

Original Article

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Sex and age differences among tramadol users in three Nordic countries

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ABSTRACT

Introduction: The aim of this study was to examine the prevalence and characteristics of tramadol users in Denmark, Norway and Sweden.

Methods: Data from the national prescription databases comprising the entire population of Denmark, Norway and Sweden between 2007 and 2015 were used to assess prescription medicine use and sold amount (in defined daily doses (DDDs)) of tramadol, other opioids and non-steroidal anti-inflammatory drugs.

Results: From 2007 to 2015 the prevalence of tramadol users increased in Denmark from 45 to 52 per 1,000 residents, and in Norway from 20 to 41 per 1,000 residents. In Sweden, the prevalence decreased from 36 to 17 per 1,000 residents. In comparison, the prevalence of other opioid users decreased in Denmark and Norway, but increased in Sweden. During the study period, there were more female than male tramadol users in all three countries, and the prevalence of tramadol users tended to increase with age. The average tramadol DDD per treated patient remained fairly constant in Norway, while it increased in Denmark and Sweden. In Denmark and Norway, women received a higher DDD than men. The amount of sold tramadol and other opioids combined per 1,000 residents was highest in Denmark.

Conclusions: From 2007 to 2015, the prescription patterns of tramadol and other opioids differed between the three countries. Tramadol was generally used more frequently by women. Women received higher DDD than men in Norway and Denmark, but not in Sweden. The prevalence of tramadol users tended to increase with age in all countries.

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Tramadol is a synthetic opioid. Its metabolite O-desmethyltramadol binds opioid receptors with the highest affinity to the μ -opioid receptor. In addition to its opioid actions, tramadol inhibits the neuronal reuptake of noradrenaline and serotonin, which contributes to the analgesic action [1].

Concern has been voiced in Danish media regarding tramadol's addictive properties and the high prevalence of tramadol users [2, 3]. This has led the Danish Medicines Agency to include tramadol as a drug under stricter reporting requirement as from late 2017, as well as requiring tramadol to be subject to the same laws as other opioids traditionally considered to be strong opioids, as from the beginning of 2018 [4, 5].

A previous study found an increase in the prevalence of tramadol users in Denmark and Norway between 2007 and 2015, and a decrease in Sweden [6]. This study did not focus on sex and age differences among tramadol users. Even so, this is important to investigate as use among the elderly should be avoided [7].

To assess whether use of tramadol is a concern to public health, it is important to analyse utilisation patterns. In this population-based study, we examined and compared the prevalence and characteristics of tramadol users in primary healthcare in Denmark, Norway and Sweden between 2007 and 2015. The prevalence was compared with the use of other opioids and non-steroidal anti-inflammatory drugs (NSAIDs) to assess interactions in prescription patterns.

METHODS

The study cohort constitutes the entire population of Denmark, Norway and Sweden between 1 January 2007 and 31 December 2015, covering approximately 20.7 million inhabitants in 2015 [8-10].

Data sources

We used information from the three publicly available national prescription databases [11-13] including information on Anatomical Therapeutic Classification (ATC) codes, number of users, number of residents and defined daily doses (DDDs) per year. One DDD is the average maintenance dose per day and the measure can be used to identify differences between healthcare schemes. Each unique combination of drug and administration route is assigned a specific DDD, e.g., only considering the oral administration route, one DDD for tramadol is 300 mg, 100 mg for morphine and 75 mg for oxycodone.

The databases supply the information divided into regions or counties and stratified on age and sex. The databases include information on an individual level and from the primary sector only (i.e., redemptions made at community pharmacies).

Drugs included in the analysis

The ATC codes of tramadol (N02AX02) or tramadol and paracetamol (N02AJ13) were used to define the use of tramadol. For use of other opioids, we used the following ATC codes and subordinate levels: Natural opium alkaloids (N02AA), phenylpiperidine derivatives (N02AB), diphenylpropylamine derivatives (N02AC), benzomorphan derivatives (N02AD), oripavine derivatives (N02AE), morphinan derivatives (N02AF), opioids in combination with antispasmodics (N02AG), codeine and paracetamol (N02AJ06), codeine and acetylsalicylic acid (N02AJ07), codeine and ibuprofen (N02AJ08), codeine and other non-opioid analgesics (N02AJ09), tapentadol (N02AX06) or codeine (R05DA04). For NSAIDs, we used the following ATC codes and subordinate levels: Butylpyrazolidines (M01AA), acetic acid derivatives and related substances (M01AB), oxicams (M01AC), propionic acid derivatives (M01AE), fenamates (M01AG), coxibs (M01AH), nabumetone (M01AX01) and anti-inflammatory/antirheumatic agents in combination (M01B).

Data analysis

In the analyses of tramadol, we combined tramadol and combinations containing tramadol. In a separate analysis, we also investigated the proportions of tramadol sold alone or in combinations. All other opioids and NSAIDs described above were binned in two separate groups. Drug use was defined as one or more redeemed prescriptions in a given year. The prevalence was defined as the number of patients redeeming a prescription per 1,000 residents. The prevalence is presented for each country for the years 2007, 2011 and 2015. We used the same years to stratify the tramadol prevalence by age groups (0-4, 5-9, 10-14, 15-19, 20-39, 40-64, 65-79 and ≥ 80 years). The prevalence of male and female tramadol users was investigated for each year during the study period. Furthermore, we estimated the average DDD per 1,000 residents and per treated patient per year for each country.

The combination of codeine and acetylsalicylic acid (N02AJ07) is also sold over the counter (OTC),

but only in Denmark. We therefore applied the following two conditions: We included all sold DDDs of codeine and acetylsalicylic acid in the calculation of the average DDD per 1,000 residents, but only the proportion of codeine and acetylsalicylic acid in combination sold through a prescription when calculating average DDD per treated patient in Denmark.

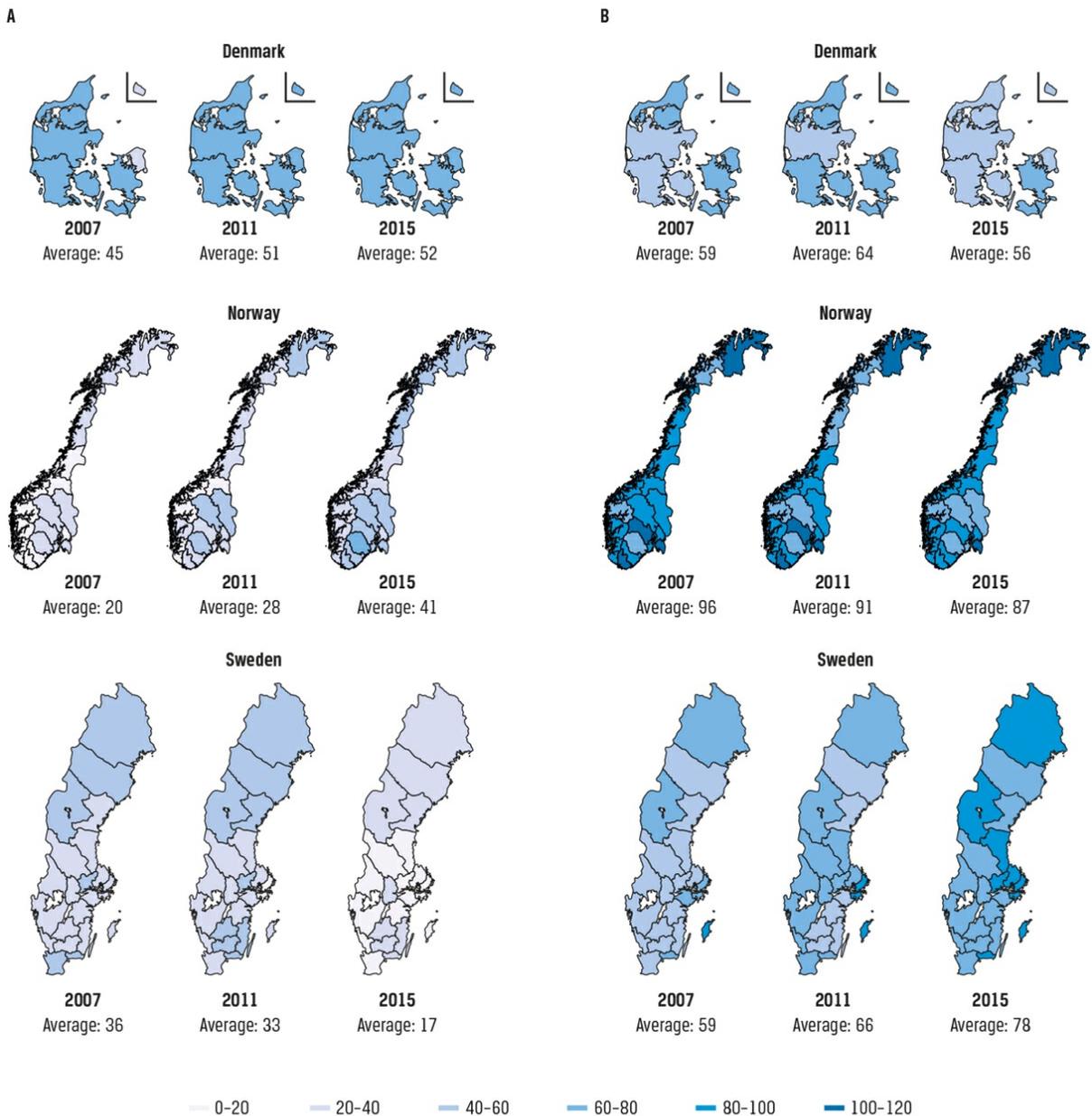
Trial registration: not relevant.

RESULTS

Tramadol use

Overall, the prevalence of users increased between 2007 and 2015 in Denmark from 45 to 52 per 1,000 residents, and in Norway from 20 to 41 per 1,000 residents, whereas the prevalence decreased in Sweden from 36 to 17 per 1,000 residents (**Figure 1A**).

FIGURE 1 / A. Prevalence of tramadol: number of patients redeeming a prescription per 1,000 residents, in Denmark, Norway, and Sweden in 2007, 2011, and 2015. B. Prevalence of other opioid users: number of patients redeeming a prescription per 1,000 residents, in Denmark, Norway, and Sweden in 2007, 2011, and 2015.



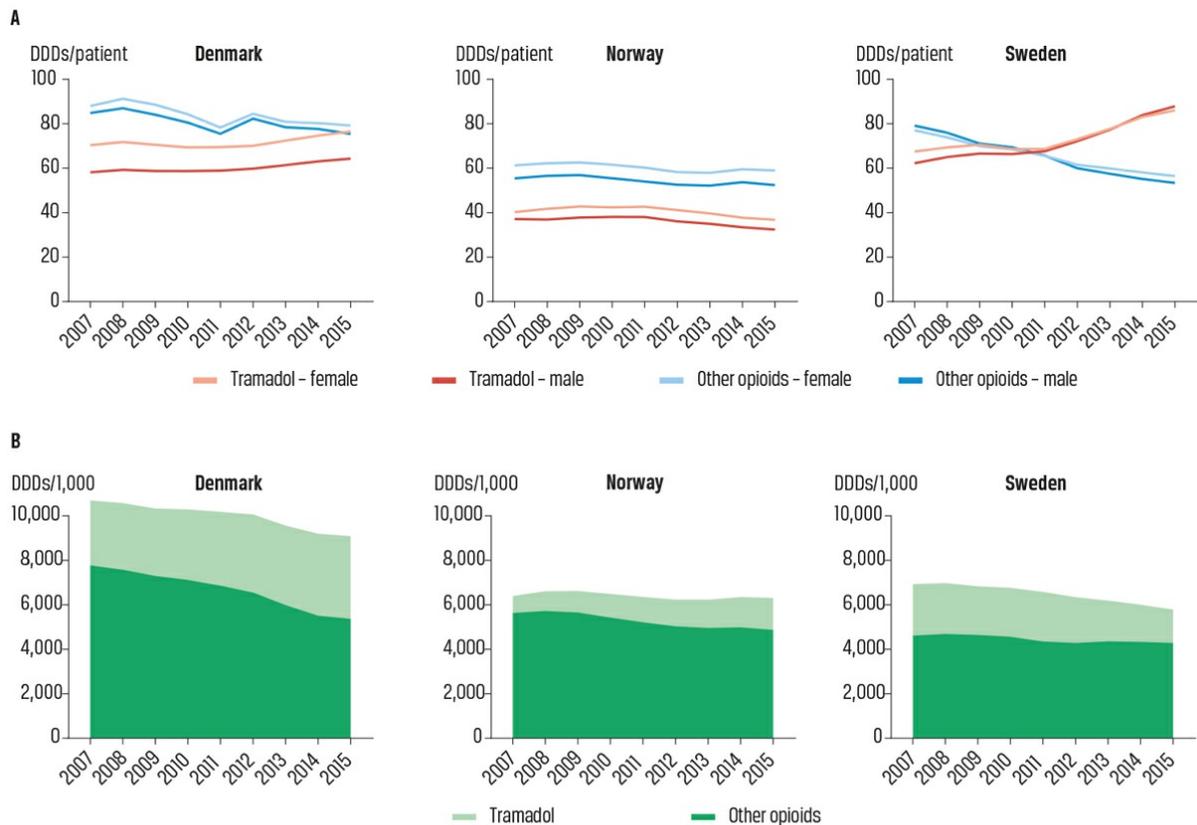
During the study period and in all three countries, there were more female than male users. The prevalence of users for both sexes increased during the study period in Denmark and Norway, but decreased in Sweden (Table 1).

TABLE 1 / Prevalence: number of patients redeeming a prescription per 1,000 residents, of tramadol users among males and females between 2007 and 2015 in Denmark, Norway, and Sweden.

Year	Denmark, n/1,000		Norway, n/1,000		Sweden, n/1,000	
	male	female	male	female	male	female
2007	37	52	15	24	31	40
2008	37	53	18	27	30	38
2009	38	54	19	29	28	35
2010	41	57	21	31	29	36
2011	43	59	23	33	29	37
2012	45	61	26	36	25	32
2013	45	61	28	40	21	27
2014	45	61	32	44	18	23
2015	44	60	35	48	15	20

The average DDD per treated patient for both sexes increased during the study period in Denmark and Sweden. In Norway, the average DDD per treated patient for both sexes remained fairly constant. In Denmark and Norway, women received a higher DDD than men, whereas the DDDs between sexes in Sweden were similar (Figure 2A).

FIGURE 2 / A. Defined daily doses (DDDs) per treated patient per year for tramadol and other opioids in Denmark, Norway, and Sweden between 2007 and 2015. B. DDDs per 1,000 residents per year for tramadol and other opioids in Denmark, Norway, and Sweden between 2007 and 2015.



The average sold amount of tramadol per 1,000 residents was consistently higher in Denmark than in Norway and Sweden. The average DDD per 1,000 residents increased in Denmark and Norway, whereas it decreased in Sweden (Figure 2B). Combinations of tramadol were only marketed in Norway and Sweden during the study period. We identified combinations of tramadol redeemed in Norway the last two years of the study period. During these two years, the majority of tramadol was sold as tramadol alone. Formulations consisting of tramadol alone accounted for 6,906,881 DDDs (99%) in 2014 and 7,241,348 DDDs (97%) in 2015. In Sweden, a single patient redeemed a combination of tramadol and paracetamol in 2015.

For all three countries in 2007, 2011 and 2015, the prevalence of users increased with age, except for Sweden in 2015, where the prevalence of users remained fairly steady among people aged 40 years and above. Among the elderly (≥ 65 years of age), considerable differences were observed in the prevalence of users between the three countries. In 2015, the prevalence of users among the elderly aged 80 years or above was two and six times higher in Denmark than in Norway and Sweden, respectively (Table 2).

TABLE 2 / Prevalence: number of patients redeeming a prescription per 1,000 residents, of tramadol users in 2007, 2011, and 2015 stratified on age groups in Denmark, Norway, and Sweden.

Age, yrs	Denmark, n/1,000			Norway, n/1,000			Sweden, n/1,000		
	2007	2011	2015	2007	2011	2015	2007	2011	2015
0-4	0	0	0	0	0	0	0	0	0
5-9	0	0	0	0	0	0	0	0	0
10-14	1	1	1	0	1	1	1	0	0
15-19	6	7	8	4	6	10	6	5	2
20-39	26	31	31	13	19	29	21	20	11
40-64	58	66	67	26	39	56	48	45	27
65-79	103	113	108	42	58	73	74	67	32
≥ 80	165	173	170	56	74	84	97	78	28

Use of other opioids

We observed different trends between the countries in the prevalence of patients using other opioids than tramadol. The prevalence decreased in Denmark from 59 to 56 per 1,000 residents and in Norway from 96 to 87 per 1,000 residents, while it increased in Sweden from 59 to 78 per 1,000 residents (Figure 1B).

The average DDD per treated patient decreased during the study period for both sexes in Denmark and Sweden, while it remained stable in Norway. In Denmark and Norway, women consistently received a higher DDD than men, whereas the sexes received close to the same DDD in Sweden (Figure 2A).

During the study period, the average sold amount per 1,000 residents decreased in Denmark and Norway, while it was stable in Sweden (Figure 2B). Combining the sold amount of all opioids, residents in Denmark redeemed more opioids per 1,000 residents than was the case in the other two countries.

Use of nonsteroidal anti-inflammatory drugs

The prevalence of NSAID users decreased during the study period in all three countries. Norway had the highest prevalence, followed by Denmark and Sweden. Between 2007 and 2015, the average DDD per 1,000 residents decreased in Denmark and Sweden, whereas it increased in Norway (Table 3).

TABLE 3 / Prevalence: number of patients redeeming a prescription per 1,000 residents, of non-steroidal anti-inflammatory drug users and defined daily dose (DDDs) per 1,000 residents between 2007 and 2015.

Year	Denmark	Norway	Sweden
<i>n/1,000</i>			
2007	161	195	133
2008	159	192	133
2009	150	185	130
2010	149	184	129
2011	146	185	128
2012	138	185	126
2013	134	179	120
2014	146	177	116
2015	146	177	114
<i>DDDs/1,000</i>			
2007	13,505	10,497	10,390
2008	13,652	10,417	10,513
2009	13,140	10,194	10,245
2010	13,213	10,253	10,019
2011	13,359	10,378	10,027
2012	13,139	10,888	10,126
2013	12,337	10,823	9,883
2014	11,717	10,918	9,558
2015	11,790	11,254	9,478

DISCUSSION

In this population-based cohort study, we observed a higher prevalence of tramadol users among women than among men in all three countries. It has previously been shown that women report

pain more often than men, and that women more frequently suffer from pain disorders such as migraine and fibromyalgia [14]. A recent Danish report concluded that a larger proportion of women than men has reported pain or discomfort within the past 14 days, and that they more often have consulted their general practitioner within the past 12 months [15]. These factors might explain why women more often than men were prescribed analgesics, including tramadol.

The prevalence of chronic pain conditions increases with age [16]. This is in agreement with the analgesic utilisation observed in our study, where the prevalence of tramadol users in general increased with age. However, other factors might also contribute to the observed pattern.

The prevalence of tramadol users was markedly lower among the elderly (≥ 65 years of age) in Sweden than in Denmark and Norway. During the study period, the National Board of Health and Welfare in Sweden published an updated guideline stating that tramadol should be avoided in the elderly due to a high risk of adverse drug reactions and an increased risk of clinically relevant drug interactions [17]. Our observations might reflect the Swedish physicians' compliance with this guideline.

Our findings regarding the prevalence of tramadol users during the study period are in line with a recently published study that reported a high prevalence of tramadol users in Denmark and Norway compared with Sweden in 2015 [6].

The increase in Denmark and Norway may possibly be attributed to a decrease in the number of other opioid users, and the decrease in Sweden might be explained by an increase in users of other opioids. Tramadol is commonly called a "weak" opioid, which may lower the barrier for initiating treatment with the drug [18]. However, since the active metabolite of tramadol has high affinity to the μ -opioid receptor, tramadol should not be classified as a weak opioid. Furthermore, caution against NSAID use might have led to an increase in tramadol use [18]. We observed a decrease in the prevalence of NSAID users in all three countries between 2007 and 2015. For Denmark and Norway, part of this decrease might be due to a shift from NSAIDs to tramadol.

Within many areas, the Scandinavian countries' healthcare legislation is rather similar. However, tramadol requires a special prescription in Norway and Sweden [19]. Until 1 January 2018, this was not the case in Denmark, where tramadol could be prescribed with a regular prescription. This circumstance might explain the higher prevalence of tramadol users observed in Denmark than in Norway and Sweden. With regards to Denmark, it would be of interest to conduct further studies to investigate whether changes in legislation will change Danish physicians' prescription patterns.

Despite the previously stated similarities between the Scandinavian countries, we observed that the amount of tramadol sold and all opioids combined (i.e., tramadol and all other opioids combined) per resident was markedly higher in Denmark than in the other two countries. We argue that the large differences at the population level alone are an incitement to investigate further the use of tramadol and opioid in general, and to assess the impact and possible health

consequences of the larger opioid use in one of three similar populations.

A major strength of this study includes access to national registries covering the entire population in all three countries. The healthcare systems of Denmark, Norway and Sweden are fairly similar [20], making comparisons of analgesic use between the countries feasible. A limitation of our study is that we are likely underestimating the number of DDDs per treated patient. This is due to the properties of the data exported from the national prescription databases. The data extracts contain the number of patients and DDDs sold for each ATC code, but since we cannot link patients from different ATC groups, we are likely overestimating the number of patients treated with the sum of the DDDs. The opposite applies to the prevalence estimations, as it is possible that individual patients redeemed prescriptions from different ATC groups within one of the three prespecified analgesic groups (tramadol, other opioids and NSAIDs) during our study period, resulting in an overestimation of the prevalence. Furthermore, NSAIDs and combinations of codeine and acetylsalicylic acid are also available OTC, and we therefore cannot estimate the number of patients obtaining these types of medications. Lastly, our study did not investigate the use of other analgesics, such as paracetamol, gabapentinoids or tricyclic antidepressants, and an exposure switch to these analgesics cannot be excluded.

CONCLUSIONS

The prevalence of tramadol users was higher among women than among men; and in Denmark and Norway, women received a higher DDD than men. During the study period, there was a trend in all three countries that the prevalence of tramadol users increased with age. Between 2007 and 2015, the prevalence of tramadol users increased in Denmark and Norway whereas it decreased in Sweden. The changes might be explained, in part, by shifts between analgesics.

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LITERATURE

1. World Health Organization. Tramadol update review report. Expert Committee on Drug Dependence. 2017. www.who.int/medicines/access/controlled-substances/PreReview_Tramadol.pdf?ua=1 (4 Jan 2020).
2. Morfinpillens skyggeside | DRTV. www.dr.dk/tv/se/afhaengighed-morfin-1-dr2dokumentar-2017/morfinpillens-skyggeside/danskere-fanget-i-pille-helvede (6 May 2019).
3. Læger advarer mod populær smertepille: Du kan blive afhængig. www.dr.dk/nyheder/indland/laeger-advarer-mod-populaer-smertepille-du-kan-blive-afhaengig (6 May 2019).
4. Danish Medicines Agency. Stricter reporting requirements.

<https://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-from-medicines/medicines-with-stricter-reporting-requirements/> (4 Oct 2017).

5. Tramadol og andre opioider ændrer udleveringsstatus. www.sst.dk/da/nyheder/2017/tramadol-og-andre-opioider-aendrer-udleveringsstatus (22 Oct 2018).
6. Muller AE, Clausen T, Sjøgren P et al. Prescribed opioid analgesic use developments in three Nordic countries, 2006-2017. *Scand J Pain* 2019;19:345-53.
7. . Hovstadius B, Petersson G, Hellström L et al. Trends in inappropriate drug therapy prescription in the elderly in Sweden from 2006 to 2013: assessment using national indicators. *Drugs Aging* 2014;31:379-86.
8. . Danmarks Statistik. Statistikbanken. www.statistikbanken.dk/10021 (10 Jan 2019).
9. . Folkmängden efter region, civilstånd, ålder och kön. År 1968 - 2017. Statistikdatabasen. www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__BE__BE0101__BE0101A/BefolkningNy/ (10 Jan 2019).
10. . Statistisk sentralbyrå Statistics Norway. Fakta om befolkningen. www.ssb.no/befolkning/faktaside/befolkningen. (10 Jan 2020).
11. . Sundhedsdatastyrelsen - statistikker. www.medstat.dk/ (20 Dec 2018).
12. . The Norwegian Institute of Public Health (NIPH). Norwegian prescription database. www.norpd.no/ (2 Aug 2017).
13. . Socialstyrelsen. Statistikdatabas för läkemedel. www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel (2 Aug 2017).
14. . Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *Br J Anaesth* 2013;111:52-8.
15. Danish Health Authority. Danskernes sundhed - den nationale sundhedsprofil 2017. Version: 1.0. Copenhagen: Danish Health Authority, 2017.
16. Tsang A, Von Korff M, Lee S et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain* 2008;9:883-91.
17. Socialstyrelsen. Indikatorer för god läkemedelsterapi hos äldre. Stockholm: Socialstyrelsen, 2010.
18. Christrup L, Sædder EA. Potential pharmacological consequences of the development of the opioid consumption in Denmark. *Ugeskr Læger* 2017; 179:V01170077.
19. Hamunen K, Paakkari P, Kalso E. Trends in opioid consumption in the Nordic countries 2002-2006. *Eur J Pain* 2009;13:954-62.
20. Holm S, Liss PE, Norheim OF. Access to health care in the Scandinavian countries: ethical aspects. *Health Care Anal* 1999;7:321-30.