic pain is independently associated with long-term prognosis of chronic LBP. The association is dose-dependent with increasing number of chronic pain sites being associated with a reduced probability for recovery from chronic LBP. There was no interaction between number of chronic pain sites and other common comorbidities such as pain-related disability, psychological symptoms and self-rated general health. These findings underscore the importance of taking comorbid symptoms into account, and in particular number of chronic pain sites, when designing management programs or treatment for secondary prevention of chronic LBP.

Author Contributions

PJM, TILN and ALN designed the study, and all authors contributed in the discussion of the design and interpretation. ALN performed the analyses supervised by PJM and TILN. The first draft of the manuscript was written by PJM and ALN. All authors contributed to the final manuscript.

Conflicts of interest

None declared.

Data sharing

No additional data available.

Funding sources

This study was supported by The Norwegian Fund for Post-Graduate Training in Physiotherapy and by grants from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU).

Ethical approval

The current study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/2044 REK midt, Norway). The study was carried out according to the Declaration of Helsinki.

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Table 1. Baseline characteristics of the study population stratified by gender and number of chronic pain sites.

	Women		Men	
	<4 pain sites	4-9 pain sites	<4 pain sites	4-9 pain sites
No. of persons (%)	1,506 (33.6)	2,978 (66.4)	1,605 (52.8)	1,434 (47.2)
Age (years), mean (SD)	47.9 (13.6)	50.7 (11.9)	48.4 (12.1)	51.8 (11.4)
Body mass index (kg/m^2), mean (SD)	26.1 (4.1)	27.0 (4.5)	26.5 (3.3)	27.0 (3.4)
Physically inactive, no. (%)	82 (5.4)	208 (7.0)	96 (6.0)	103 (7.2)
Education ≤13 years, no. (%)	1142 (75.8)	2470 (82.9)	1244 (77.5)	1220 (85.1)
Current smoker, no. (%)	427 (28.4)	1021 (34.3)	416 (25.9)	412 (28.7)
Poor/not so good self-rated health, no. (%)	443 (29.4)	1786 (60.0)	461 (28.7)	831 (57.9)
Pain-related disability, work and leisure, no. (%)	726 (48.2)	2034 (68.3)	784 (48.8)	970 (67.6)
HADS score depression >8, no. (%)	65 (4.3)	187 (6.3)	96 (6.0)	124 (8.6)
HADS score anxiety >8, no. (%)	149 (9.9)	425 (14.3)	110 (6.9)	147 (10.3)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation

Table 2. Risk ratio with 95% confidence interval for recovery from chronic low back pain at 11-years follow-up according to number of chronic pain sites, pain-related disability, the Hospital Anxiety and Depression Scale score, and self-rated general health.

	Women				Men			
	No. of persons	No. of cases	Age-adjusted[a] RR	Multi-adjusted[b] RR (95% CI)	No. of persons	No. of cases	Age-adjusted[a] RR	Multi-adjusted[b] RR (95% CI)
No. of pain sites								
1	326	189	1.12	1.10 (0.98-1.22)	454	284	1.12	1.10 (1.01-1.21)
2-3	1,180	608	1.00	1.00 (reference)	1,151	651	1.00	1.00 (reference)
4-5	1,330	557	0.81	0.83 (0.76-0.90)	873	422	0.85	0.86 (0.79-0.94)
6-9	1,648	468	0.55	0.58 (0.52-0.63)	561	221	0.69	0.70 (0.63-0.79)
Pain-related disability								
No disability	649	355	1.00	1.00 (reference)	487	304	1.00	1.00 (reference)
Work disability	591	271	0.84	0.87 (0.78-0.98)	430	249	0.92	0.94 (0.85-1.05)
Leisure disability	257	131	0.93	0.94 (0.82-1.08)	250	143	0.91	0.90 (0.79-1.02)
Work and leisure disability	2,760	964	0.64	0.68 (0.62-0.74)	1,754	818	0.73	0.76 (0.70-0.83)
HADS								
No depression or anxiety	2,572	1,103	1.00	1.00 (reference)	2,050	1,110	1.00	1.00 (reference)
Depression	252	90	0.86	0.90 (0.76-1.07)	220	101	0.84	0.85 (0.73-0.99)
Anxiety	574	215	0.87	0.88 (0.78-0.98)	257	120	0.87	0.88 (0.77-1.01)
Depression and anxiety	342	107	0.74	0.77 (0.66-0.91)	195	80	0.76	0.79 (0.67-0.94)
Self-rated general health								
Very good/good	2,208	1,099	1.00	1.00 (reference)	1,730	1,017	1.00	1.00 (reference)
Poor/not so good	2,229	704	0.64	0.66 (0.61-0.71)	1,292	551	0.70	0.72 (0.67-0.78)

Abbreviations: confidence interval, CI; Hospital Anxiety and Depression Scale, HADS; risk ratio, RR

[a]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60).

[b]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education > 4 years, and unknown), body mass index (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, and unknown), smoking (never smoker, previous smoker, current smoker, and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, and unknown).

Table 3. Risk ratio with 95% confidence interval for recovery from chronic low back pain at 11-years follow-up according to the combined effect of number of chronic pain sites and pain-related disability, score on the hospital anxiety and depression scale, and self-rated general health.

	1-3 pain sites			4-9 pain sites			
	No. of persons	No. of cases	Multi-adjusted[a] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[a] RR (95% CI)	P value[b]
Pain-related disability							
No disability	714	448	1.00 (reference)	422	211	0.84 (0.75-0.94)	0.002
Work disability	466	270	0.94 (0.85-1.03)	555	256	0.77 (0.69-0.86)	0.002
Leisure disability	271	172	0.98 (0.88-1.09)	236	102	0.71 (0.61-0.83)	<0.001
Work and leisure disability	1,510	756	0.81 (0.75-0.87)	3,004	1,026	0.59 (0.54-0.64)	<0.001
HADS							
No depression or anxiety	2,151	1,225	1.00 (reference)	2,471	988	0.75 (0.70-0.80)	<0.001
Depression	161	84	0.92 (0.79-1.07)	311	107	0.66 (0.56-0.77)	0.002
Anxiety	259	142	1.00 (0.89-1.12)	572	193	0.65 (0.58-0.73)	<0.001
Depression and anxiety	138	69	0.92 (0.77-1.09)	399	118	0.58 (0.49-0.68)	<0.001
Self-rated general health							
Very good/good	2,187	1,302	1.00 (reference)	2,617	838	0.57 (0.53-0.61)	<0.001
Not all good/poor	904	417	0.78 (0.72-0.85)	1,751	814	0.82 (0.77-0.87)	0.301

Abbreviations: confidence interval, CI; hospital anxiety and depression scale, HADS; risk ratio, RR.

[a]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education > 4 years, and unknown), body mass index (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, and unknown), gender, smoking (never smoker, previous smoker, current smoker, and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work and unknown).

[b]P value from stratified analysis of number of pain sites by general health, physical function, and HADS score.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**4**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4/5
Methods			**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
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6/7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6/7*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6/7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7/8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			8

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8/9
		(b) Indicate number of participants with missing data for each variable of interest	10/11
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	10/11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 and 12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			12
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13/16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: Longitudinal data from the Norwegian HUNT Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015312.R1
Article Type:	Research
Date Submitted by the Author:	21-Mar-2017
Complete List of Authors:	Nordstoga, Anne Lovise; Norwegian University of Science and Technology, Department of Public Health and Nursing Nilsen, Tom; Norwegian University of Science and Technology, Department of Public Health and Nursing Vasseljen, Ottar; Norwegian University of Science and Technology, Department of PublicHealth and Nursing Unsgaard-Tøndel, Monica; Norwegian University of Science and Technology, Department of Neuromedicine and Movement Science Mork, Paul Jarle; Norwegian University of Science and Technology, Department of Public Health and Nursing
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health
Keywords:	Spine < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY

The influence of multisite pain and psychological comorbidity on prognosis of chronic low back pain: Longitudinal data from the Norwegian HUNT Study

Running head: Comorbidities and prognosis of chronic low back pain

AL Nordstoga[1], TIL Nilsen[1], O Vasseljen[1], M Unsgaard-Tøndel[1,2], PJ Mork[1]

[1]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

Corresponding author:

Anne Lovise Nordstoga, Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway.

E-mail: anne.l.nordstoga@ntnu.no, Phone number : +4799268260

Word count: 3308

ABSTRACT

Objectives: This study aimed to investigate the prospective influence of multisite pain, depression, anxiety, self-rated health, and pain-related disability on recovery from chronic low back pain (LBP).

Setting: The data is derived from the second (1995-98) and third (2006-08) wave of the Nord-Trøndelag Health Study (HUNT) in Norway.

Participants: The study population comprises 4,484 women and 3,039 men in the Norwegian HUNT Study who reported chronic LBP at baseline in 1995-97.

Primary outcome measures: The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons not reporting pain and/or stiffness for at least three consecutive months during the last year, were defined as recovered. A Poisson regression model was used to estimate adjusted risk ratios (RRs) with 95% confidence intervals (CIs).

Results: At follow-up, 1,822 (40.6%) women and 1,578 (51.9%) men reported recovery from chronic LBP. The probability of recovery was inversely associated with number of pain sites in (P-trend<0.001). Compared to reporting 2-3 pain sites, persons with only LBP had a slightly higher probability of recovery (RR1.10, 95% CI 0.98 to 1.22 in women and RR 1.10, 95% CI, 1.01 to 1.21 in men) whereas people 6-9 pain sites had substantially lower probability of recovery (RR 0.58, 95% CI, 0.52 to 0.63 in women and RR 0.70, 95% CI, 0.63 to 0.79 in men). Poor/not so good self-rated general health, symptoms of anxiety and depression, and pain related disability in work and leisure were all associated with reduced probability of recovery, but there was no statistical interaction between multisite pain and these comorbidities.

Conclusions: Increasing number of pain sites was inversely associated with recovery from chronic LBP. Additionally, factors such as poor self-rated health, psychological symptoms, and pain related disability may further reduce the probability of recovery from chronic LBP.

Strengths and limitations of this study

- The strengths of the current study are the large and unselected population of women and men with chronic LBP, the prospective design, and the possibility of adjusting for several potential confounding factors.
- A limitation is the lack of information about the course of LBP and the other variables between the HUNT2 and HUNT3 study.
- Furthermore, we cannot rule out that changes in lifestyle differed between those who experienced remission of symptoms and those who did not, e.g., individuals with a high number of pain sites at baseline could be less prone to adopt a healthy lifestyle during the follow-up period because of pain-related disability.

INTRODUCTION

Low back pain (LBP) is a common cause of disability and is ranked as the most burdensome disease globally [1, 2]. LBP is the fourth most common diagnosis (after upper respiratory infection, hypertension, and coughing) seen in primary care [3] and approximately every fifth adult suffer from chronic LBP [4]. Thus, in addition to the suffering experienced by affected individuals, LBP represents a substantial economic burden to the society. This underscore the importance of increased knowledge about factors that can improve the prevention and management of chronic LBP.

Chronic LBP rarely exist as a separate entity and co-occurrence of multisite pain and other co-morbidities are common [5-9]. A large case-control study comprising more than 100,000 people showed that individuals with chronic low back had higher occurrence of other musculoskeletal conditions, depression, anxiety, and sleep disorders compared to controls without chronic LBP [10]. In particular, other chronic pain conditions are very prevalent among people with chronic LBP [5]. Number of pain sites by itself has been suggested to be dose-dependently related to reduced physical and mental function [11, 12] and there is data to support the notion that generalized pain differs markedly from conditions with only one or a few pain sites with respect to other risk factors [13]. Currently, there is a lack of longitudinal studies addressing how the extent of multisite pain influences the prognosis of chronic LBP. Moreover, it is unclear to what extent multisite pain interacts with other comorbid factors such as poor self-rated general health, pain-related disability and poor mental health to influence the prognosis of chronic LBP.

The main objective of this study was therefore to prospectively investigate the influence of common somatic and psychological comorbidities on prognosis of chronic LBP. We hypothesized 1) that multi-site chronic pain, poor self-rated general health, pain-related disability, and poor psychological health are factors that are inversely and independently

related to the probability of recovery from chronic LBP, and 2) that the possible association between number of pain sites and prognosis of LBP is modified by other somatic and psychological comorbidities.

METHOD

Study population

In Nord-Trøndelag County, Norway, all inhabitants aged 20 years or older were invited to participate in three health surveys (the Nord-Trøndelag Health Study [the HUNT Study]), the first in 1984-86 (HUNT1), the second in 1995-97 (HUNT2), and last in 2006-08 (HUNT3). The current study is based on data from HUNT2 and HUNT3. Of 93,898 eligible participants, 65,237 (65.5%) accepted the invitation to participate in HUNT2. In HUNT3, a total of 93,860 were invited, and 50,807 (54.1%) accepted the invitation. More detailed information about selection procedures, participation, and questionnaires used in the HUNT Study can be found at http://www.ntnu.edu/hunt.

Information on lifestyle and health related factors were collected by questionnaires and a clinical examination at both HUNT2 and HUNT3. For the purpose of this study, we included data from the 37,070 people who participated at both surveys. We excluded 15,062 women and 12,861 men who reported to be free from chronic LBP at HUNT2. Moreover, we excluded 1,557 persons with missing information on musculoskeletal pain at HUNT3 and 23 persons without complete values on body mass index (BMI) from the clinical examination. Further, 44 persons defined as underweight (BMI <18.5 kg/m^2) were additionally excluded from the analyses to reduce the possibility for reverse causation due to undetected disease. Thus, the prospective analyses were based on 4,484 women and 3,039 men. Each participant signed a written consent, and the study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/2044 REK midt, Norway).

Chronic low back pain

The questions about musculoskeletal pain were adopted from the Standard Nordic Questionnaire [14]. The participants were asked "During the last year, have you had pain and/or stiffness in your muscles and joint that lasted for at least three consecutive months?". Response options were "yes" and "no". If answering "yes", the participants were asked to indicate the affected body area(s), i.e., up to nine body areas (neck, shoulders/upper arms, upper back, elbows, low back, wrists/hands, hips, knees, and ankles/feet). Chronic LBP was in both surveys defined by "yes" to the first question and low back indicated as an affected body area by the second questions. Persons who responded "yes" to the first questions but did not indicate low back as an affected body area were considered to be free from chronic LBP. Number of chronic pain sites were estimated by adding together pain-afflicted body areas, of which the total number of pain sites includes low back pain. The primary outcome was recovery from chronic LBP at the 11-year follow-up. Persons categorized with chronic LBP at HUNT2 responding "no" at HUNT3 to the question "During the last year, have you had pain and/or stiffness in your muscles and joint that lasted for at least three consecutive months?" were defined as recovered.

Pain related comorbidities

The participants' self-rated general health was evaluated using the question "How is your health at the moment?", with response options "very good", "good", "not so good", and "poor". The answers were dichotomized into two groups: "very good/good" and "not so good/poor" in line with previous studies [15].

Pain-related disability was evaluated separately for work ability and leisure time activity. The question about work ability was: "Have the pain and/or stiffness reduced your

ability to work during the last year?" with four possible responses: "no, not significantly", "to some degree", "significantly", and "don't know". The first and last response options were merged and categorized as "no disability", and the two middle categories as "work disability". For leisure time activity, the question was: "Have the pain/or stiffness reduced your leisure activity?" with possible responses: "yes" and "no". The responses on disability due to musculoskeletal symptoms were then categorized into four groups; "no disability", "work disability", "leisure disability", and "work and leisure disability".

Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). HADS is a validated and well-established self-rating questionnaire including seven questions on anxiety and seven questions on depression [16]. As recommended, the cut-off score value was set to ≥8 on both anxiety and depression and were dichotomized as presence or no presence of anxiety and/or depression [16, 17]. Additionally, a mixed HADS variable were constructed consisting of four groups: "no depression or anxiety", "only depression", "only anxiety", and "both depression and anxiety" [18]. Symptoms of only depression or only anxiety was defined by a HADS score ≥8 on the respective subscales, while symptoms of both depression and anxiety was defined by a HADS score ≥8 on both subscales.

Possible confounders

All estimated associations were adjusted for possible confounders. Age was categorized in 20-29, 30-39,…≥60 years. BMI was calculated as weight divided by the square of height (kg/m^2) by standardized measurements of height and weight from the clinical examination, and classified into BMI groups according to the suggestions by the World Health Organization (normal weight, overweight, obesity) [19]. Physical work demands was assessed by the question: 'If you have paid or unpaid work, how would you describe your

work?' with the possible responses: "mostly sedentary", "much walking", "much walking and lifting", or "heavy physical work". Leisure time physical activity was assessed by the question: "How much of your leisure time have you been physically active during the last year?" where the participants reported number of hours of light and/or hard activity. Four categories were constructed based on this information; "inactive" (no light or hard activity), "low activity" (<3 hours of light and no hard activity), "moderate activity" (≥3 hours light and/or <1 hours of hard activity) and "high activity" (any light and ≥1 hour of hard activity). Further, education was assessed by the question "what is your highest level of education?", and were divided in 4 categories; "primary school", "high school", "college ≤4 years", and "college >4 years". Smoking was assessed by questions about past or present use of cigarettes, and were divided in three categories; "never smoker", "previous smoker" and "current smoker".

Statistical analysis

We used a generalized linear model of the Poisson family to estimate the relative probability of recovery from chronic LBP as risk ratios (RR) with 95% confidence intervals (CI) . A RR above 1.0 indicates higher probability of recovery compared to the reference category, while a RR less than 1.0 indicates a reduced probability of recovery. All estimated associations were adjusted for age, BMI , physical activity , education , smoking and physical work demands . All main analyses were conducted separately for men and women. Furthermore, a test for linear trend (i.e., dose-response) across categories of number of pain sites was conducted by treating the categories as an ordinal variable in the regression model.

Additionally, we conducted analyses combining number of pain sites (<4 vs. 4-9 sites) and comorbid conditions in relation to the probability of recovery from chronic LBP. Previous studies have shown that reporting of four or more pain sites is associated with a

markedly poorer prognosis of pain relief [20], as well as increasing likelihood of health care utilization and sickness absence [21]. Statistical interaction was evaluated by likelihood ratio tests of a product term of number of pain sites and each of the comorbid factors (self-reported health, pain-related disability and HADS). All statistical analyses were performed using Stata for Windows, version 13.1 (StataCorp LP, College Station, Texas).

RESULTS

Table 1 presents the baseline characteristics of the study population according to number of chronic pain sites. At baseline, 66.4% of the women and 47.2% of the men reported ≥4 pain sites. Of the 4,484 women and 3,039 men who reported chronic LBP at baseline (HUNT2), 1,822 (40.6%) women and 1,578 (51.9%) men were reported recovered from chronic LBP at the 11-year follow-up (HUNT3).

Table 2 shows the association between number of pain sites, pain-related disability, psychological symptoms, and self-rated general health with the probability of recovery from chronic LBP at follow-up. Increasing number of pain sites was inversely associated with the probability of recovery (P-trend<0.001 in both women and men). In specific, women and men who reported 6-9 pain sites had substantially lower probability of recovery (RR 0.58, 95% CI, 0.52 to 0.63 and RR 0.70, 95% CI, 0.63 to 0.79, respectively), compared to women and men who reported 2-3 pain sites. People with only LBP had a slightly higher probability of recovery (RR 1.10, 95% CI 0.98 to 1.22 in women and RR 1.10, 95% CI 1.01 to 1.21 in men) compared to women and men who reported 2-3 pain sites. Pain-related disability that influenced both work ability and leisure activity was associated with reduced probability of recovery in both women (RR 0.68, 95% CI, 0.62 to 0.74]) and men (RR 0.76, 95% CI, 0.70 to 0.83). HADS score ≥8 on both depression and anxiety subscales was associated with reduced probability of recovery in both women (RR 0.77, 95% CI, 0.66 to 0.91) and men (RR

Table 1. Baseline characteristics of the study population stratified by gender and number of chronic pain sites.

	Women		Men	
	<4 pain sites	4-9 pain sites	<4 pain sites	4-9 pain sites
No. of persons (%)	1,506 (33.6)	2,978 (66.4)	1,605 (52.8)	1,434 (47.2)
Age (years), mean (SD)	47.9 (13.6)	50.7 (11.9)	48.4 (12.1)	51.8 (11.4)
Body mass index (kg/m^2), mean (SD)	26.1 (4.1)	27.0 (4.5)	26.5 (3.3)	27.0 (3.4)
Physically inactive, no. (%)	82 (5.4)	208 (7.0)	96 (6.0)	103 (7.2)
Education ≤13 years, no. (%)	1142 (75.8)	2470 (82.9)	1244 (77.5)	1220 (85.1)
Current smoker, no. (%)	427 (28.4)	1021 (34.3)	416 (25.9)	412 (28.7)
Poor/not so good self-rated health, no. (%)	443 (29.4)	1786 (60.0)	461 (28.7)	831 (57.9)
Pain-related disability, work and leisure, no. (%)	726 (48.2)	2034 (68.3)	784 (48.8)	970 (67.6)
HADS score depression >8, no. (%)	65 (4.3)	187 (6.3)	96 (6.0)	124 (8.6)
HADS score anxiety >8, no. (%)	149 (9.9)	425 (14.3)	110 (6.9)	147 (10.3)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; SD, standard deviation

Table 2. Relative probability of recovery from chronic low back pain at 11-years follow-up according to number of chronic pain sites, pain-related disability, the Hospital Anxiety and Depression Scale score, and self-rated general health at HUNT 2.

	Women				Men			
	No. of persons	No. of cases	Crude RR	Multi-adjusted[a] RR (95% CI)	No. of persons	No. of cases	Crude RR	Multi-adjusted[a] RR (95% CI)
No. of pain sites								
1	326	189	1.13	1.10 (0.98 to 1.22)	454	284	1.11	1.10 (1.01 to 1.21)
2-3	1,180	608	1.00	1.00 (reference)	1,151	651	1.00	1.00 (reference)
4-5	1,330	557	0.81	0.83 (0.76 to 0.90)	873	422	0.85	0.86 (0.79 to 0.94)
6-9	1,648	468	0.55	0.58 (0.52 to 0.63)	561	221	0.70	0.70 (0.63 to 0.79)
Pain-related disability								
No disability	649	355	1.00	1.00 (reference)	487	304	1.00	1.00 (reference)
Work disability	591	271	0.84	0.87 (0.78 to 0.98)	430	249	0.93	0.94 (0.85 to 1.05)
Leisure disability	257	131	0.93	0.94 (0.82 to 1.08)	250	143	0.92	0.90 (0.79 to 1.02)
Work and leisure disability	2,760	964	0.64	0.68 (0.62 to 0.74)	1,754	818	0.75	0.76 (0.70 to 0.83)
HADS								
No depression or anxiety	2,572	1,103	1.00	1.00 (reference)	2,050	1,110	1.00	1.00 (reference)
Depression	252	90	0.83	0.90 (0.76 to 1.07)	220	101	0.85	0.85 (0.73 to 0.99)
Anxiety	574	215	0.87	0.88 (0.78 to 0.98)	257	120	0.86	0.88 (0.77 to 1.01)
Depression and anxiety	342	107	0.73	0.77 (0.66 to 0.91)	195	80	0.76	0.79 (0.67 to 0.94)
Self-rated general health								
Very good/good	2,208	1,099	1.00	1.00 (reference)	1,730	1,017	1.00	1.00 (reference)
Poor/not so good	2,229	704	0.64	0.66 (0.61 to 0.71)	1,292	551	0.73	0.72 (0.67 to 0.78)

Abbreviations: CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; RR, risk ratio

[a]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education > 4 years, and unknown), body mass index (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, and unknown), smoking (never smoker, previous smoker, current smoker, and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work, and unknown).

Table 3. Relative probability of recovery from chronic low back pain at 11-years follow-up according to the combined effect of number of chronic pain sites and pain-related disability, score on the hospital anxiety and depression scale, and self-rated general health at HUNT 2.

	1-3 pain sites			4-9 pain sites			
	No. of persons	No. of cases	Multi-adjusted[a] RR (95% CI)	No. of persons	No. of cases	Multi-adjusted[a] RR (95% CI)	P value[b]
Pain-related disability							
No disability	714	448	1.00 (reference)	422	211	0.84 (0.75 to 0.94)	0.002
Work disability	466	270	0.94 (0.85 to 1.03)	555	256	0.77 (0.69 to 0.86)	0.002
Leisure disability	271	172	0.98 (0.88 to 1.09)	236	102	0.71 (0.61 to 0.83)	<0.001
Work and leisure disability	1,510	756	0.81 (0.75 to 0.87)	3,004	1,026	0.59 (0.54 to 0.64)	<0.001
HADS							
No depression or anxiety	2,151	1,225	1.00 (reference)	2,471	988	0.75 (0.70 to 0.80)	<0.001
Depression	161	84	0.92 (0.79 to 1.07)	311	107	0.66 (0.56 to 0.77)	0.002
Anxiety	259	142	1.00 (0.89 to 1.12)	572	193	0.65 (0.58 to 0.73)	<0.001
Depression and anxiety	138	69	0.92 (0.77 to 1.09)	399	118	0.58 (0.49 to 0.68)	<0.001
Self-rated general health							
Very good/good	2,187	1,302	1.00 (reference)	2,617	838	0.57 (0.53 to 0.61)	<0.001
Not all good/poor	904	417	0.78 (0.72 to 0.85)	1,751	814	0.82 (0.77 to 0.87)	0.301

Abbreviations: CI, confidence interval; HADS, hospital anxiety and depression scale; RR, risk ratio.

[a]Adjusted for age (19-29, 30-39, 40-49, 50-59, >60), education (primary school and lower secondary school, upper secondary school, higher education <4 years, higher education > 4 years, and unknown), body mass index (normal weight, overweight, obesity), physical activity (inactive, low activity, moderate activity, high activity, and unknown), gender, smoking (never smoker, previous smoker, current smoker, and unknown) and physical work demands (mostly sedentary, much walking, much walking and lifting, heavy physical work and unknown).

[b]P-value from stratified analysis of number of pain sites by general health, physical disability, and HADS score.

0.79, 95% CI, 0.67 to 0.94). Persons reporting poor or not so good general health had a markedly reduced probability of recovery, both in women (RR 0.66, 95% CI, 0.61 to 0.71) and men (RR 0.72, 95% CI, 0.67 to 0.78), compared to those reporting good or very good general health.

Table 3 presents the combined effect of number of pain sites and pain-related disability, psychological symptoms, and self-rated general health on the probability of recovering for chronic LBP. We did not observe any statistical interaction between number of pain sites and pain-related disability, psychological symptoms or self-rated health (P≥0.24 for all tests). However, stratified analysis within categories of the exposure variables showed that reporting of ≥4 pain sites was associated with lower probability of recovery independently of level of pain-related disability, and psychological symptoms. Within strata of pain-related disability, persons who reported ≥4 pain sites had 16% to 27% lower probability of remission compared to persons with 1-3 pain sites in the same pain-related disability categories. Likewise, within the different strata of psychological symptoms, persons with ≥4 pain sites had 25% to 35% lower probability of recovery compared to persons with 1-3 pain sites.

DISCUSSION

In this large population-based study, we found that musculoskeletal comorbidity, reduced self-rated general health, and psychological symptoms were independently associated with reduced probability of recovery from chronic LBP at 11-year follow-up. The factors with the strongest association with poor prognosis were widespread chronic pain (6-9 pain sites) and poor or not so good self-rated general health. The strength of the associations between the various comorbidities and pain prognosis was fairly similar for women and men. Probability of recovery from chronic LBP was inversely associated with increasing number of chronic pain sites. Although there was no interaction between number of chronic pain sites and other

comorbidities, we observed in the combined analysis that persons with four or more pain sites had was associated with lower probability of recovery from chronic LBP within all strata of pain-related disability and symptoms of depression and/or anxiety. The current findings indicate that musculoskeletal comorbidity has a strong and independent influence on long-term prognosis of chronic LBP.

It is noteworthy that about 66% of the women and 47% of the men in this study reported four or more chronic pain sites at baseline. This supports the view that co-occurrence of musculoskeletal pain is very common in chronic LBP [5, 6]. To our knowledge, this is the first population-based study to investigate the prospective influence of graded musculoskeletal comorbidity on the prognosis of chronic LBP. The dose-response association between number of chronic pain sites and reduced probability of recovery from chronic LBP suggest that musculoskeletal comorbidity should be considered an important predictor in identifying target groups for public health secondary prevention. This was also supported by our combined analysis, showing that number of pain sites was the main driving factor for predicting persistence of chronic LBP.

More than 40% of the women and 50% of the men in the current study reported recovery from chronic LBP at 11-year follow-up. Interestingly, a previous study showed that the prevalence of chronic LBP was relatively stable from HUNT2 to HUNT3 with about 26% of women and 20% of men reporting chronic LBP at both surveys [22]. Thus, our results indicate that during an 11-year period a substantial proportion of the population shift from having chronic low back to remission, but that a substantial proportion also develops pain in the same period. Similar large fluctuations in reporting of chronic LBP at the individual level have also been observed by others [23, 24]. Thus, our findings lend further support to the notion that chronic LBP on the individual level may fluctuate substantially over time while the population prevalence remains relatively stable. The current study adds to this knowledge

by showing that individuals who shift from having chronic low back symptoms to remission of symptoms are more likely to have fewer chronic pain sites, less pain-related disability, better self-rated health, and no major symptoms of anxiety or depression.

Increasing number of chronic pain sites were inversely associated with probability of recovery, i.e., women and men who reported six or more pain sites had about 30-40% lower probability of recovery from chronic LBP compared to women and men with 2-3 pain sites. Previous cross-sectional studies have indicated a dose-response association between number of pain sites and a range of negative health outcomes such as psychological distress, poor sleep, poor self-rated health, reduced social and functional ability [11] as well as increased sickness absence and health care utilization [25]. The current prospective study extends this body of knowledge showing that number of chronic pain sites have a strong dose-response influence on prognosis of chronic LBP. Although we observed no interaction between number of chronic pain sites and other comorbid factors, the probability of relief from chronic LBP was consistently lower for the group with multisite pain within all strata of pain-related disability and psychological symptoms scores. These findings support the long-held view that it may be useful to classify patients with chronic LBP into "back pain alone" or "back pain plus other pain" to improve clinical decision-making [26].

The current finding of a dose-response association between number of chronic pain sites and prognosis of chronic LBP may indicate that the extent of musculoskeletal comorbidity could provide additional complementary information to improve classification in stratified care approaches. The idea that assessment of multisite pain can assist clinical judgment of prognosis and improve targeted treatment has been proposed before [6] and the current data lend further support to this idea. Furthermore, since number of chronic pain sites *per se* seem to be a strong prognostic factor in chronic LBP it may also be useful to consider this variable when recruiting subjects into research studies to facilitate baseline comparisons.

Although previous data indicate that psychological symptoms are more common in patients with LBP than in comparable controls [10], our results do not indicate that such symptoms strongly influence the prognosis of chronic LBP. However, another study of subjects with neck and/or LBP in HUNT 3 showed that symptoms of mental distress were significant determinants for seeking health care, which could have moderated the associations [27]. Our findings are in line with Dunn and colleagues [28] who found no significant association between depression, and only a modest association between anxiety, and the risk of disabling LBP at 12-months follow-up in patients presenting with LBP in general practice. In the same study, it was observed that self-rated health had a relatively strong impact on prognosis of LBP with patients who rated their health as poor having more than twofold increased risk of disabling back pain. Very few individuals in our study population rated their health as poor and we were therefore not able to estimate probability for recovery among these individuals. However, we observed that women and men who rated their health as less than good (i.e., poor or not so good) had about 30% lower probability of recovery from chronic LBP compared to those who rated their health as good or very good.

The strengths of the current study are the large and unselected population of women and men with chronic LBP, the prospective design, and the possibility of adjusting for several potential confounding factors. The questions on chronic musculoskeletal pain used in HUNT2 have acceptable reliability and validity [14, 29, 30]. Likewise, the HADS scale has been shown to be at a valid indicator of possible depression and anxiety in clinical practice as well as in the general population [16, 17, 31]. A limitation is the lack of follow-up information about the course of LBP and the other variables between the HUNT2 and HUNT3 study. Thus, any changes occurring during the follow-up period could not be taken into account in the analyses. For example, information regarding treatment during the follow-up period or information on changes in lifestyle could be of interest. A healthy lifestyle has

been associated with improved long-term outcome in individuals with recurrent LBP episodes [32]. Thus, it may be possible that individuals who changed their lifestyle during the follow-up period also altered their course of chronic LBP. Furthermore, we cannot rule out that such changes in lifestyle was differential between participants who experienced remission of symptoms versus those who did not, e.g., individuals with a high number of pain sites at baseline could be less prone to adopt a healthy lifestyle during the follow-up period because of pain-related disability.

In conclusion, the current study indicates that multisite chronic pain is independently and inversely associated with the probability of recovery from chronic LBP. Poor self-rated health, psychological symptoms, and pain related disability might further reduce the probability of recovery from chronic LBP. There was no interaction between number of chronic pain sites and other comorbidities, including pain-related disability, psychological symptoms and self-rated general health. These findings underscore the importance of taking comorbid symptoms into account, and in particular number of chronic pain sites, when designing management programs or treatment for secondary prevention of chronic LBP.

Acknowledgements

The HUNT Study is a collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology), Nord-Trøndelag County Council and The Norwegian Institute of Public Health

Author Contributions

PJM, TILN and ALN designed the study, and all authors contributed in the discussion of the design and interpretation. ALN performed the analyses supervised by PJM and TILN. The first draft of the manuscript was written by PJM and ALN. All authors contributed to the final manuscript.

Conflicts of interest

None declared.

Data sharing

No additional data available.

Funding sources

This study was supported by The Norwegian Fund for Post-Graduate Training in Physiotherapy and by grants from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU).

Ethical approval

The current study was approved by the Regional Committee for Ethics in Medical Research (project no. 2014/2044 REK midt, Norway). The study was carried out according to the Declaration of Helsinki.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**4**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4/5
Methods			**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
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6/7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6/7*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6/7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7/8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			8

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8/9
		(b) Indicate number of participants with missing data for each variable of interest	10/11
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	10/11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8 and 12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			12
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13/16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.