

## ORIGINAL ARTICLE

# Use of proton pump inhibitors among Danish children: A 16-year register-based nationwide study

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## Abstract

**Objectives:** Proton pump inhibitors (PPI) are among the most frequently used drugs in the developed countries. In recent years, their use among children and adolescents has been on the increase. Guidelines recommend use for a period no longer than 4-8 weeks. The aim of this study was to describe time trends in prescribing patterns of PPI use among children, with emphasis on persistence to therapy.

**Methods:** We used the Danish nationwide healthcare registries and identified all Danish children (0-17 years old) who were provided with a filled in PPI prescription between 2000 and 2015. Based on descriptive analyses, we reported trends over time in annual use, prevalent and incident users. Moreover, we evaluated persistence to treatment and doses used over time. Analyses were stratified by age groups (0-4, 5-11 and 12-17 years).

**Results:** We identified 212 056 filled in PPI prescriptions prescribed to 78 489 children. The total annual use of PPIs among children increased eight times from 2000 to 2015. Omeprazole was most frequently used (60% of all use). The proportion of prevalent users increased from 0.1 in 2000 to 3.1 per 1000 children in 2015, while the rate of new users increased from 1.2 to 8.0 per 1000 child years. In general, persistence to PPIs was low: in the youngest age groups (14%), slightly more children were covered by treatment 12 months after the first prescription compared with the oldest age groups (5%).

**Conclusion:** The use of PPIs among Danish children has increased substantially during the last 15 years. In general, treatment with PPIs among children was of short duration. Attention should be paid to indications and rationality behind initiation of therapy.

## KEYWORDS

persistence, pharmacoepidemiology, prescription registry, prevalence, treatment patterns

## 1 | INTRODUCTION AND BACKGROUND

The use of proton pump inhibitors (PPIs) in the adult population has increased steadily since the early 2000s,<sup>1,2</sup> and PPIs are now among the most frequently used drugs in the

developed countries. A similar increase is observed among children and adolescents in countries like Belgium and the United States.<sup>4,5</sup> The reason behind these findings is unclear, though the authors suggest that the patterns of use

may be explained by a change in parents' perception of these drugs and a greater availability on the market.<sup>4,5</sup>

A previous study showed that 20% of all young adults who received a first PPI prescription still were in treatment 2 months later.<sup>2</sup> Long-term PPI treatment (exceeding 4-8 weeks) is rarely seen among children and its long-term use may pose some concerns. Firstly, long-term use of PPIs is suggested to cause PPI dependency<sup>6</sup> and defective absorption of certain nutrients (such as calcium, magnesium, vitamin B12).<sup>7</sup> Moreover, due to modified gastrointestinal microflora caused by pH alteration, it may cause a weakened defence against infections. Other adverse effects, such as rebound hypersecretion, bone fractures and an increased risk of microscopic colitis, have been suggested.<sup>8,9</sup>

Detailed knowledge on trends in consumption patterns of PPIs in an unselected population of children and adolescents from a real-world setting is essential when international policy makers are to make decisions to ensure safety and rational use of these drugs.<sup>11,12</sup> Therefore, we described prescribing patterns of PPIs among Danish children and adolescents over time from 2000 to 2015, with special focus on trends in use over time and persistence to therapy.

## 2 | MATERIAL AND METHODS

In this nationwide, register-based, drug utilization study, we described trends in the use of PPIs among children and adolescents in Denmark from 2000 to 2015.

### 2.1 | Data sources

In Denmark, the entire population (5.8 million) has access to tax-funded health care (Danish National Health Service). The Danes have free access to primary care and hospitals, irrespective of age, sex and income. The National Health Service System stores information through nationwide registers covering the entire population. All Danish inhabitants are provided with a unique Civil Person Registration (CPR) Number, which enables linkage between health registers.<sup>13</sup>

We used two nationwide registries, The Danish Civil Person Registry and the Danish National Prescription Database. The Danish Civil Person Registry contains data on vital status, date of birth and death and migrations to and from Denmark.<sup>14</sup> The Danish National Prescription Database contains information on all prescriptions to Danish residents at community pharmacies during the study period (2000-2015). Over-the-counter drugs are not recorded in the register.<sup>15</sup> We received information on drug type, quantity, date of purchase, person age and sex. Drug type is defined by the Anatomic Therapeutic Chemical (ATC)

index, and drug quantity is expressed in defined daily doses (DDDs). Both systems are developed by the World Health Organization (WHO). In Denmark, low-dose PPIs do not require a prescription, and as only 1%-3% of PPIs are sold over the counter, the recording of these drugs in the register is close to complete.<sup>16</sup> Population statistics are obtained from Statistics Denmark, a governmental institution which collects and maintains electronic records for a broad spectrum of statistical and scientific purposes.

### 2.2 | Study population and setting

We identified all Danish children aged 0-17 years, who were provided with a filled in prescription for a PPI from 1 January 2000 to 31 December 2015. The size of the Danish child population (approximately 1.2 million) was stable throughout the study period.

### 2.3 | Study drugs

PPIs were defined as all drugs within ATC group A02BC (proton pump inhibitors). The duration of a treatment was calculated to last from the filling in date of a new PPI prescription till the end of the treatment, an estimate based on the number of tablets dispensed in each prescription. We assumed a consumption of one tablet per day and added a grace period of 25% to account for non-compliance and irregular prescription refills. New users were defined as first-ever users, that is individuals who did not have a record of filling in a PPI prescription since the establishment of the Danish National Prescription Database in 1995. Thus, the proportion of prevalent users, at any given point during the study period, was estimated to be the proportion of children who had been provided with a filled in prescription with enough DDDs to cover that specific day.

The Danish Medicines Agency has approved PPIs for children in treatment of gastroesophageal reflux disease (GERD) and *Helicobacter pylori*-associated ulcers (Table 1). However, PPIs are also used off label, for example for eosinophilic esophagitis and peptic ulcers in the absence of *Helicobacter pylori*. Treatments with an extent of eight consecutive weeks or more are rarely indicated.

### 2.4 | Analyses

All analyses were performed as overall, and/or stratified by age groups based on the European Medicines Agency classification, and by merging the two youngest groups (<5 years, 5-11, 12-17 years; supplementary analyses were performed in the youngest group, ie <2 years).<sup>17</sup> Sex, age and drugs prescribed within a period lasting from 4 weeks before to 4 weeks after the first PPI prescription were discovered.

**TABLE 1** Paediatric PPI dosage (ATC code) for GERD/*Helicobacter pylori*-associated ulcer

Drug	Dose
Esomeprazole (A02BC05)	10-20 mg o.d./10-20 bid
Lansoprazole (A02BC03)	Not indicated
Omeprazole (A02BC01)	10-40 mg o.d./10-20 mg bid
Pantoprazole (A02BC02)	20-40 mg o.d
Rabeprazole (A02BC04)	Not indicated

bid, twice daily; od, once daily.

Dosage depends on age and weight of child.

Firstly, we used the following three approaches to analyse trends in use over time.

Initially, we investigated changes in the overall annual use over time by estimating the amount of dispensed PPIs each year (measured in DDDs) specified by chemical substance level (ATC 5th level). Next, we investigated trends in the proportion of prevalent users and the rate of new (incident) users over time. The proportion of prevalent users was assessed by calculating the average proportion of prevalent users on the last day of each month. The total number of Danish children on 1 January in the relevant year was used as the denominator. Finally, the rate of new users each year (ie the annual incidence rate) was calculated as the number of new (first-ever) users per 1000 children in each year. To acknowledge that the reasons for prescribing PPIs vary considerably across age groups and that treatments might be short-term, we performed a sensitivity analysis in which we defined new users as individuals with a first prescription for PPIs within the previous 2 years (instead of first ever). The latter two analyses were performed overall and per age category.

Secondly, we assessed persistence to treatment by combining two methods, the “proportion of patients covered” (PPC)<sup>18</sup> method and a survival analysis which produced a Kaplan-Meier curve (KMC). In both methods, we followed all incident (first-ever) users for 12 months from the date of their first prescription. Children age considered was their age when their first prescription was made. Children were censored at the end of the study period, at the date of migration or upon death. The main difference between the two methods is that individuals, who did not refill a prescription for a PPI within the permissible gap, were excluded in the KMC, while, in the PPC analysis, they were allowed to re-enter the analysis upon filling in a new PPI prescription. Thus, the PPC estimated the proportion of patients who were still alive and were using PPIs on a given day, whereas the KMC estimated the proportion of patients, who were still alive and covered by PPIs on a given day, without having exceeded the permissible gap between fillings (ie continuously treated).

Thirdly, we investigated whether long-term users (over 5 years) experienced a change in the dose of PPIs over time. In those patients who were provided with more than one filled prescription every year in the five consecutive years, following the first filling of a PPI prescription, we estimated the median and the 10th, 25th, 75th and 90th percentiles of used DDDs per year. Only individuals, eligible for a 5-year follow-up, that is those provided with their first filled prescription before 31 December 2011, were included.

## 2.5 | Other

All analyses were performed using STATA MP15.0 (Stata-Corp LLC, College Station, TX, USA).

## 2.6 | Ethics

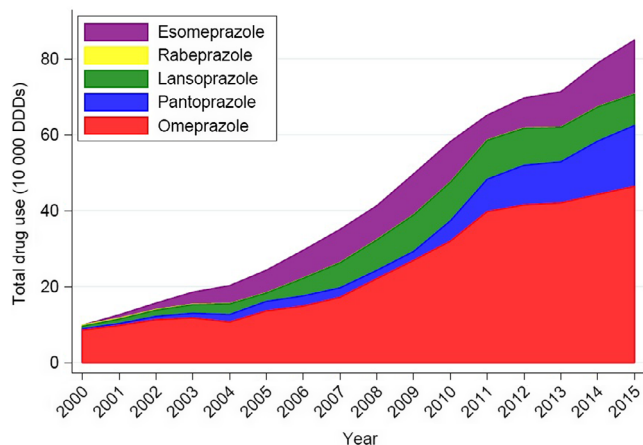
According to Danish law, studies based solely on register data do not require approval from an ethics review board. The study was approved by the Danish Data Protection Agency. Data were anonymized to the authors, and no identification of individuals was possible.

## 3 | RESULTS

We identified 212 056 filled PPI prescriptions issued to 78 489 children aged 0-17 years from 2000 to 2015. Six of every 10 children ( $n = 48\ 115$ ) were provided with only one filled prescription, whereas 25% ( $n = 19\ 383$ ) and 14% ( $n = 10\ 991$ ) were provided with 2-3 and four or more filled prescriptions, respectively. The median number of tablets filled per prescription was 28 (interquartile range 28-56) which corresponds to the median number of DDDs per prescription (interquartile range 14-37.33). Sixty per cent of the children, for whom a PPI prescription was redeemed, were female, while the median age at the time of being provided with their first filled prescription, was 14 years (interquartile range 10-16). The most commonly prescribed drugs, within a limited period around the first PPI prescription (4 weeks after and before), were antibacterial agents for systemic use; ATC code J01 (32%).

### 3.1 | Amount dispensed

The annual use of PPIs in children increased gradually from around 100,000 DDDs filled in 2000 to more than 800 000 DDDs filled in 2015 (Figure 1). The increase was particularly pronounced in the last 7 years of the study period. Omeprazole was the most commonly used PPI during the entire period (almost 4 million DDDs corresponding to 95 575 prescriptions). Specifically, the use of omeprazole increased more than five times, from 85 000 DDDs in



**FIGURE 1** Total amount of proton pump inhibitor (in DDDs) used per calendar year during the study period

2000 to 460 000 DDDs in 2015. The use of esomeprazole and lansoprazole increased slightly during the last 10 years of the study period (between 60 000 and 100 000 DDDs and between 40 000 and 70 000 DDDs, respectively), while the use of pantoprazole increased substantially in the last 6 years (from 50 000 to 160 000 DDDs). Rabeprazole was rarely used (Figure 1).

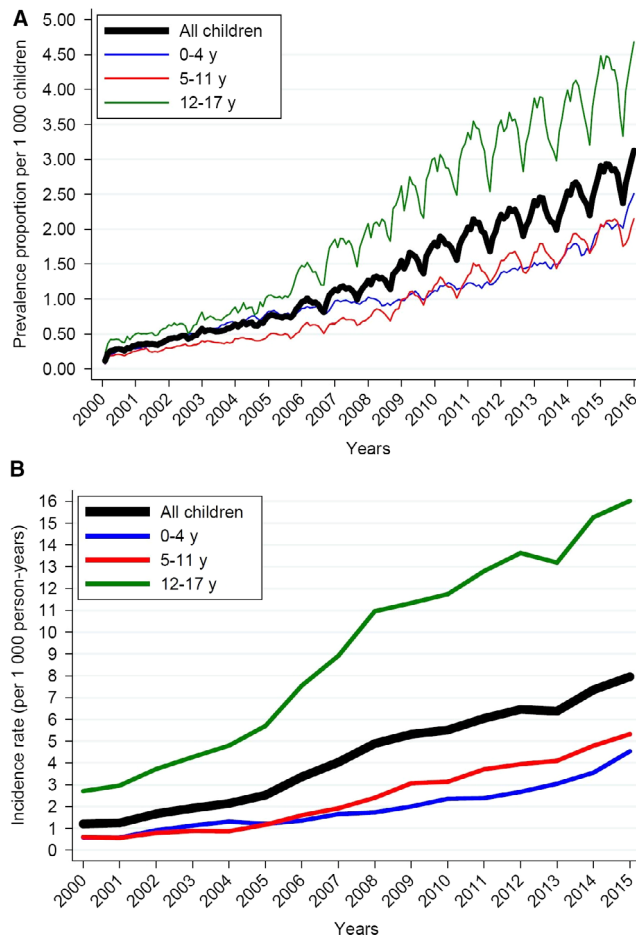
### 3.2 | Prevalence and incidence

The increase in annual use was accompanied by an increase in the proportion of prevalent users from a very limited use in 2000 (0.1 user per 1000 children) to 3.1 users per 1000 children in 2015. The pattern of prevalent use differs across age groups with around 2.3 users per 1000 children younger than 12 years in 2015, and 4.7 users per 1000 in the oldest age group (Figure 2A). This latter rate is similar to the rate observed in infants (Figure S2A).

The overall rate of new users (ie the annual incidence rate) increased from 1.2 per 1000 child years in 2000 to 8 per 1000 child years in 2015 (Figure 2B). This trend corresponded to the observed pattern among prevalent users. However, compared to prevalent users, the difference in annual incidence rate between the oldest age group and the two youngest age groups in 2015 was more marked for new users. The rate observed in infants (Figure S2B) is higher than rates found in the 0-4 and 5- to 11-year groups. When defining new users as individuals who were provided with a first filled prescription within the last 2 years, we found results similar to results from the main analysis (data not shown).

### 3.3 | Persistence to treatment

When estimating persistence to PPI treatment, we found an initial steep drop in the proportion of patients covered by treatment within the first months following their first



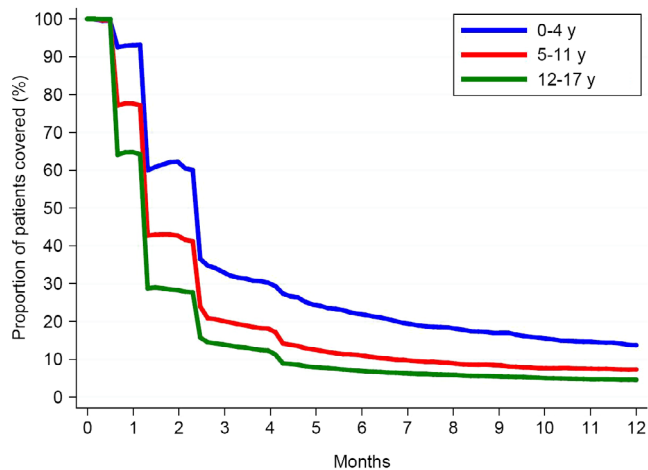
**FIGURE 2** Monthly prevalence proportion (A) and annual rate of new users (ie the incidence rate) (B) of PPIs among children in Denmark from 2000 to 2015. Overall and stratified by age group

prescription for a PPI (Figure 3). This pattern was consistent for all age groups, although the pattern was more marked in the older groups. The proportion of children covered by a PPI prescription 12 months after initiation of therapy was highest in the youngest age groups (14%, no difference between 0-4 and 0-1-year group; Figure S3). In the middle and oldest age groups, slightly fewer children were covered by therapy 12 months after their first prescription (7% and 5%, respectively). The sensitivity analysis using survival analysis (Kaplan-Meier curve) showed a very similar profile of persistence (Figure S1).

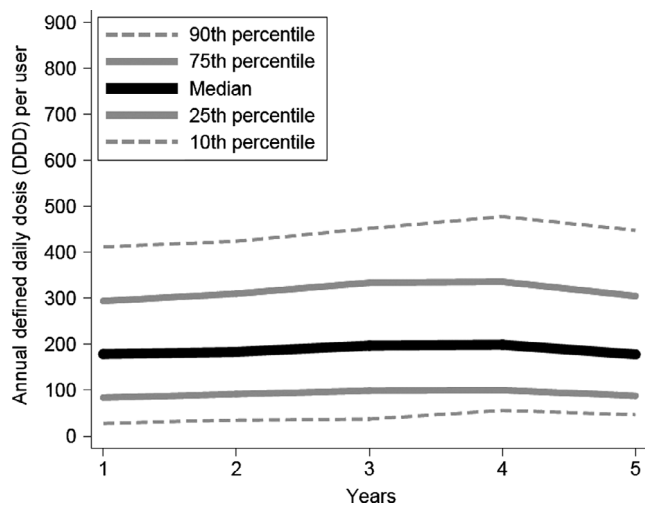
Among most of children using PPIs for a longer period, we found more or less consistent amounts of used PPIs (in DDDs) in the five consecutive years following their first prescription, although a slight increase was noted in the 75th and 90th percentile of use per year (Figure 4).

## 4 | DISCUSSION

In this nationwide drug utilization study, we investigated time trends in individual-level patterns of use of PPIs



**FIGURE 3** The proportion of patients covered by PPIs 12 mo after their first prescription. Stratified by age group



**FIGURE 4** Doses used over time in the first 5 y among children provided with a minimum of one filled prescription for each year for at least 5 y after the first prescription

among children from 2000 to 2015. Overall, we demonstrated an 8-fold increase in the annual use of PPIs in children in Denmark between 2000 and 2015. Omeprazole was by far the most frequently used drug. The proportion of new and prevalent users increased concurrently over time in all age groups though it was most pronounced in children older than 12 years. The use of lansoprazole is remarkable as it indicates off-label use. In general, the persistence to PPIs was low, indicating that long-term use is rare.

The main strength of the study is the nationwide approach. The Danish National Prescription Registry provides a unique opportunity to evaluate trends in individual-level prescribing patterns of PPIs in children, during a period of 16 years, with no risk of selection bias and drop-out. In addition, the identification of PPI

prescriptions is close to complete,<sup>15</sup> as only 1%-3% of all PPIs are sold over the counter in Denmark. Further, our data represent PPIs that were bought at the pharmacy; bias from primary non-adherence is thereby reduced.

An important limitation of this study is the lack of information on the underlying indications for the prescriptions for PPIs, as this has not been recorded systematically in the National Prescription Registry. Such information could improve our understanding of initiation and persistence to therapy as well as choice of treatment. Particularly, in the youngest age groups, both indications for prescribing PPI and the anticipated effect of PPI might differ substantially.<sup>19</sup> An example showing this is that although PPI-metabolizing enzymes such as CYP 450 and 219 are not fully matured at birth, it has been shown that meal-stimulated acid productions are weaker in newborns compared to other age groups, and that toddlers obviously are not able to describe symptoms of GERD in the same way as children or young adult.<sup>20,21</sup> The lack of information on indications for prescribing hinders the assessment of the true level of off-label use, too. However, the reported use of lansoprazole indicates that off-label is not negligible in children, as it is a drug not approved for use in children. Further, we did not have information on the intended daily dosage but relied on the assumption of one tablet/capsule per day. While the dose per tablet/capsule availability is wide enough to let patients take one tablet/capsule per day, this does introduce some uncertainty in our estimation of, for example, duration of use.

The total use of PPIs increased similarly in Denmark and Belgium between 2000 and 2010. Likewise, the total PPI use among children in Denmark was consistently similar to the reported use in Belgium during the period.<sup>4</sup> In both countries, omeprazole was the most widely used PPI. This is probably explained by omeprazole being the PPI that was first marketed as suited for children (in 1989) followed by pantoprazole (in 1996) and esomeprazole (in 2000). Further, it might reflect that omeprazole is a drug with a longer trajectory on the market and parents may be more familiarized with it.<sup>4</sup> Though not labelled for children, use of lansoprazole constitutes 6% of the total PPI used in 2015. This indicates that some off-label use in children is quite common. In contrast, the other not labelled PPI, rabeprazole, was consistently not used.

Based on 4 commercial health plans in the United States, Barron and colleagues showed that the proportion of prevalent users, younger than 12 years, increased from 0.50 in 1999 to 4.75 per 1000 children in 2004.<sup>5</sup> Although the proportion of prevalent users in 2004 in Denmark was lower, similarly the increase was substantial. The reason behind this is unclear. The increasing prevalent and incident use of PPI since 2000 might reflect that the

prevalence of GERD in children has been rising during the last decades, as has been reported among adults.<sup>22</sup> However, GERD is unlikely to be the only explanation for the observed increase. Restrictions in the use of propulsives due to cardiac side effects during last decades<sup>23,24</sup> may have caused a drift towards increasing use of PPIs, and the increase in the number of visits to paediatricians and a possible pressure in prescribing from community in general might contribute to the increase of prescriptions for PPIs. Additionally, the observed trends in PPI use are contradicted by the declining prevalence of *Helicobacter pylori* infection in children,<sup>25</sup> which would suggest a reduction in paediatric peptic ulcers and, subsequently, a fall in PPI use.

The observed differences across age groups in our study are worthy of note. The incidence and prevalence are highest in the oldest children. Furthermore, the incidence in the youngest children (infants) is higher, compared to the middle age group. These results are in line with higher prevalence rates of presumed GERD observed in the youngest and oldest children<sup>26</sup> while a previous study, that was published 10 years ago, showed that in the youngest children, prokinetics are more used than PPIs<sup>27</sup>; however, as it is already noted, the current use of prokinetics is minimal as most of these drugs no longer are on market. The reason for prescribing PPIs could be different between age groups and even between the youngest children, as we observed in rates in children younger than 5 years and children younger than 2 years. Factors such as symptomatology, reluctance or willingness to prescribe may be different in each age group, and they may condition the observed prescribing patterns.

GERD is the major indication for prescribing PPIs in children. GERD mainly requires short-term treatment<sup>28</sup> and occurs more often in the youngest children (younger than 1 year) and oldest children (older than 11 years).<sup>26</sup> This is supported by our findings, where the highest prevalence and incidence rates were observed among the youngest age groups (0-1 year; supported by supplementary analyses) and the oldest age groups (age: 11-17). Similarly, the proportion of children staying on PPI for at least 1 year is close to 0 for children older than 5 years and around 3% for the youngest (0-4 years). Rebound acid hypersecretion is a possible explanation for continuous PPI use without a well-established indication.<sup>2</sup> Especially, in the youngest age groups, where symptoms might be difficult to recognize and communicate, rebound acid hypersecretion may influence prescribing patterns.<sup>28</sup> The high prescription rate might be equivalent to erroneous diagnosis of GERD that might be related to the lack of effect observed of PPI in RCT.<sup>29</sup> Further, rebound acid hypersecretion may be an explanation for the increase in use among long-duration “heavy” users.

## 5 | CONCLUSION AND FURTHER RESEARCH

In conclusion, we observed an extensive increase in the use of PPIs in Danish children from 2000 to 2015, particularly pronounced in older children and infants. In general, the use of PPIs in children is short-term and occasional, though long-term treatment seems to be more frequent in the youngest children. The use of lansoprazole indicates a certain level of off-label use in children. Attention should be paid to the increasing use of PPIs. Further, the indication for prescribing PPIs in children needs to be elucidated in future studies to assess the rationality of the use of PPIs among children.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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