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# Long term time trends in use of medications associated with risk of developing osteoporosis: Nationwide data for Denmark from 1999 to 2016

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ABSTRACT

*Purpose:* To evaluate the development in the use of medications associated with an increased risk of developing osteoporosis over the time period from 1999 to 2016.

*Methods:* We extracted data on total sale, sales rate and usage rate for the medications of interest from www.medstat.dk, which is an online, open-source database reporting the monthly sale of both over-the-counter and prescription-based medications in Denmark. The dataset covers both the primary and secondary health sectors.

*Results:* Most medications exhibited an increasing use from 1999 to 2016, though some had stable (e.g. glucocorticoids) or declining use. Notably, some medications showed widespread and increasing use, including proton pump inhibitors (PPI), selective serotonine reuptake inhibitors (SSRI) and venlafaxine. For PPI, sales rates increased by 461% from 1999 to 2016, with 9% of men and 11.4% of women filling at least one prescription in 2016. The use of SSRI and venlafaxine increased by 114% and 613%, respectively. This was more pronounced in women and for SSRI also in the elderly (80+ years). The sale of aromatase inhibitors was moderate (1–10 DDD per 1000 capita per day) in 2016, yet grew by 2400% from 1999, almost exclusively in women aged 80 years or older.

*Conclusion:* We found a trend of increasing use from 1999 to 2016 of most medications with a potential for causing osteoporosis, often most pronounced in fracture risk groups (postmenopausal women and/or in the elderly). This may play a clinically relevant role in both current and future causality of osteoporosis.

## 1. Introduction

Osteoporosis is characterized by low bone mass and micro-architectural changes. Clinically it manifests itself mainly with femoral, pelvic, humeral, antebrachial, and vertebral low energy fractures. However, fractures at any other skeletal sites may also be sustained and patients with osteoporosis are also at increased risk of high energy fractures [1].

In recent years, hip fracture incidence has shown a declining trend across Europe, initially in women and later in men [2]. However, in Sweden and Denmark some of the decrease in hip fracture rates appears to be a temporary respite due to a particularly low rate of hip fractures in persons born in the 1930's with high overall incidence rates in subsequent generations [3].

In addition to certain chemicals and different systemic diseases - many of which exhibit significant time trends – some medications can be a potential cause of secondary osteoporosis and of injurious falls and fractures [4]. For example, one study demonstrated that 30–50% of patients treated with glucocorticoids developed bone fractures on treatment [5]. Likewise, a meta-analysis recently demonstrated a significantly increased risk of hip and vertebral fractures with proton pump inhibitor therapy, with some studies suggesting a dose-dependent relationship [6,7]. Similarly, selective serotonin reuptake inhibitor (SSRI) therapy is associated with accelerated bone loss and increased fracture risk [8–10].

In this study, we aimed to assess temporal trends in the use of medications associated with an increased risk of osteoporosis and osteoporotic fractures for the time period from 1999 to 2016. Specifically, we wanted to identify risk medications with an inclining use in the age groups subject to the largest osteoporotic fracture burden. Hence, it would be a concern to find widespread and fast increasing use of risk medications in the oldest age groups while rare and fast disappearing drug exposures in the youngest patients would be of low clinical concern.

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**Table 1**
Usage rate and sale in 1999 and 2016. The table displays the usage rate per 1000 capita in 1999 and 2016; the total sale (DDD) for both genders and all age groups (including below 40 years) in 1999 and 2016; the sale (DDD) per 1000 capita per day for both genders and all age groups in 1999 and 2016; and the relative change in sale per 1000 capita per day between 1999 and 2016.

| | Usage rate per 1000 capita | | Total sale (DDD) | | Sale per 1000 capita (DDD) per day | | Relative change in sale per 1000 capita per day from 1999 to 2016 (%) |
|---|---|---|---|---|---|---|---|
| | 1999 | 2016 | 1999 | 2016 | 1999 | 2016 | |
| High and increasing use | | | | | | | |
| Proton pump inhibitors | 32.2 | 102.4 | 23,044 | 139,143 | 11.9 | 66.8 | 461 |
| SSRI | 31.1 | 43.6 | 42,945 | 98,387 | 22.1 | 47.2 | 114 |
| Venlafaxine | 2.6 | 9.1 | 3025 | 23,700 | 1.6 | 11.4 | 613 |
| High and stable use | | | | | | | |
| Glucocorticoids | 31.6 | 29.8 | 24,625 | 28,231 | 12.7 | 13.6 | 7 |
| Moderate and increasing use | | | | | | | |
| Warfarin | 5.2 | 14.5 | 4661 | 16,542 | 2.4 | 7.9 | 229 |
| Duloxetine[a] | 0.0 | 4.5 | 0 | 7659 | 0.0 | 3.7 | N/A |
| Methotrexate | 0.0 | 0.0 | 2007 | 7665 | 1.0 | 3.7 | 270 |
| Aromatase inhibitors | 0.0 | 0.2 | 231 | 5158 | 0.1 | 2.5 | 2400 |
| GNRH agonists | 0.4 | 0.5 | 575 | 3835 | 0.3 | 1.8 | 500 |
| Valproate | 2.4 | 2.7 | 2689 | 3457 | 1.4 | 1.7 | 21 |
| Low but increasing use | | | | | | | |
| Calcineurin inhibitors | 0.1 | 0.0 | 846 | 1312 | 0.4 | 0.6 | 50 |
| Low and stable use | | | | | | | |
| Heparin | 0.0 | 0.0 | 351 | 358 | 0.2 | 0.2 | 0 |
| Thiazolidinediones[b] | 0.0 | 0.0 | 0 | 19 | 0.0 | 0.0 | N/A |
| Cyclophosphamide | 0.1 | 0.0 | 18 | 23 | 0.0 | 0.0 | N/A |
| Low and decreasing use | | | | | | | |
| Carbamazepine | 3.8 | 1.5 | 3867 | 1817 | 2.0 | 0.9 | −55 |
| Phenobarbital | 1.6 | 0.3 | 2589 | 632 | 1.3 | 0.3 | −77 |
| Phenytoin | 0.6 | 0.0 | 855 | 1 | 0.4 | 0.0 | −100 |

Low use is defined as a sale per 1000 capita per day below 1 DDD in 2016, moderate use as a sale per 1000 capita per day of 1–10 DDD in 2016, and high use as a sale per 1000 capita per day above 10 DDD in 2016. Stable use is defined as a relative change from 1999 to 2016 of −10% to +10%. Decreasing use is a change of less than −10%, while increasing use is a change of more than +10%.

[a] Initial usage rate = year 2004.

[b] Initial usage rate = year 2000.

## 2. Methods

In Denmark it is compulsory to report the sale of medications to the National Medicines Statistics Register managed by the National Health Data Board. All retailers – including pharmacies, hospital pharmacies and supermarkets selling prescription- or over-the-counter medication – report the sale of both over-the-counter and prescription-only medications on a monthly basis. For prescription-only products dispensed in the primary sector, more detailed data are also reported, including product details, sale/dispension details, price, and reimbursement.

Medstat.dk is an online, open-access database managed by the National Health Data Board, reporting the sale of medications in Denmark since 1996 (over-the-counter medication included since 2001). Data extraction is typically done by ATC-code (Anatomic Therapeutic Chemical Classification System; WHO), product name and/or generic name [11].

We searched the literature to identify medications which have demonstrated or suggested an increase in the risk of osteoporosis and/or osteoporotic fractures. Then we identified and mapped the relevant ATC-codes for subsequent retrieval of public-domain usage data through www.medstat.dk. The medications included were thiazolidinediones (A10BG), PPI (A02BC), warfarin (B01AA03), heparin (B01AB01), glucocorticoids (H02AB), cyclophosphamide (L01AA01), methotrexate (L01BA01), gonadotropin releasing hormone (GNRH) agonists (L02AE), aromatase inhibitors (L02BG), calcineurin inhibitors (L04 AD), phenobarbital (N03AA02), phenytoin (N03AB02), carbamazepine (N03AF01), valproate (N03AF01), SSRI (N06AB), venlafaxine (N06AX16), and duloxetine (N06AX21) [12,13].

We extracted the following variables for these medications from 1999 to 2016 for Denmark:

- Usage rate per 1000 capita: A user was defined as a person filling at least one prescription of a given pharmaceutical product in a given year. Data on the sale must be traceable, and thus this variable is only available for prescription-based sales in the primary sector. The data used here are stratified according to gender and age group (40–64 years, 65–79 years, 80 years or older, and all age groups including persons below 40 years). Due to the demographics of osteoporosis we did not retrieve age range specific data for use in persons below 40 years of age.
- Total sale: The sale per year for both genders and all age groups across the primary and secondary sector, given in DDD (Defined Daily Dose; WHO) [11].
- Sale per 1000 capita per day: Based on the total sale across both sectors, and on population statistics, the sale per 1000 capita per day is calculated, given in DDD.

A cut-off year of 1999 was applied, as data on the usage rate per 1000 capita was only available from that year and onwards. The reason for this was, among others, that the medicine use of nursing home residents was not linked to personal registration number – and thus not traceable -until 1999. Data was extracted between 26 October and 11 November 2017. It should be noted that for this type of study, no patient consent or data protection agency approval is needed as the data has already been placed in the public domain by the regulatory authorities.

### 2.1. Statistical methods

We applied descriptive statistics, and data are presented as time series diagrams. The usage rate per 1000 capita is presented as line series diagrams, while the sale per 1000 capita per day is presented as

stacked bar charts. No formal statistical analyses were applied.

Data are presented according to drug group (assuming a class effect on the skeleton), except for chemotherapeutics, antiepileptics, and anticoagulants, as the authors judged the differences in pharmacodynamics to be potentially too significant for these drugs for grouping as a class. As such, for these medications data are presented on a generic level (methotrexate and cyclophosphamide; phenobarbital, phenytoin, carbamazepine, and valproate; and heparin and warfarin, respectively).

We classified the medications according to use and change in use, as given by sale per 1000 capita per day and the change in sale per 1000 capita per day from 1999 to 2016, respectively. Low use was defined as a sale per 1000 capita below 1 DDD per day in 2016, moderate use from 1 to 10 DDD per 1000 capita per day in 2016, and high use as above 10 DDD per 1000 capita per day in 2016. Increasing use was defined as a change in sale per 1000 capita per day from 1999 to 2016 of more than +10%, stable use as the range of −10% to 10%, and decreasing use as < −10%.

## 3. Results

In Table 1 we present an overview of the data in 1999 and 2016 for usage rate per 1000 capita, total sale, and sale per 1000 capita per day, respectively, ordered according to high, moderate or low use, and subsequently according to an increasing, stable or decreasing sales pattern. We have also calculated the relative change in sale per 1000 capita per day from 1999 to 2016 for all the medications investigated here.

The medications which exhibited high use (sale > 10 DDD per 1000 capita per day in 2016) included proton pump inhibitors (PPI), selective serotonin reuptake inhibitors (SSRI), venlafaxine, and glucocorticoids. While glucocorticoids demonstrated a pattern of stable sales rates (+7%), PPI, SSRI and venlafaxine was found to have an increasing sales pattern from 1999 to 2016. It is worth noting that the absolute change in sale per 1000 capita per day was particularly large for PPI which increased 54.9 DDD per 1000 capita per day, and SSRI which increased 25.1 DDD per 1000 capita per day.

Six medications were at moderate use in 2016, including warfarin, duloxetine, methotrexate, aromatase inhibitors, GNRH agonists, and valproate. In general, these therapeutics demonstrated an increasing sales rate pattern, particularly aromatase inhibitors which grew 2400% from 1999 to 2016 in the sale per 1000 capita per day.

For some medications, the sale per 1000 capita per day was minute (< 1.0 DDD per 1000 capita) in 2016. This included calcineurin inhibitors, heparin, thiazolidinediones, cyclophosphamide, carbamazepine, phenobarbital, and phenytoin. While one demonstrated a moderate increase in sales pattern from 1999 to 2016 (calcineurin inhibitors), others had a stable use. A few medications demonstrated a reduction in sale per 1000 capita per day, including carbamazepine (−55%), phenobarbital (−77%), and phenytoin (−100%).

In the following we examine the patterns of use for osteoporosis risk medications with a high prevalence of use. In addition we provide information on aromatase inhibitors due to the very high relative change in sale per 1000 capita per day from 1999 to 2016 seen for this class of medications.

### 3.1. Proton pump inhibitors

As demonstrated in Fig. 1B, the proportion of the population collecting at least one prescription of a proton pump inhibitor (including pantoprazole, lansoprazole, omeprazole, rabeprazole, and esomeprazole) increased continuously from 1999 to 2016 in the population in general, as well as in all age and gender groups investigated (respectively covering both genders aged 40–64 years, 65–79 years, and 80 years or older). During 2016, 9.0% of all men and 11.4% of all women collected at least one prescription of PPI, as compared to 3.0% and 3.4%, respectively, in 1999 (Supplementary appendix 1).

The increase in the usage rate was matched by an increase in the sale per 1000 capita (Fig. 1A), particularly in the primary sector.

### 3.2. Selective serotonin reuptake inhibitors

Fig. 2A and B shows the changing sale per 1000 capita per day and the usage rate of SSRI, respectively. Following a continuous increase from 1999 to 2010, the sale of SSRI per 1000 capita per day declined marginally and seem to have stabilised around 47 DDD per 1000 capita per day. The sale predominantly originates from the primary sector.

The usage rate demonstrated a remarkably similar tendency across the three age groups and both genders with an increase until around 2010, followed by a decrease during which most age groups returned to a level comparable to their 1999-level. The exceptions were seen in the younger age groups (40–64 years) for both men and women, who demonstrated a 37% and 34% increase from 1999 to 2016, respectively (supplementary appendix 2). The usage rate was almost twice as high for women (across all age groups) compared to men (Supplementary appendix 2).

### 3.3. Venlafaxine

The sales rate of venlafaxine grew significantly from 1.6 DDD per 1000 capita per day in 1999 to 11.4 DDD per 1000 capita per day in 2016 (Supplementary appendix 3), as demonstrated in Fig. 3A. A stabilization followed by a minor decrease was observed in 2012. The overall increase in sales rate was solely due to an increase in prescription-based sales in the primary sector.

The usage rate increased concomitantly in all the subgroups investigated, as shown in Fig. 2B. However, as for SSRI, when examining the usage rate in 2016 stratified according to gender, it was almost double for women compared to men (Supplementary appendix 3).

### 3.4. Glucocorticoids

The sale per 1000 capita per day was stable throughout the 1999 to 2016 time period. While we saw a minor decrease in the sale in the primary sector, an increase was observed in the secondary sector (from 2.5 to 3.6 DDD per 1000 capita per day), as demonstrated in Fig. 4A (and Supplementary appendix 4).

While the usage rate in general was stable during the observation period, an increase was seen in the elderly subgroup (80+ years) of 21% and 16% for men and women, respectively. On an overall level, this was offset by a comparable decrease in the 65–74 years subgroups for both genders (Supplementary appendix 4).

### 3.5. Aromatase inhibitors

Albeit at moderate use (2.5 DDD per 1000 capita per day in 2016), the relative increase from 1999 to 2016 of 2400% in the sale per 1000 capita per day was the highest among the medications investigated (Table 1 and Fig. 5A). This increase primarily occurred in the secondary sector, although – interestingly – prescriptions on aromatase inhibitors from the primary sector were noted from 2012 and onwards.

When examining the usage rate per 1000 capita, the increase in sale per 1000 capita was primarily due to the increase observed in women aged 65–79 years or 80+ years (Fig. 5B). The other groups investigated demonstrated a very low and stable usage rate per 1000 capita.

## 4. Discussion

In this paper we have reviewed the changing sale and usage of medications associated with an increased risk of osteoporosis from 1999 to 2016 in Denmark. We found that while a few medications or groups exhibited a decreasing or stable use over this time period, most exhibited increasing use. The absolute use of most of these were low or

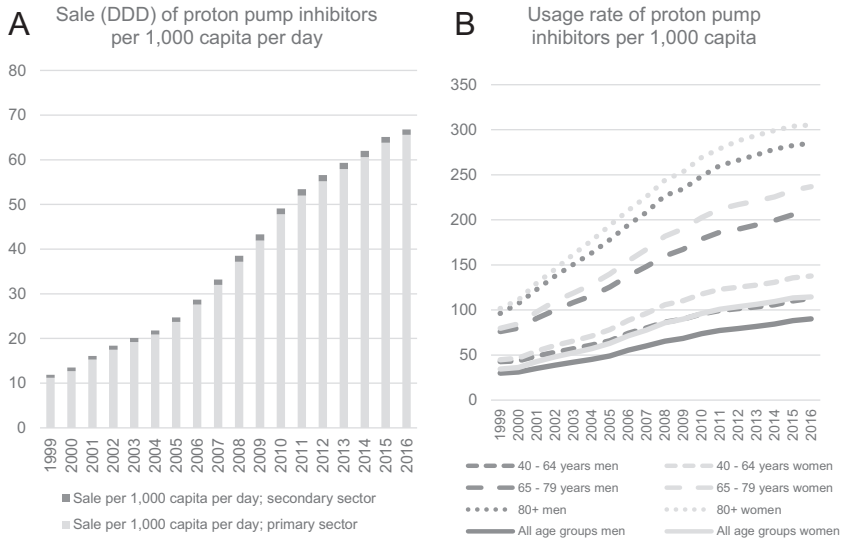


**Fig. 1.** A: Sale (DDD) of proton pump inhibitors per 1000 capita per day from 1999 to 2016. B: Usage rate of proton pump inhibitors per 1000 capita from 1999 to 2016. Data are stratified according to gender (men vs women) and age (40–64 years, 65–79 years, 80 + years, all age groups including below 40 years).

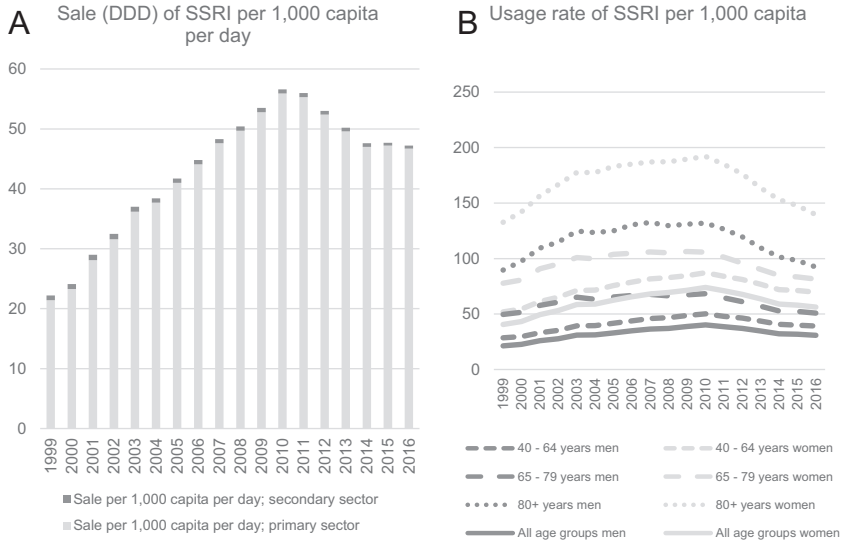


**Fig. 2.** A: sale of SSRI per 1000 capita per day from 1999 to 2016. B: Usage rate of SSRI per 1000 capita from 1999 to 2016. Data are stratified according to gender (men vs women) and age (40–64 years, 65–79 years, 80 + years, all age groups including below 40 years). SSRI, selective serotonin reuptake inhibitors.

modest (including aromatase inhibitors), but the use of PPI, SSRI and venlafaxine was high.

While the incidence of hip fractures, a key manifestation of osteoporosis, is high in Denmark as compared to other European countries, decreasing incidence rates have been reported for most of the study period covered in this analysis [14]. One study reported a decreasing incidence rate of hip fractures in the population aged 55 years or older from the mid-1990's, particularly in women [15]. Another study of the Danish population aged 50 years or older reported an annual reduction in hip fracture incidence rate of −1.8% in men from 2001 to 2010, as compared to −1.1% and − 3.1% annually in women from 1997 to 2005 and 2005 to 2010, respectively [3]. In a setting with a decreasing incidence of such osteoporotic fractures, the trend towards an increasing use of medications associated with osteoporosis may imply that a growing proportion of fracture cases could be pharmacologically induced, or that the uptake and effect of preventive lifestyle interventions and medical therapy is better than expected for these patients [16–19]. Also, we may not yet have observed the full impact on osteoporosis epidemiology of the increased use of medications associated with an increased risk of osteoporosis, thus a risk of stagnating or even increasing hip fracture incidence rates in the near future is plausible.

The use of PPI demonstrated the largest absolute increase of all the medications investigated here, primarily due to increased prescribing practices in the primary sector. The increasing use is in line with what has previously been reported, yet it is uncertain why the use is increasing [20]. It could be speculated that increasing over-the-counter sale of PPI was a reason, yet only 2% of the primary sector sale was over-the-counter in 2016. This is in line with a 2013 report from the National Board of Health which highlighted that 3% of the sale was over-the-counter [21]. This report also described an increase in the number of long-term users, suggesting that this may be attributable to an increased attention to identification and PPI-treatment of patients at high risk of gastric ulcers, which may contribute to the increasing use [21]. The association between PPI and fracture risk is reported to be moderate, with a recent meta-analysis demonstrating a relative risk of hip fractures of 1.26 (95% CI 1.16–1.36) and of vertebral fractures of 1.58 (95% CI 1.38–1.82) [6]. A substantial increase in the use of PPI may thus be associated with a clinically relevant increase in PPI-

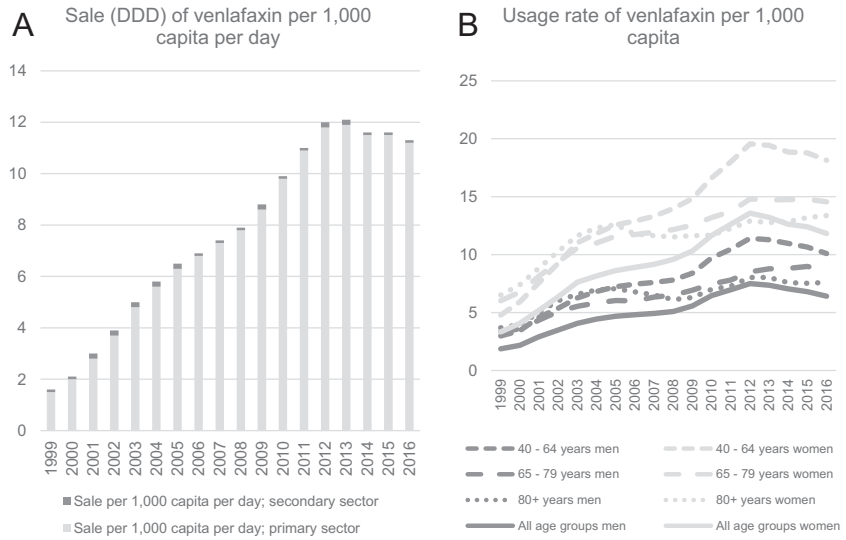


**Fig. 3.** A: sale of venlafaxine per 1000 capita per day from 1999 to 2016. B: Usage rate of venlafaxine per 1000 capita from 1999 to 2016. Data are stratified according to gender (men vs women) and age (40–64 years, 65–79 years, 80+ years, all age groups including below 40 years).

associated fractures.

The use of SSRI and venlafaxine followed a comparable pattern, demonstrating an initial continuous increase peaking in 2010 and 2012, respectively, followed by a declining use. This may potentially be explained by a change in treatment guidelines for depression, as in 2010 the Danish College of General Practitioners published a new guideline for general practice regarding treatment of unipolar depression [22]. This stipulates that watchful waiting should be applied for mild depression, while for moderate to severe depression treatment with SSRI should be first-line medical therapy, and dual-action therapies (including venlafaxine) or tricyclic antidepressants should be second-line therapy [22]. Prior guidelines cannot be identified, yet the temporal association of a significant change in use of SSRI and venlafaxine with the publication of new guidelines for treatment of depression makes a relationship plausible.

The analysis demonstrated that the use of SSRI and venlafaxine is more prevalent in women than in men, and for SSRI particularly in the older (postmenopausal) age groups (65–79 years and 80+ years). Use of SSRI has been associated with a relative risk of fractures of 1.72 (95% CI 1.51–1.95; $p < 0.001$) vs non-users, while a similar analysis has not been identified for venlafaxine [23]. With use of SSRI (and likely also venlafaxine) demonstrating a clinically relevant increase in fracture risk and a prevalent usage in postmenopausal women, this may substantially contribute to the incidence of osteoporotic fractures.

The use of aromatase inhibitors demonstrated the largest relative increase from 1999 to 2016. This was primarily observed in older women (aged 65–79 years and 80+ years), likely reflecting an increased use for postmenopausal breast cancer. It should be noted that aromatase inhibitors is a relatively new class of drugs, and while letrozole and anastrozole was available throughout the time period examined here, formestan was only used until 2002/03, while exemestane use began in 2000. Aromatase inhibitors increase bone turnover and have been reported to result in a 2-fold fracture risk, and calls have been made to ensure that patients receiving aromatase inhibitor therapy are screened for osteoporosis and low bone mineral density by dual x-ray absorptiometry (DXA), and that they receive preventive therapy [24,25].

The use of glucocorticoids was stable over the time span investigated here, with a minor drift in the prescribing prevalence towards the secondary sector. As the use of biologicals is replacing some

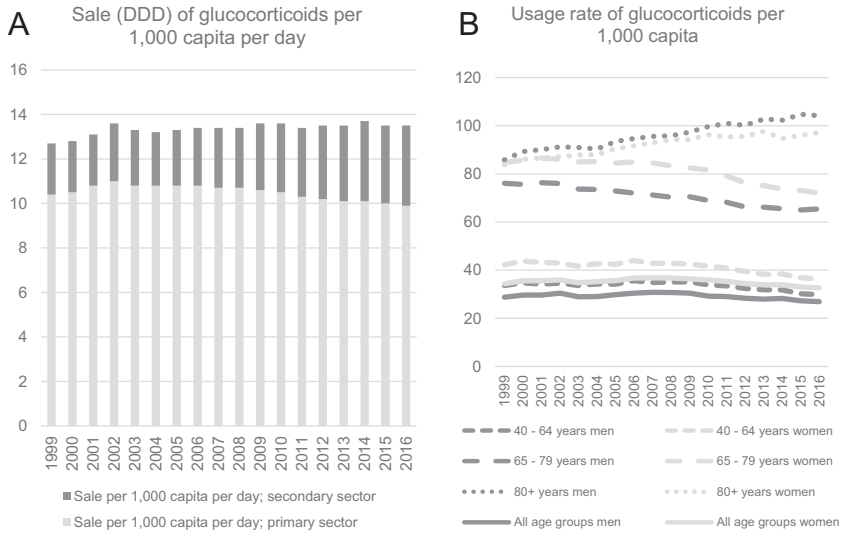


**Fig. 4.** A: sale of glucocorticoids per 1000 capita per day from 1999 to 2016. B: Usage rate of glucocorticoids per 1000 capita from 1999 to 2016. Data are stratified according to gender (men vs women) and age (40–64 years, 65–79 years, 80+ years, all age groups including below 40 years).

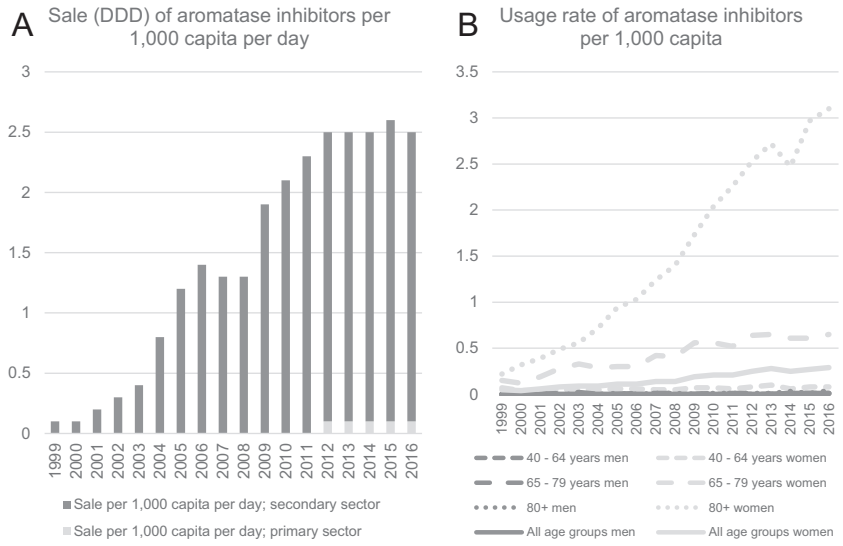


**Fig. 5.** A: sale of aromatase inhibitors per 1000 capita per day from 1999 to 2016. B: Usage rate of aromatase inhibitors per 1000 capita from 1999 to 2016. Data are stratified according to gender (men vs women) and age (40–64 years, 65–79 years, 80+ years, all age groups including below 40 years).

of the previous indications for glucocorticoid therapy, it is intriguing that it has not been possible to reduce the use of glucocorticoids. This seem from our data to be driven by an increasing use among the oldest subgroup (80+ years). With an aging population, some diseases predominantly seen among the elderly, like polymyalgia rheumatica, may contribute to the sustained use of GC as good therapeutic alternatives remain scarce.

The implications of our findings for daily clinical practice is a need to ensure proper screening for osteoporosis (including DXA-scans) or risk factors of osteoporosis prior to commencing treatment with medications associated with osteoporosis. Insofar therapy with these products is mandated in at-risk groups, steps should be taken to ensure proper prevention of osteoporosis in accordance to guidelines. Some guidelines do not include the risk of osteoporosis associated with some or all of the medications investigated in this study, despite evidence of a detrimental effect on bone health [26–28]. The increasing use of these products (also in high-risk groups) suggests that an update to these guidelines could be ensured to improve attention and prevention.

The strengths of this study include the complete data capture over a long time span, with the same method used without data breaks. Furthermore, detailed information on prescribers (primary vs secondary sector) and user segmentation enables an in-depth understanding of the changing prescribing practices across sectors of medications associated with osteoporosis.

One of the limitations of this study is that we had access only to aggregate statistics without a link to person level health registers. Hence, accounting for differences in comorbid conditions or collecting fracture outcomes is beyond the scope for this demographic study. Another limitation due to the lack of individual patient data is that it is not possible to estimate the individual dose nor the variation in the duration of exposure, which would be relevant in making inferences about the population impact regarding fractures associated with the use of the medications. Specifically, estimating the cumulative exposure in the individual patient over time is of clear interest and well worth investigating in subsequent studies with individual patient data. Finally, the dataset is specific to Denmark and guidelines and prescription practices may differ in other countries.

Future research could link data on these medications to individual patient data, to assess whether patients receiving these products include those with or at risk of osteoporosis – and if so, whether they receive preventive therapy. Similarly, it would be interesting to see if patients who have sustained osteoporotic fractures and/or receive osteoporosis drugs are experiencing a similar trend in their exposure to co-medications which yields a negative effect on bone health.

## 5. Conclusion

In this study, we found that while some medications associated with an increased risk of osteoporosis did exhibit a declining or stable use from 1999 to 2016, the use of most products increased considerably during this time span. This was particularly the case for PPI, SSRI and venlafaxine, which demonstrated a high and increasing use, especially in at-risk groups (women and/or elderly). First, this will present a new challenge to successful prevention of osteoporotic fractures. Second, it highlights the magnitude of exposure in the population and hence provides data which will be useful when planning osteoporosis screening and fracture prevention in patients treated with such medications.

This report does not contain clinical studies or patient level data. This article does not contain any studies with human participants or animals performed by any of the authors.

## Conflict of interest

MKS and YO: No conflicts of interest. BA: institutional research contracts with Nycomed and UCB with funds paid to the institution.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2018.08.019.

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