A Population-based Cohort Study on Chronic Pain: The Role of Opioids

Per Sjøgren, MD, DMSC, Morten Grønbæk, PhD,† Vera Peuckmann, PhD,‡ and Ola Ekholm, PhD†*

Objectives: The aims of this study were 2-fold: (1) to investigate the consequences of opioid use in individuals with chronic pain in the Danish population, and (2) to investigate the development of and recovery from chronic pain from 2000 to 2005.

Methods: Data derived from the Danish Health Interview Survey in 2000, which were linked on the individual level with register-based follow-up data. The survey was based on a county-stratified random sample of 16,684 individuals, out of which 10,434 individuals (62.5%) completed a face-to-face interview and returned a self-administered questionnaire. In addition, a subsample of the sample in 2000 was reinvited to a follow-up survey in 2005. In total, 3649 individuals (61.7%) of this subsample completed the interview and returned the questionnaire at baseline in 2000. At follow-up, 2354 of these participants completed the interview and returned the self-administered questionnaire. Respondents with cancer diagnosis were excluded from all analyses. Respondents with chronic pain were identified as having chronic/long-lasting pain more than 6 months.

Results and Discussion: The annual incidence for the development of and the recovery from chronic pain was 2.7% and 9.4%, respectively. Increasing age up to 64 years, short education, poor self-rated health, high body mass index, and physical strain at work were predictors of chronic pain. The odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids. In addition, use of strong opioids was associated with poor health-related quality of life. Furthermore, the results indicated that individuals with chronic pain using strong opioids pain had a higher risk of death than individuals without chronic pain (HR: 1.67; 95% CI: 1.03-2.70). However, this study cannot exclude disease severity as the primary cause of increased mortality.

Key Words: chronic non-cancer pain, cohort study, epidemiology, opioids

(*Clin J Pain* 2010;26:763–769)

Denmark has had an extremely high usage of opioids for years, mainly prescribed for chronic noncancer pain conditions.[1–3] Clinical needs, recommendations from pain clinicians, and massive sales promotion activities from the pharmaceutical companies have been the driving force, rather than scientific data on efficacy and safety. Caution about opioid treatment of chronic pain has long been based on the fear of addiction and diversion of opioids into society.[4] However, other important clinical issues such as physical dependency, tolerance development, cognitive disorders, opioid-induced hyperalgesia, dysfunction of the immune and reproductive systems, and even increased mortality may give rise to concerns.[4–10] Guidelines for responsible use of opioids in chronic noncancer pain conditions reflect concerns over these problems.[11–14] Pain clinics and centers seem to follow these guidelines, and in these facilities opioid doses can be kept stable for years in the majority of patients.[15,16] However, outside the specialized treatment facilities the guidelines may either not be followed or not be known.[10]

In epidemiologic surveys excluding cancer patients Eriksen et al[2] showed that 3% of the Danish population used opioids on a regular or continuous basis, and that the opioid usage was significantly associated with reporting of high pain intensity, poor functional capacity, and health-related quality of life.[17] Owing to the cross-sectional nature of this study, causality could not be proven.[17]

This study is based on data from the Danish Health Interview Surveys in 2000 and 2005. The Health Interview Surveys are nationwide surveys of adult Danish citizens (16y or older), which have been carried out in 1987, 1994, 2000, and 2005. The main purpose of these surveys is to describe the status and trends in health and morbidity in the adult Danish population and factors that influence health status.[18] Owing to the fact that the survey in 2000 and in 2005 was based on the very same basic questions regarding chronic pain: "Do you have chronic/long-lasting pain lasting 6 months or more?" this cohort study was much more accurate and reliable than the cohort from 1994 to 2000, in which the pain intensity verbal rating scale (with the recall period of 4 weeks included in the SF-36) was used to identify chronic pain.[19] The aims of this study were 2-fold: (1) to investigate the consequences of opioid use in the individuals with chronic pain in the Danish population, and, (2) to investigate the development of and recovery from chronic pain from 2000 to 2005.

MATERIALS AND METHODS

Population and Design

The Danish Health Interview Surveys were designed and carried out by the National Institute of Public Health; however, the specific pain questions were developed by our pain research group. Data from the Danish Health Interview Survey in 2000 linked with individual-level register

Received for publication October 23, 2009; revised May 3, 2010; accepted May 23, 2010.

From the *Section of Acute Pain Management and Palliative Medicine, Rigshospitalet; †National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; and ‡Department of Anaesthesiology and Department of Palliative Medicine, RWTH Aachen University Hospital, Aachen, Germany.

Reprints: Per Sjøgren, MD, DMSc, Section of Acute Pain Management and Palliative Medicine, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen ø, Denmark (e-mail: rh12244@rh.dk; p.sjogren@mail.dk).

Copyright © 2010 by Lippincott Williams & Wilkins

data on vital status (ie, death or emigration) were used to investigate the relationship between (opioid-treated) chronic pain and mortality. In the baseline survey in 2000, a county-stratified random sample of 16,684 individuals was drawn from the Danish Civil Registration System (each Dane has a unique personal registration number). Data in the Danish Health Interview Surveys were collected through personal interview at the respondents' home and after the interview, the respondents were asked to complete a self-administered questionnaire. In total, 10,434 individuals (62.5%) completed the interview and returned the self-administered questionnaire at baseline. Respondents with a self-reported earlier or present cancer diagnosis were excluded from the analyses (369 individuals). Hence, the final study population consisted of 10,065 individuals. The Danish Civil Registration System was used to obtain information on vital status and the date of change of vital status. Observation time was calculated from the interview date until death, emigration, or 26 November 2008 (end of follow-up).

To investigate the association between chronic pain and potential risk factors, a subsample consisting of 5912 individuals from the survey in 2000 was used. This subsample was also used to examine the relationship between development of or recovery from chronic pain and potentially associated factors. In total, 3649 individuals (61.7%) of this subsample completed the interview and returned the self-administered questionnaire. Five years later (in 2005), 3430 of these participants were available when the cohort was reexamined (219 were lost to follow-up because of death or emigration). In total, 2354 individuals completed the interview and returned the self-administered questionnaire at follow-up. Respondents with a self-reported earlier or present cancer diagnosis were also excluded from these analyses (112 individuals) and, hence, the final follow-up study population consisted of 2242 individuals.

Assessment

Respondents with chronic pain were identified through the question "Do you have chronic/long-lasting pain lasting 6 months or more?" The question concerning chronic pain was asked in the self-administered questionnaire at both baseline and follow-up. Educational status was classified according to The International Standard Classification of Education, that combines school and vocational education. Self-rated health was assessed by the question: In general, how would you characterize your health?: Really good; good; fair; poor; very poor.

The Short Form 36 (SF-36) was also included in the self-administered questionnaire.[20,21] The SF-36 is a 36-item survey that measures 8 dimensions of health (bodily pain; general health; mental health; physical functioning; role limitation owing to emotional problems; role limitations owing to physical health; social functioning; vitality). Higher scores on the SF-36 (range 0 to 100) indicate better health-related quality of life.

Usage of self-reported medications was obtained by an open-ended question asking whether the respondent regularly or continuously takes any medication. The self-reported use of medications was categorized according to The Anatomical Therapeutic Chemical (ATC) Classification System. In the ATC classification system, the drugs are grouped into different groups according to the organ or system on which they act and their chemical, pharmacologic, and therapeutic properties (http://www.whocc.no/atc_ddd_index/). Weak opioids in Denmark are codeine, tramadol, and dextropropoxyphene. All other opioids are categorized as strong opioids.

Information on long-standing diseases (circulatory diseases, infectious and parasitic diseases, and mental disorders) derived from an open-ended question "Do you have any long-standing disease, disorder or illness, long-standing effects of injury, any functional impairment, or any other long-standing health problem?" An affirmative answer led to questions about the specific nature of the disease. The diseases were classified according to the International Classification of Disease (ICD-10). Individuals with diabetes were identified on the basis of responses to a chronic condition checklist.

Self-reported height and weight were used to calculate the Body Mass Index (BMI). The physical working environment was assessed by a question regarding the physical strain of the main occupation among actively employed 16 to 64 years of age, and the 4 response categories were categorized into 3 groups: low (mainly sedentary work that does not require any physical effort), medium (work that is largely carried out standing or walking but otherwise does not require any physical effort), and high (standing or walking work with much lifting or carrying, or heavy or rapid work that is strenuous). Finally, actively employed 16 to 64 year olds were asked if they often (more than twice a week) are exposed to any of these factors at work: working while bent over or in a twisted position; repetitive motion; heavy objects (at least 10 kg) to be carried or lifted.

Statistical Analysis

The Cox proportional hazards model was assessed to investigate the association between chronic pain (opioid-treated and nonopioid-treated) and mortality after adjustment for potentially confounding factors. The covariates included were gender, the international standard classification of education, marital status, BMI, smoking behavior, regular use of antidepressants, regular use of anxiolytics, self-reported circulatory diseases, infectious and parasitic diseases, diabetes, and mental disorders. In the analysis, age was used as the underlying time scale, thus treating age at interview as the time of delayed entry. The proportional hazard assumption was checked graphically. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI).

The incidence of new/recovered cases of chronic pain per 1000 person-years was calculated with the assumption of a date of development/recovery in the middle of the follow-up period. Multiple logistic regression analysis was carried out to estimate the association between chronic pain at follow-up and the possible risk factors. Multiple logistic regression analysis was also carried out to investigate the relationship between recovery from chronic pain at follow-up (among individuals with chronic pain at baseline) and potential associated factors. The results are presented as gender-adjusted and age-adjusted odds ratios (OR) with 95% confidence intervals (CI).

At follow-up, age-standardized mean scores of the 4 groups concerning pain status were estimated for each SF-36 domain (no chronic pain 2000 – no chronic pain 2005; no chronic pain 2000—chronic pain 2005; chronic pain 2000—no chronic pain 2005; chronic pain 2000—chronic pain 2005). Furthermore, cross-sectional data from 2000 were used to estimate age-standardized mean scores according to the chronic pain status and the use of opioids in

 © 2010 Lippincott Williams & Wilkins

2000 for each domain. The Danish population in 2005 was used as the standard population in the SF-36 analyses. All statistical analyses were done using the SAS version 9.1.

RESULTS

Table 1 shows the baseline sociodemographic characteristics of the sample and the study population for the questionnaire follow-up study. The proportion of men is slightly lower in the final study population than in the original sample. As expected, the elderly are more likely to be lost at follow-up than younger individuals. During 81,965 person-years of follow-up in the health interview survey in 2000, 782 deaths occurred. A statistically significant association was found between (opioid-treated) chronic pain and mortality ($P = 0.0427$). The results showed that individuals with chronic pain using strong opioids pain had a higher risk of death than individuals without chronic pain (HR: 1.67; 95% CI: 1.03-2.70) (Fig. 1). The results also showed that the risk of death was higher among individuals with chronic pain not using opioids compared with individuals without chronic pain (HR: 1.21; 95% CI: 1.02-1.44). However, the analysis did not indicate a higher risk of death among individuals with chronic pain using weak opioids compared with individuals without chronic pain.

Table 2 shows that the estimated incidence rate for developing chronic pain in Denmark was 26.9 per 1,000 person-years (26.8 for men and 27.0 for women). The incidence rate increased with age up to the age of 64 and then decreased subsequently. Table 3 shows the overall incidence rate for recovering from chronic pain was 94.2 per 1000 person-years in Denmark. The table shows that the pain recovery was significantly associated with the use of opioids. The odds for reporting recovery from chronic pain at follow-up were almost 4 times higher among individuals not using opioids at the baseline compared with individuals using opioids. In addition, an analysis among individuals with chronic pain and a fair, poor, or very poor self-rated health at the baseline showed that opioid users were more likely to report a fair/poor self-rated health at follow-up than nonopioid users (OR: 3.89; 95% CI: 1.45-10.46) (data not shown). However, analyses of the mean changes (from baseline to 5 years later) in the SF-36 domain scores did not indicate a poorer health-related quality of life for opioid users than nonopioid users.

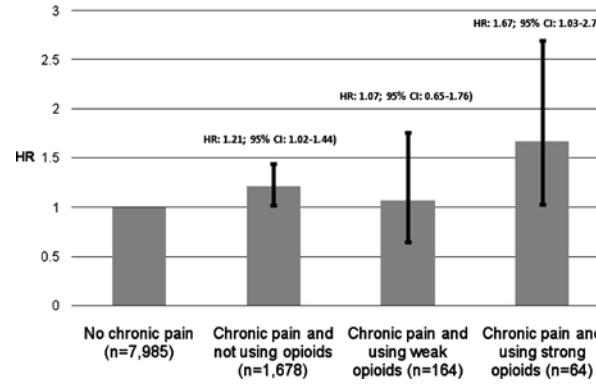

FIGURE 1. Hazard Ratios (HR) and 95% confidence intervals for all-cause mortality according to the chronic pain status and the use of opioids in 2000.

There was a clear association between combined school and vocational education and the development of chronic pain. The odds for reporting chronic pain were higher among individuals with shorter education compared with participants with 15 or more years of education (Table 2). The table indicates that there was no association between marital status and developing chronic pain ($P = 0.961$). Table 2 also shows, that persons, who rated their health as fair, bad, or very bad at baseline, were more likely to develop chronic pain in the follow-up period (OR: 2.45; 95% CI: 1.63-3.71). Furthermore, the table shows that obese persons (BMI $\geq$ 30) were more likely to develop chronic pain than persons with a BMI of less than 25.

The age-standardized SF-36 mean scores for each domain in 2005 are shown in Figure 2. The figure shows that individuals without chronic pain at both baseline and follow-up have the highest mean score in all 8 subscales. Individuals with chronic pain at both baseline and follow-up have the lowest mean scores in each domain, indicating a poor physical and mental health-related quality of life.

TABLE 1. Sociodemographic Characteristics of the Sample and the Study Populations for the Questionnaire Follow-up Study

	Original Sample in 2000	Interviewed and Returned Self-administrated Questionnaire in 2000	Final Follow-up Study Population*	Chronic Pain at Baseline	No Chronic Pain at Baseline
Sex					
Men	48.9	47.1	46.7	40.9	48.2
Women	51.3	52.9	53.3	59.1	51.8
Age					
16-24 y	13.1	12.8	12.5	7.9	13.7
25-44 y	36.4	37.4	38.8	27.9	41.5
45-64 y	31.8	33.3	36.7	48.5	33.9
65 + y	18.8	16.6	12.0	15.7	10.9
Marital status					
Married	50.1	54.3	57.9	62.9	56.7
Divorced	8.3	7.3	7.2	11.9	6.3
Widowed	8.1	6.9	4.3	5.1	4.1
Never married	33.5	31.5	30.6	20.1	33.0
No. respondents	5912	3649	2242	394	1824

*Individuals with an earlier or present cancer diagnosis are excluded.

© 2010 Lippincott Williams & Wilkins

TABLE 2. Incidence Rate per 1000 Person-years and Odds Ratios Regarding Potential Risk Factors for the Development of Chronic Pain Among Individuals With No Chronic Pain at Baseline

	Incidence/1000 y	OR	95% CI	No. Respondents
Total	26.9			1800
Gender				
Men	26.8	1.00	(0.74-1.34)	867
Women	27.0	1		933
Age*				
16-24 y	14.3	0.39	(0.19-0.79)	247
25-44 y	25.1	0.89	(0.62-1.26)	754
45-64 y	34.7	1		608
65 + y	26.8	0.64	(0.38-1.08)	191
Combined school and vocational education*				
≤ 10 y	33.9	1.42	(0.92-2.18)	294
11-12 y	34.5	1.51	(1.02-2.23)	397
13-14 y	24.4	1		627
≥ 15 y	18.7	0.77	(0.51-1.17)	448
In school, other	32.0			27
Marital status				
Married	28.9	1		1010
Cohabiting	22.4	0.94	(0.61-1.47)	311
Single (divorced, separated, widowed)	35.8	1.12	(0.67-1.85)	152
Single (unmarried)	20.4	0.95	(0.57-1.57)	320
Self-rated health*				
Really good/good	24.3	1		1651
Fair/bad/very bad	58.5	2.45	(1.62-3.71)	149
BMI				
< 25	23.9	1		1071
25-30	27.8	0.98	(0.70-1.37)	562
> 30	47.1	1.69	(1.07-2.66)	152

*$P < 0.05$.

Individuals with high physical strain at work had 1.65 (95% CI: 1.07-2.56) higher odds for developing chronic pain in the follow-up period than individuals with low physical strain at work (Table 4). Moreover, individuals reporting to work while bent over or in a twisted position more than 2 times a week were more likely to develop pain in the follow-up period (OR: 1.70; 95% CI: 1.19-2.41) than individuals working while bent over or in a twisted position less than 3 times a week.

Age-adjusted SF-36 mean scores according to chronic pain status and use of opioids in 2000 are shown in Figure 3. The figure shows that individuals without chronic pain at baseline have the highest mean score in all the 8 subscales. Individuals with chronic pain and taking strong opioids in 2000 have the lowest mean scores in each domain, indicating a poor physical and mental health-related quality of life.

DISCUSSION

Randomized controlled studies of long-term opioid treatment in chronic noncancer pain patients are generally

TABLE 3. Incidence Rate per 1000 Person-years and Odds Ratios for Recovery From Chronic Pain Among Individuals With Chronic Pain at Baseline

	Incidence/1000 y	OR*	95% CI	No. Respondents
Physical strain of main occupation				
Low	20.9	1		454
Medium	29.8	1.48	(0.95-2.30)	346
High	36.8	1.65	(1.07-2.56)	392
More than 2 times a week exposed to:				
Working while bent over or in a twisted position†				
Yes	38.6	1.70	(1.19-2.41)	420
No	22.9	1		793
Repetitive motion				
Yes	29.8	1.03	(0.71-1.48)	418
No	27.4	1		795
Heavy objects (at least 10 kg) to be carried or lifted				
Yes	35.8	1.37	(0.95-1.98)	420
No	24.3	1		793

*Adjusted for the potential confunders gender, age, combined school and vocational education, BMI, and self-rated health.
†$P < 0.05$.

© 2010 Lippincott Williams & Wilkins

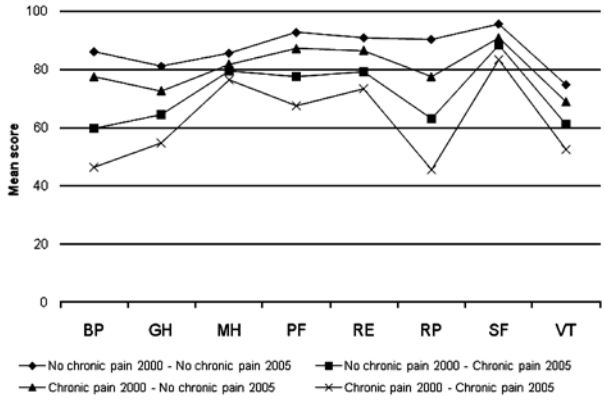

FIGURE 2. Age-adjusted SF-36 mean scores at follow-up (2005) according to chronic pain status at baseline (2000) and follow-up (2005).

of short duration[22] and long-term follow-up studies are few and often carried out in meticulously selected patients.[15,16] Although these studies have mainly positive outcomes the experience outside the frames of carefully controlled and time-limited studies has not been entirely positive, and the limitations of current evidence in terms of assessing the consequences of the extensive and liberal use of opioids in noncancer pain seem to be critical.[17] Furthermore, one must question if the controlled randomized trial is the optimal form of evidence for assessing opioid treatment of chronic noncancer pain given the artificiality of the trial setting, the tendency of trials to select "ideal" patients, and the lack of generalizability to the general population that is being treated outside trials. To assess the consequences and the broader role of liberal opioid consumption in western societies, attention must be given to different sources of information such as population-based studies.[2,18]

To our knowledge, very little data exist regarding opioid use and mortality in individuals with chronic noncancer pain. However, a 2000 to 2001 national survey from the US of medical examiners' reports of deaths attributable to prescription of oxycodone use[23] and a report from Utah[24] documenting a dramatic increase in accidental poisoning death owing to prescription opioids, are worrisome. Furthermore, a study in opioid dosing trends and motality from 1996 to 2002 in Washington State workers found that the general increase in opioid use and the shift from weaker to stronger opioids were associated with an increase in workers' deaths attributable to accidental overdose of prescription opioids.[10] These authors also speculate that the increase in opioid dosing could be ascribed to the development of pharmacologic tolerance or opioid-induced hyperalgesia. However, these data from the US may have little to do with the findings in our population-based cohort study and owing to latency of the Danish Causes of Death Registry, the causes of death

TABLE 4. Incidence Rate Per 1000 Person-years and the Results of Multiple Logistic Regression Analyses Showing Odds Ratios for Potential Work-related Physical Risk Factors of Chronic Pain Development Among Actively Employed 16-64 y Old

	Incidence/1000 y	OR	95% CI	No. Respondents
Total	94.2			383
Sex				
Men	102.0	1.02	(0.63-1.65)	155
Women	89.0	1		228
Age				
16-24 y	190.5	2.56	(0.88-7.50)	31
25-44 y	94.8	1.56	(0.86-2.81)	107
45-64 y	76.9	1		186
65+ y	107.5	1.54	(0.78-3.03)	59
Combined school and vocational education				
≤10 y	94.3	0.97	(0.51-1.87)	97
11-12 y	76.8	0.90	(0.48-1.66)	121
13-14 y	93.4	1		103
≥15 y	133.3	1.51	(0.73-3.11)	58
In school, other	—			3
Marital status				
Married	88.8	1		234
Cohabiting	101.0	0.84	(0.42-1.67)	62
Single (divorced, separated, widowed)	60.0	0.75	(0.35-1.62)	46
Single (unmarried)	171.4	1.54	(0.65-3.69)	40
Self-rated health*				
Really good/good	144.2	1		183
Fair/bad/very bad	55.8	0.32	(0.20-0.50)	200
BMI				
<25	94.8	1		201
25-30	86.2	0.98	(0.59-1.63)	141
≥30	115.3	1.60	(0.73-3.49)	38
Use of opioids*				
Yes	24.7	1		43
No	104.6	3.97	(1.43-11.02)	340

*$P < 0.05$.
BMI indicates body mass index.

© 2010 Lippincott Williams & Wilkins

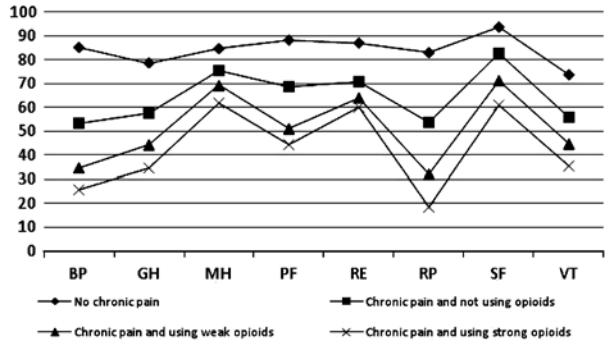

FIGURE 3. Age-adjusted SF-36 mean scores at baseline according to chronic pain status and the use of opioids in 2000.

are not yet available for this study. Thus, we can only speculate that some of the long-term consequences of opioid use may be involved. Addiction, opioid-induced hyperalgesia, and cognitive dysfunction may cause depressed mood and poor judgement involving suicide and hazards, and dysfunction of the immune and reproductive systems may course increased morbidity and mortality for example owing to infections.[4,5,7–9] However, accidental overdosing may also be among the death causes in our study.

Furthermore, our study also indicated that chronic pain itself may increase mortality (Fig. 1). During a 12-years follow-up population study from the south of Sweden, a significantly increased mortality was found in individuals with widespread chronic noncancer pain.[25] Similar to our study, the causes of death could not be elucidated in the Swedish study, but the authors suggested that the influence of distress and pain on the immune system may be the cause.[25] Finally, in our study and in the other studies, chronic pain and opioids may likely be involved in some of the covariates we adjusted for in the statistical model for example high BMI, smoking behavior, self-reported circulatory diseases, infectious and parasitic diseases, diabetes, and mental disorders.[26]

We have no ready explanation for the finding that the so called weak opioids (in Denmark: tramadol, codeine, and dextropropoxyphene) superimposed on chronic pain did not contribute to increased mortality (Fig. 1). On the basis of the study by Franklin et al,[10] it could be speculated that development of tolerance/opioid-induced hyperalgesia and other potential consequences owing to dose increase have been limited in this group and some of the benefits of improved analgesia may be preserved. However, further research is needed in this area.

Prospective, longitudinal studies are mandatory to investigate the incidence and/or recovery rates of chronic pain in the general population to study the causes and effects of the chronic pain.[19,27–31] Most of the studies have a limited number of participants and have almost always followed persons reporting pain at baseline. Few studies have estimated the numbers of new or recovered cases of chronic pain.[19,31] In this study, we found an average annual incidence rate for developing chronic pain of approximately 2.7%, which is slightly higher than the annual incidence we formerly have reported from 1994 to 2000 in the Danish population.[19] However, in this survey, the incidence rate is considered more accurate and reliable than the former, as it was based on the very same questions regarding chronic pain in 2000 and 2005. In the survey 1994 to 2000, the pain intensity verbal rating scale (with the recall period of 4 weeks included in the SF-36) was used to identify chronic pain.[19]

The estimated annual incidence recovery rate from chronic pain was 9.4%/year. We have formerly reported a somewhat lower annual pain recovery incidence rate of 8.7%, however, the abovementioned limitations of the earlier study should be taken into account.[19] A noteworthy finding of this survey is that the odds of recovery from chronic pain was 4-fold decreased in individuals using opioids, and, in contrast to earlier cross-sectional studies from our research group,[2,17] causality could be established in this cohort study.

In accordance with the former surveys by our research group, we found that high age, short education, poor self-rated health, and high BMI were predictors of chronic pain.[2,19] However, in contrast to earlier surveys by our group and others, we could not identify the female gender and marital status as predictors of pain.[19,25] Other investigators have reported that psychological distress is strong predictor of chronic pain.[28,32] Owing to the investigational design, associations between psychological distress and chronic pain could not be evaluated in this survey.

In a cross-sectional study by Eriksen et al,[2] it was shown, that high physical job strain was associated with reporting of long-term/chronic pain. However, neither physical strain of job nor heavy workload was found to be significant predictors for development of or recovery from chronic pain.[19] In this survey, more detailed questions regarding the impact of physical strain at work indicated that high physical strain at work predicted development of chronic pain (Table 4). Furthermore, health-related quality of life as measured by SF-36 was reduced most severely in those individuals suffering from chronic pain during the entire period (Fig. 2).

A major strength of this study is that it is based on large national representative survey with an adequate response rate. However, nonresponders may pose problems in all studies based on survey data. Hence, we compared mortality rates among responders and nonresponders in the baseline survey in 2000. We found a lower mortality rate among responders (12.8 per 1000 person-years) than among nonresponders (19.8 per 1000 person-years). Furthermore, we found that the elderly were more likely to be lost at follow-up than younger individuals in the questionnaire follow-up study. These findings were as expected and there is no indication that nonresponse has seriously biased the results of this study. It may be argued that self-reporting of opioid use may be unreliable, however, a recent study, based on data from the Danish Health Interview Survey in 2000, showed a good agreement (Cohen κ value: 0.62; 95% CI: 0.58-0.67) between self-reported use of opioids and national prescription records.[33] A κ value between 0.61 and 0.80 indicates a good agreement.[34]

In conclusion, the annual incidence for development of and recovery from chronic pain was 2.7% and 9.4%, respectively. Increasing age up to 64 years, short education, poor self-rated health, high BMI, and physical strain at work were predictors of chronic pain. The odds of recovery from chronic pain were almost 4 times higher among individuals not using opioids compared with individuals using opioids. Furthermore, chronic pain and use of strong opioids was associated with poor health-related quality of life (both physical and mental). In addition, chronic pain

 © 2010 Lippincott Williams & Wilkins

and strong opioid use seem to be a risk factor for mortality, although this study cannot exclude disease severity as the primary cause of increased mortality.

REFERENCES

1. Joranson DE, Ryan KM, Gilson AM, et al. Use, trends in medical use and abuse of opioid analgesics. *JAMA*. 2000;283:1710–1714.
2. Eriksen J, Jensen M, Sjøgren P, et al. Epidemiology of chronic non-malignant pain in Denmark. *Pain*. 2003;106:221–228.
3. Jarlbaek L, Andersen M, Kragstrup J, et al. Cancer patients' share in a population's use of opioids. A linkage study between a prescription database and the Danish Cancer Registry. *J Pain Symptom Manage*. 2004;27:36–43.
4. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain*. 2007;20:451–455.
5. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain*. 2002;100:213–217.
6. Ballentyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943–1953.
7. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression. A review. *Am J Ther*. 2004;11:354–365.
8. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to morphine. *Cancer*. 2004;100:851–858.
9. Sjøgren P, Christrup LL, Petersen MA, et al. Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. *Eur J Pain*. 2005;9:453–462.
10. Franklin GM, Mai J, Wickizer T, et al. Opioid dosing trends and mortality in Washington State Workers' Compensation, 1996-2002. *Am J Industrial Med*. 2005;48:91–99.
11. Kalso E, Allan L, Dellemijn PLI, et al. Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain*. 2003;7:381–386.
12. The Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain. A consensus statement prepared on behalf of the Pain Society, the Royal College of Anaesthetists, the Royal College of General Practitioners and the Royal College of Psychiatrists. March 2004. *www.britishpainsociety.org/pdf/opioids*_doc_2004.pdf
13. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain Physician*. 2008;11:5–62.
14. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10:113–130.
15. Jensen MK, Thomsen AB, Højsted J. 10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization. *Eur J Pain*. 2006;10:423–433.
16. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23:287–299.
17. Eriksen J, Sjøgren P, Bruera E, et al. Critical issues on opioids in chronic non-malignant pain: an epidemiological study. *Pain*. 2006;125:172–179.
18. Ekholm O, Hesse U, Davidsen M, et al. The study design and characteristics of the Danish national health interview surveys. *Scand J Public Health*. 2009;37:758–765.
19. Eriksen J, Ekholm O, Sjøgren P, et al. Development of and recovery from long-term pain. A 6-year follow-up study of a cross-section of the adult Danish population. *Pain*. 2004;108:154–162.
20. Ware JE, Snow KK, Kosinski M, et al. *SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: New England Medical Center, The Health Institute; 1993.
21. Bjørner JB, Thunedborg K, Kristensen TS, et al. The Danish SF-36 health survey: translation and preliminary validity studies. *J Clin Epidemiol*. 1998;51:991–999.
22. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–380.
23. US Department of Justice, 2002. Drug Enforcement Agency. Summary of medical examiners reports on oxycodone-related deaths, May 16. http://www.deadiversion.usdoj.gov/drugs_concern/oxycodone/oxycodone.htm.
24. Caravati EM, Grey T, Nangle BRT, et al. Increase in poisoning deaths caused by non-illicit drugs-Utah, 1991-2003. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5402a1.htm. Accessed January 21, 2005.
25. Andersson HI. The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. *Eur J Pain*. 2004;8:47–53.
26. Zhu K, Devine A, Dick IM, et al. Association of back pain frequency with mortality, coronay heart events, mobility, and quality of life in elderly women. *Spine*. 2007;32:2012–2018.
27. Waxman R, Tennant A, Helliwell P. A prospective follow-up study of low back pain in the community. *Spine*. 2000;25:2085–2090.
28. Croft PR, Lewis M, Papageorgiou AC, et al. Risk factors for neck pain: a longitudinal study in the general population. *Pain*. 2001;93:317–325.
29. McBeth J, Macfarlane GJ, Hunt IM, et al. Risk factors for persistent chronic widespread pain: a community-based study. *Rheumatology*. 2001;40:95–101.
30. Bergman S, Herrström P, Jacobsson LTH, et al. Chronic widespread pain: a three year follow-up of pain distribution and risk factors. *J Rheumatol*. 2002;29:818–825.
31. Elliott AM, Smith BH, Hannaford PC, et al. The course of chronic pain in the community: results of a 4-years follow-up study. *Pain*. 2002;99:299–307.
32. Croft PR, Papageorgiou AC, Ferry S, et al. Psychological distress and low back pain: evidence from a prospective study in the general population. *Spine*. 1995;20:2731–2737.
33. Nielsen MW, Søndergaard B, Kjøller M, et al. Agreement between self-reported data on medicine use and prescription records vary according to method of analysis and therapeutic group. *J Clin Epidemiol*. 2008;61:919–924.
34. Altman DG. *Practical Statistics for Medical Research*. London: Chapman & Hall; 1991.

© 2010 Lippincott Williams & Wilkins