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# Chronic pain, opioid prescriptions, and mortality in Denmark: A population-based cohort study

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ABSTRACT

This study aimed to investigate the risk of death, development of cancer, and hospital inpatient admissions resulting from injuries and toxicity/poisoning among opioid users with chronic noncancer pain. A population-based cohort of 13,127 adults, who have participated in the Danish Health Interview Surveys in 2000 or 2005 and have been followed up prospectively by registers until the end of 2011, were classified according to the absence or presence of chronic pain (ie, pain lasting ⩾6 months) and long-term or short-term opioid use (individuals using at least 1 prescription per month for 6 months in the previous year and at least 1 prescription in the previous year, respectively). The risk of all-cause mortality was 1.72 (95% confidence interval [CI] = 1.23–2.41) times higher among long-term opioid users than among individuals without chronic pain. The risk of death was lower, but still significantly higher in short-term (1.36, 95% CI = 1.07–1.72) and non-opioid users with chronic pain (1.39, 95% CI = 1.22–1.59) than in the background population. There was no statistically significant association between long-term opioid use and cardiovascular and cancer mortality. No deaths among opioid users were caused by accidents or suicides, although opioid users had higher risks of injuries and toxicity/poisoning resulting in hospital inpatient admissions than individuals without chronic pain. The risk of all-cause mortality was significantly higher among long-term opioid users, but no obvious associations between long-term opioid use and cause-specific mortality were observed. However, opioid use increased the risk of injuries and toxicity/poisoning resulting in hospital inpatient admissions.



## 1. Introduction

In the last 2 decades, a startling increase in opioid prescribing for chronic noncancer pain has been observed in western countries, despite the lack of strong evidence that opioids are effective for providing analgesia and for improving functional capacity and quality of life [14]. Epidemiological data from the United States and Denmark have shown that 3% to 5% of the populations use opioids regularly for treatment of chronic pain [11,23,36]. The widespread prescription of opioids for chronic noncancer pain has raised concerns about long-term side effects derived from dysfunction of endocrine and immune systems, accidents related to opioid overdosing, opioid addiction, and diversion [2,6,12]. Following these potential serious consequences of opioid consumption, death causes have also been investigated. In the United States (from 1999 to 2010), the number of dispensed opioid prescriptions doubled (120 million to 210 million), and annual deaths related to opioid overdoses were quadrupled (from 4030 to 16,651) [5]. These figures reveal an indisputable parallel increase in the consumption of prescription opioids and opioid-related deaths (ORD).

Many studies have been focused on ORD in general, based on national (or regional/state) statistics and post-mortem studies. Inferences regarding the connection between opioid prescription and risk of overdose have been derived from retrospective case-control studies and epidemiologic investigations, in which sample selection bias and ecological fallacy may have played a role [24,27]. A large-scale epidemiologic cohort study assessing associations between medically prescribed opioid therapy and opioid-related overdose in chronic noncancer patients has been conducted,

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demonstrating increased risk for overdose in patients receiving medically prescribed opioids at higher doses [9]. However, ORD in a population-based cohort of chronic noncancer pain patients receiving medically prescribed opioids have been identified only in a prior study by our group [33].

Therefore the objective of this population-based cohort study was to investigate the association between mortality and long- and short-term prescribed opioids among patients with chronic noncancer pain. In addition, the aim was to determine the risk of cancer and hospital admissions due to injuries and toxicity/poisoning among opioid users with chronic noncancer pain.

## 2. Methods

The present prospective survey was retrieved from pooled data from the Danish Health and Morbidity surveys from 2000 and 2005 [8,10], which in turn were combined with data from official Danish health care statistics and socioeconomic registers. The survey was approved by the Danish Data Protection Agency.

The survey from 2000 consisted of a county-stratified random sample of 16,684 individuals. The sample was supplemented with a sample from Frederiksborg County (n = 612). Thus, the total sample size in 2000 was 17,296 Danish citizens. The survey from 2005 consisted of a region-stratified random sample of 10,916 Danish citizens. The 2 samples were drawn randomly from the adult (16 years or older) Danish population (including institutionalized individuals) using the Danish Civil Registration System (each citizen has a unique personal registration number) [30]. The Danish Civil Registration System was also used to retrieve information on vital statistics and the date of potential changes of vital status. Observation intervals were calculated from the interview date until death, emigration, or December 31. 2011 (end of follow-up).

All selected individuals received a letter that explained the purpose of the survey and emphasized that participation was voluntary. Data were collected at the respondent's home by a face-to-face interview and a self-administered questionnaire. Details of survey design are described elsewhere [10].

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 in both surveys. On an individual level, information of dispensed opioids was drawn from the Danish National Prescription Registry [22]. Opioids were further classified by the Anatomical Therapeutic Chemical (ATC) Classification System using the following codes: N02A, N02BE51, N02BA51, and R05DA04. Long-term users were classified as individuals who, in the previous year, have used at least 1 prescription/month for 6 months. Short-term opioid users were classified as individuals who, in the previous year, have used at least 1 prescription (and were not defined as long-term users). This definition has been suggested by the Danish Health and Medicines Authority. Death date and the underlying cause of death were retrieved from the Danish Register of Causes of Death [19]. Furthermore, ICD-10 was used to identify deaths due to, for example, malignant neoplasm (codes C00–D09), cardiovascular diseases (codes I00–I99), suicides (codes X60–X84 and Y870), and diseases of the respiratory system (codes J00–J99). Furthermore, cancer cases (codes C00–D09 excluding C44) were obtained from the Danish National Patient Register [26]. Finally, this register was used to retrieve data on hospital (inpatient) admissions resulting from the following categories: (1) injury, toxicity/poisoning, and certain other consequences of external causes (codes S00–T75); and (2) toxicity/poisoning by drugs, medications, and biological substances (codes T36–T50). All patients admitted to Danish hospitals are registered in The Danish National Patient Register.

The 17-item Charlson Comorbidity Index was used to adjust for comorbidity [7]. The Danish National Patient Register was used to identify the first-listed diagnoses for all hospital contacts in the year preceding the survey [26].

The respondents' highest education level was retrieved from the Population Education Register [21]. Education was further categorized into 3 categories: basic school, upper secondary or vocational school, and higher education.

The respondents' smoking behavior was assessed by asking them whether they smoked or not. Those respondents smoking on a daily basis were asked how many cigarettes they smoked per day on average. Thus, smoking behavior was categorized into heavy smokers (15 or more cigarettes per day); daily smokers (1–14 cigarettes per day); occasional smokers; and nonsmokers.

The respondents' alcohol intake was assessed by a beverage-specific question: "How many alcoholic drinks do you typically have each day in a week?" The alcohol intake was further assessed in number of standard drinks (a standard drink equals approximately 12 g, or 15 mL, of pure alcohol). High alcohol intake was defined as above the sensible drinking limits (21 drinks per week for men and 14 drinks per week for women) defined by the Danish National Board of Health.

The respondents' self-reported height and weight were used for calculating body mass index (BMI) (weight in kilograms divided by height in square meters).

For statistical analysis, the Cox proportional hazards model was used to assess the risk of death, development of cancer, and hospital admissions (due to injury, toxicity/poisoning, and certain other consequences of external causes and toxicity/poisoning by drugs, medications, and biological substances), respectively, and use of opioids adjusted for age, sex, education, cohabitation status, smoking behavior, alcohol intake, BMI, and Charlson Comorbidity Index. Age was used as the underlying time scale treating age at interview as the time of delayed entry. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard assumption was also checked graphically.

## 3. Results

In all, 10,650 individuals in 2000 and 5442 individuals in 2005 completed both the face-to-face interview and answered the question on chronic pain. However, the survey in 2005 consisted of both participants of the survey in 2000 and a new sample of adult Danes. Hence, respondents in 2005 who also participated in the survey in 2000 were excluded, leaving 3145 eligible individuals in 2005. Respondents with a self-reported cancer diagnosis or a cancer diagnosis (all malignant neoplasms excluding nonmelanoma skin cancer: ICD-10 C00–D09 excluding C44) recorded in the Danish National Patient Register [26] before baseline were excluded (n = 668). Thus, the final study population consisted of 13,127 individuals. The study population was further divided into 4 groups based on combined survey and register data: long-term opioid users with chronic pain (n = 167); short-term opioid users with chronic pain (n = 375); non-opioid users with chronic pain (n = 2015); and individuals without chronic pain and no opioid use (n = 10,570).

Basic characteristics of the study population are displayed in Table 1. The proportion of both long-term and short-term opioid users increased with increasing age. In addition, the proportion of individuals with chronic pain who were not using opioids (ie, non–opioid users) increased with increasing age. Furthermore, the prevalence of chronic pain was higher among women (22.0%) than among men (16.7%).

The risk of death was 1.72 (95% CI = 1.23–2.41) times higher among long-term opioid users than among individuals without chronic pain (Table 2). There was no difference in risk of death between short-term opioid users and non–opioid users with chronic pain; however, in both groups, the risk of death was higher than among individuals without chronic pain.