Development and course of chronic widespread pain: The role of time and pain characteristics (the HUNT pain study)

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Abstract:

Chronic widespread pain (CWP) is common and associated with loss of functioning and health. Subjects with chronic non-widespread pain (CnWP) are at increased risk of developing CWP, but few studies have described the nature of the development over time.

We followed a random sample of 3105 participants from the population-based HUNT-3 study with five annual measurements of pain over four years. While 29% reported CWP on at least one occasion, only 7% reported it consistently on four or five occasions. The average annual cumulative incidence was 5% and the recovery rate was 38%. In mutual adjusted analysis, the risk of developing CWP from one year to the next was higher in subjects with chronic pain (RR=2.4; 95% CI: 1.8-3.4), two or more pain regions (RR= 3.3; 95% CI: 2.5-4.4), moderate pain or more (RR=1.8; 95% CI: 1.5-2.6) and with comorbid chronic disease (RR=1.6; 95% CI: 1.3-1.9). Developing CWP was associated with a modest concurrent change in self-reported mental and physical health. The risk of developing CWP between the fourth and fifth occasions was 80% lower for subjects without a history of CWP, compared to those with. For subjects without previous CWP, the development was associated with previously reported CnWP, but not with the number of occasions with CnWP, in analyses adjusted for sex, age and pain severity.

A substantial proportion of the new cases of CWP originates from subjects floating below and above the definition for CWP over time, and thus, do not seem to involve major transitions in health.

Background:

Chronic pain affects about one third of the adult population and has a detrimental impact on health care utilization, work capacity and self-reported health and functioning [18; 29]. Chronic pain rarely occurs in a single anatomical location, and the more widespread the pain is, the higher the impact on functioning and health [12]. Chronic widespread pain (CWP) was in 1990 defined by the American College of Rheumatology (ACR) as pain on the left and the right side of the body, pain above and below the waist, and axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) [39]. The definition has generated a large amount of research and it has helped to establish the condition in clinical settings. For example, the International Classification of Functioning, Disability and Health (ICF) established in 2004 its own core set on CWP [4], and in the 11th version of the International Classification of Diseases (ICD-11), CWP has received a distinct diagnostic code under the heading "chronic primary pain" [31]. Thus, the use of CWP as a diagnosis on its own will in all likelihood become more common in the future, and research on the condition increasingly relevant.

The division between CWP and chronic non-widespread pain (CnWP) also termed regional, local or localized pain, is ambiguous. This was demonstrated by showing high inconsistencies in the use and interpretation of its definition [3]. Moreover, several studies have shown that transitions to and from CWP are common in the general population and an important risk factor for developing CWP is the number of pain sites at baseline [2; 20; 26]. As several studies have shown that the number of pain sites tends to be stable in the general population [11; 25], one may suppose that most subjects who develop CWP only fluctuate just above and below the cutoff. Hence, for a large proportion of those who develop CWP in population-based studies, the transition does not reflect a major change in health. This is in contrast with a commonly held view that chronic pain tends to "amplify" across time, leading to a continuous increase in the risk of it becoming widespread [1; 27]. Limited evidence exists to evaluate these contradicting views on the development of CWP in the general population, since most studies include only two measurement occasions and thereby offer limited information on the course of pain before and after a new episode of CWP has occurred.

In the current study, we investigated the development of CWP using annual measures of pain over four years in a population-based sample. Specifically, we wanted to estimate the risk of developing CWP and investigate pain related factors that predict this development. We hypothesized pain to be present in more than one body region before the transition into CWP and that previously reported CWP is a strong predictor of recurrence. A secondary aim was to investigate whether a transition into CWP is associated with a concurrent reduction in self-reported health and functioning.

Methods:

Participants and setting:

This study is a part of a population health study, the HUNT study, in which the total population aged 20 years and more in the northern part of Trøndelag County, Norway was invited to participate. In 2006-2008 a total of 50827 subjects enrolled in the HUNT 3 study, 54% of those invited. The population of northern Trøndelag is homogenous (97% Caucasian) with demographic characteristics similar to the average of the Norwegian population, except for a lower average income and educational level [15].

After approval by the Regional Committee for Medical and Health Research Ethics Central-Norway, a random sample of HUNT 3 participants from the municipalities of Levanger and Verdal (N=6419) was invited to participate in a sub study of pain (the HUNT pain study). Among them, 4768 (75%) agreed to participate and to answer postal questionnaires every three months over one year (five questionnaires in total) and thereafter one annual questionnaire for the following three years. At the end of the four-year follow up, 3405 subjects (71% of respondents and 53% of those initially invited) returned the last annual questionnaire, which was mailed in the period September 2011 to February 2012. Further information on the methods and participants of the HUNT pain study have been published elsewhere [16-18].

Measures:

In the questionnaire, participants were asked to report the anatomical localization of their pain on a body map including check boxes of 25 layman labeled body sites. The check boxes were distributed beside the body map with lines indicating their respective sites at both left and right sides. The body sites were collapsed into five body regions in the following way: shoulder/ arm, elbow and wrist /hand were considered upper quadrant pain, at both left and right hand sides, respectively. Calves, hips, thighs, knees and feet /ankles were considered lower left or right quadrant pain, respectively. Neck pain, upper and lower back pain were considered axial pain. We used this classification as a variable ranging from none to five body regions. To meet the criteria for widespread pain, subjects had to report pain in both sides of the body, pain above and below the waist, as well as axial pain i.e. a minimum of three regions [39]. This definition does not specify which body areas should be included in the assessment. However, we used the same areas as were described in a recent evaluation of the Widespread Pain Index (WPI), a similar instrument but without the body map [38]. To meet the criteria for CWP subjects also had to report chronic pain, defined as pain lasting six

months or more, on a separate question[17]. Pain severity was measured using the SF-8 bodily pain scale. A cut off at the midpoint separating moderate pain or more from mild or no pain has previously been shown to identify subjects with more complex chronic pain [9].

Chronic diseases and injuries were measured by self-report by enquiring about the presence of the following conditions during the past year: Lung disease, cancer, gastro intestinal disease, kidney disease, neurological disorder, diabetes, rheumatoid arthritis, arthrosis, osteoarthritis, fracture, nerve injury and other injury. Self-reported chronic disease has previously been shown to be fairly accurate [14]. The diseases were collapse into one categorical variable as either no disease, one disease, or two or more diseases.

As a measure of self- reported health and functioning, we included the SF-8 health survey, which is a shorter form of the SF-36 health survey. It contains one item representing each of the following eight scales: General health, mental health, bodily pain, vitality, physical function, social function, and limitations in work due to physical (role physical) and emotional (role emotional) problems. Two component scores, one representing physical health (PCS) and one representing mental health (MCS) were computed according to standard procedures. The scores are standardized T-scores so that all scales range from 0 to 100 with a mean close to 50 and a standard deviation close to 10 of the normative data [35].

Statistical analyses:

The proportions of subjects transitioning between CWP and no CWP between any of the annual measurements were given as percentages. To investigate the role of chronic pain severity and number of pain regions on the development of CWP, we used Generalized Estimations Equations (GEE) with a Poisson distribution and a log link. Altogether, we had access to self-reported data from five measurement occasions over four years. The analyses were restricted so that at occasions in which a subject reported no CWP, information on chronic pain, pain severity, number of pain regions and comorbid chronic disease were used to predict transition into CWP on the following occasion (incidence). To analyze associations between change in CWP status and change in self-reported physical and mental health, we constructed change scores of the SF-8 physical (PCS) and mental (MCS) summary components by subtracting the scores on each occasion from its preceding occasion. Then, in analyses stratified by CWP at the time before change, we used CWP at the time after change to predict the change scores on physical and mental health. These analyses were carried out using GEE with a Gaussian distribution and an identity link. To correct for dependency between the repeated observations we used an independent working correlation structure and robust standard

errors. Missing data were handled by including all available information. That is, at least two consecutive measurements had to be complete.

To evaluate the role of previously reported CWP and CnWP on the risk of developing CWP, we used the first three consecutive measurement occasions to generate two variables comprising the number of occasions with CWP and CnWP, respectively. The association of these variables with the development of CWP from the fourth to the fifth occasion was investigated using a generalized linear model with a log link and a binomial distribution. To obtain adequate numbers in each category, we collapsed one and two occasions into one category. Analyses were performed using STATA 14 (Stata Corp. College Station, Texas).

Results:

Complete data on CWP over the five measurement occasions were obtained for 3105 subjects. More women (55.6%) than men participated, and 52.7% of the participants were middle aged. CWP was more prevalent among women and among middle aged and older participants compared to the youngest age groups **(Table 1).** CWP was reported on at least four of five possible annual measurements in 6.9% (95% CI: 6.1-7.9) of the subjects, indicating a stable course. However, 8.5% (95% CI: 7.5- 9.5) reported CWP on only one and 8.4% (95% CI: 7.4-9.4) reported CWP on two or three out of five possible occasions, indicating a higher "year to year" variation.

The overall prevalence of CWP was constant at 12% on each measurement occasion, and the transition into CWP between two subsequent annual measurement occasions was stable at 5% **(Figure 1).** From baseline to 12 months follow up, the proportion of subjects changing from CWP to no CWP was 40% and thereafter it ranged between 36% and 38% over the three remaining annual intervals, with an average of 38.5%.

As shown in **Table 2**, reporting chronic pain in one year predicted risk of CWP the next year. Development of CWP from no chronic pain was seen in only 1.1%, whereas the risk was tenfold higher among subjects already reporting chronic pain (RR=10.5; 95% CI: 7.8: 13.8). Also, the risk of developing CWP was more than five times higher for subjects reporting moderate or severe pain (RR= 5.2; 95% CI: 4.5: 6.1) and more than four times higher for subjects reporting pain in at least two as compared to one region (RR= 4.3; 95% CI: 3.3: 5.4). Having one comorbid chronic disease increased the risk by 2.6 times (95% CI: 2.1: 3.2) and having two or more comorbid chronic diseases increased the risk by 5.6 times (95% CI 4.5-6.8). When mutually adjusted, both chronic pain, number of pain regions, pain severity and comorbid disease remained important predictors for the

development of CWP, with number of regions being the pain factor least influenced by the adjustment (RR= 3.3; 95% CI: 2.5: 4.4).

Between any two occasions, the mean change in the SF-8 physical component score (PCS) was -0.28 with a standard deviation of 7.02 and the mean change in SF-8 mental component score (MCS) was -0.83 with a standard deviation of 7.98. A significantly higher reduction in SF-8 PCS was seen when developing CWP, compared to when not developing CWP (mean difference= -1.19 points (95% CI; -1.79: -0.58), in analyses adjusting for age and sex. A smaller and less robust difference was seen for change in MCS (mean difference= -0.49; 95% CI: -1.16: 0.17) when comparing those who developed and those who did not develop CWP.

Among the 141 subjects developing CWP between the fourth and fifth occasions, 62.4% had reported CWP on one or more of the previous three occasions. For subjects without a history of CWP the risk of developing it was 90% lower compared to those with one or two previous occasions with CWP (RR= 0.1; 95%CI: 0.0-0.3). The risk increased by 2.6 times (95% CI: 1.6-3.8) for those having reported CWP consistently on the three previous occasions, but this difference diminished when adjusting for pain severity at the time point before the transition (RR= 1.3; 95% CI 0.9-1.8) **(Table 3)**.

Among subjects without any previous reports of CWP, 53 developed it between the fourth and fifth occasions **(Table 4)**. Among these, 49 (92.5%) had reported CnWP on at least one previous occasion. Compared to subjects with one or two previous reports of CnWP, subjects reporting CnWP on three consecutive measures had twice the risk of developing CWP (RR=2.1; 95% CI: 1.2-3.7). However, the difference diminished when adjusting for pain severity at the time point before the transition (RR=1.3; 95% CI: 0.7-2.3). A sensitivity analysis indicated no meaningful differences in the association with CWP at the fifth occasion between those reporting one and two previous measures with CnWP.

Discussion:

In this four-year longitudinal study, we found a stable annual cumulative incidence of CWP of 5% and an annual averaged recovery rate of 38%. The most typical development of CWP was from chronic pain that was non-widespread (CnWP) but involved two body regions or more and was of at least moderate severity. Also, the risk was significantly higher among subjects reporting at least one comorbid chronic disease. Development of CWP was associated with concurrent changes in self-reported physical and mental health in the range of 0.5 to 1 point on a 0-100 point scale. Although statistically significant, these changes are unlikely to reflect clinically important changes [33].

Moreover, the risk of developing CWP strongly increased when CWP was reported on one or more previous occasions. These findings give support to our hypothesis that the change, in most instances, is a part of an ongoing fluctuation in and out of CWP.

An alternate view is that as pain persists, the risk of it becoming widespread increases because it becomes increasingly more complex, i.e. involving more somatic symptoms as well as psychological and social factors [1; 5; 27]. A minority, 38%, of those developing CWP between the fourth and fifth occasion in our study, did not report CWP on any of the preceding measurements. Among these, previous reports of CnWP was associated with a higher risk of developing CWP, and in unadjusted analyses the risk increased as the number of occasions with CnWP increased from one or two to three. We do not know whether any of these subjects had experienced CWP before the start of our study, but may assume a higher probability among those with three occasions. These may have a longer trajectory of more severe pain and the different risk in developing CWP diminished when controlling for pain severity at the time point before the transition.

Previous evidence shows that subjects with chronic pain, and in particularly CWP, have substantially reduced health and functioning compared to subjects without chronic pain [18; 28]. However, other somatic symptoms and adverse psychological and social factors are often present prior to the chronic pain, and limited evidence suggests that the impact of these factors increases as the pain persist [7; 8; 16]. Another mechanism for explaining why pain becomes widespread is increased synaptic response in nociceptive neurons in the central nervous system, termed central sensitization [1; 40]. However, the neurophysiological mechanisms underlying this development need not occur during months or years, but may be rather direct effects of an injury, stress or trauma [8; 13; 32].

Comparable to our findings, a four-year follow up study among schoolchildren found that CWP showed a fluctuating course over three measurements, with prevalence and new onset rates similar to that of adults [24]. In a prospective study of subjects with chronic low back pain, a stable distribution of pain sites was documented over three measurements, and like our study, only a small group displayed constant spread of pain over time [30].

The best way to view the development of CWP in the general population may therefore not be as a continuous amplification over time. Given the high incidence and prevalence rates observed in adolescence, it might seem that the best model would include a lifelong trajectory [24]. Accordingly, the transitions we observed in adults over four years may only mirror fluctuations that have been going on for decades. However, to investigate this we would need longitudinal studies following individuals from childhood thorough adulthood.

Our findings highlight the difficulties in classifying CWP, as a considerable number of subjects move in and out of the definition across time. In the ICD-11 definition, additional criteria, such as significant emotional distress or functional disability are required [31]. Including such criteria in our definition might have reduced the variability over time. However, no standard definition exists, which includes these additional measures and it is uncertain how they should be measured. The updated criteria for fibromyalgia offer a stricter definition, which require cognitive difficulties, fatigue, depressive symptoms and sleep disorders to be present in addition to CWP [36; 37]. However, this definition encompasses a much smaller and more adversely affected group than what is generally regarded as CWP and a division between these conditions may be important in both clinical and research settings [28]. Further work may therefore be necessary to obtain a standardized and robust definition of CWP.

At each occasion, we found a point prevalence of CWP of about 12%. In a recent systematic review, the pooled prevalence was 11% and most estimates were in the range between 10%-15% [21]. Our findings are therefore highly comparable with other studies. Previous studies have also reported proportions transitioning between CnWP and CWP in the range of 9% to 25% [10; 20; 23; 34]. Our estimates were substantially lower since we also included subjects with no chronic pain. Considering the transition into CWP among subjects with CnWP, we found a probability of 11%, which is well within the range of previous reports. Among subjects without chronic pain, the probability of moving into CWP was 1% in our study. This is somewhat lower, but comparable to previous studies [2; 22; 26].

The strengths of our study include the repeated measurements of pain in a random population based sample. This gave us increased power and the opportunity to investigate the development of CWP over several occasions, which has not been done in population-based studies before. As described previously [16], the study was designed to detect incidence estimates as low as 2% with adequate precision. Our main estimates are well beyond this, but our analyses that were based on sub-samples, may have suffered from a loss of precision. In particular, this may have affected our analysis regarding the role of previously reported CnWP on the role of developing CWP. To avoid categories with few subjects, we collapsed one and two previous measures of CnWP into one category. In this way, we were not able to disentangle any difference between those reporting one or two previous occasions with CnWP. However, in a sensitivity analysis we found no difference in the risk of developing CWP between the two groups.

Another main limitation of this study relates to the participation rate, which was 54% in HUNT 3, and the attrition to follow up of the current study, both leading to overrepresentation of middle-aged

women and among subjects with higher levels of education [16]. We may therefore assume that our prevalence and incidence estimates are somewhat inflated, and may be somewhat lower in populations including younger individuals and more men. However, we would expect estimates to be higher in populations with lower education. As previously reported, the prevalence of pain complaints was higher among participants than non-participants in the HUNT 3 study [19], but we did not find evidence for a participation in the HUNT pain study being dependent on pain complaints [16; 18]. Moreover, our estimates are well within the range of previous reports. Also, the relevance for the associations studied are more likely to generalize to a wider population, as these tend to be less sensitive to participation rate in epidemiological studies [6].

Conclusion:

The proportion of individuals who develop CWP during a 12-month period in a general population is 5%. The majority of the new cases of CWP develops from chronic pain that is already of at least moderate severity and affecting at least two body regions in subjects with a previous history of CWP. Thus, the transition is rarely a major change in health, but rather minor fluctuations of an ongoing condition.

Acknowledgements: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre, (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The authors declare no conflict of interest.

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Figure 1: Proportion of transitions to and from chronic widespread pain (CWP), measured annually over 4 years in the general population in Norway (n=3105)

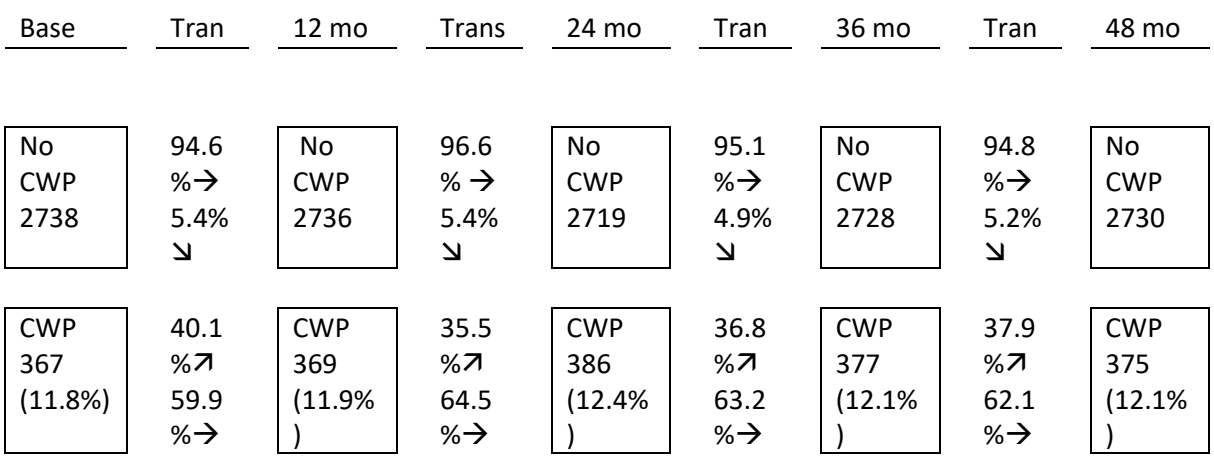

Table 1: Number of occasions with chronic widespread pain (CWP) measured annually over four year in the general population in Norway (n= 3105), overall and according to sex and age.

	Complete follow up sample			Number of occasions with CWP											
				none			One			Two or three			Four or five		
	N	%	(95 % CI)	N	%	(95 % CI)	N	%	(95 % CI)	N	%	(95 % CI)	N	%	(95 % CI)
Overall	3105			2365	76.2	(74.6-77.6)	264	8.5	(7.5-9.5)	260	8.4	(7.4-9.4)	261	6.9	(6.1-7.9)
Sex															
Female	1728	55.6	(53.9-57.4)	1222	70.7	(68.5-72.8)	167	9.7	(8.4-11.1)	173	10.0	(8.7-11.5)	166	9.6	(8.3-11.1)
Male	1377	44.4	(42.6-46.1)	1143	83.0	(80.9-84.9)	97	7.0	(5.8-8.5)	87	6.3	(5.1-7.7)	50	3.6	(2.8-4.8)
Age															
20-44	756	24.3	(22.9-25.9)	652	86.2	(83.6-88.5)	50	6.6	(5.0-8.6)	36	4.8	(3.4-6.5)	18	2.4	(1.5-3.7)
45-64	1636	52.7	(50.9-54.4)	1193	72.9	(70.7-75.0)	150	9.2	(7.9-10.7)	157	9.6	(8.3-11.1)	136	8.3	(7.1-9.7)
65+	713	23.0	(21.5-24.5)	520	72.9	(69.5-76.1)	64	9.0	(7.1-11.3)	67	9.4	(7.5-11.8)	62	8.7	(6.8-11.0)

Table 2: Absolute and relative risk (RR)[a] of developing chronic widespread pain (CWP) from one year to the next by sex, age and pain characteristics in the general population in Norway (N=3726)

		Crude			Adjusted[b]	
		%	RR	(95% CI)	RR	(95% CI)
Sex	Female	6.4	1	(ref)	1	(ref)
	Male	3.9	0.6	(0.5-0.7)	0.8	(0.7-0.9)
Age	20-44	3.0	1	(ref)	1	(ref)
	45-64	6.2	2.1	(1.7-2.7)	1.2	(1.0-1.5)
	65+	5.6	1.9	(1.5-2.5)	0.8	(0.6-1.1)
Chronic pain	No	1.1	1	(ref)	1	(ref)
	Yes	11.3	10.5	(7.8-13.8)	2.4	(1.8-3.4)
Pain regions	0	0.7	0.2	(0.1-0.3)	0.6	(0.4-0.9)
	1	3.2	1	ref	1	(ref)
	≥2	14.1	4.3	(3.3-5.4)	3.3	(2.5-4.4)
Pain severity	<mild	2.3	1	(ref)	1	(ref)
	≥moderate	13.0	5.2	(4.5-6.1)	1.8	(1.5-2.2)
Chronic disease	0	2.4	1	(ref)	1	(ref)
	1	6.7	2.6	(2.1-3.2)	1.6	(1.3-1.9)
	≥2	14.8	5.6	(4.5-6.8)	2.4	(1.9-2.9)

Table 3: Absolute and relative risk of again developing Chronic Widespread Pain (CWP) according to the number of previous occasions with CWP during four years of follow up with annual measurements in the general population (N=2782)

	Crude				Adjusted [a]	
	n	%	RR[a]	(95% CI)	RR	(95% CI)
No previous CWP	53	2.2	0.1	(0.0-0.1)	0.2	(0.1-0.2)
One or two occasions	69	24.6	1	(ref)	1	(ref)
Three occasions	19	63.3	2.6	(1.8-3.6)	1.3	(0.9-1.8)

[a] Adjusted by Sex, Age and pain severity (SF-8 bodily pain scale) at the time point before the transition.

Table 4: Absolute and relative risk of developing Chronic Widespread Pain (CWP) according number of prior reports of Chronic non-Widespread Pain (CnWP) in a population-based sample free from CWP over four years with annual measurements (N=2418)

	Crude				Adjusted[a]	
	N	%	RR[a]	(95% CI)	RR	(95% CI)
No previous CnWP	4	0.3	0.1	(0.0-0.3)	0.2	(0.0-0.6)
One or two measures with CnWP	19	2.8	1	(ref)	1	(ref)
Three measures with CnWP	30	6.0	2.1	(1.2-3.7)	1.3	(0.7-2.3)

[a] Adjusted by Sex, Age and pain severity (SF-8 bodily pain scale) at the time point before the transition.