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Epinephrine dispensings, allergy hospitalizations and the elimination of co-payments in Sweden

To the Editor,

Hospitalizations for anaphylaxis have increased amongst children, with notable differences in median age between boys and girls (ages 8 and 12 years, respectively).¹ Anaphylaxis requires prompt and correct administration of epinephrine (adrenaline), commonly via an epinephrine autoinjector (EAI),² which individuals with severe allergies are encouraged to carry at all times. EAI often has substantial out-of-pocket expenses—or co-payments—for families.³ This was the case in Sweden, until 2016, when the Swedish government eliminated co-payments for most medications, including EAIs, to children under age 18 years with a national identification number. It is unclear whether changes in EAI dispensings and related hospitalizations are impacted by the elimination of co-payments. Thus, we aimed to establish the trend of EAI dispensings and hospitalizations for the Swedish paediatric population, from 2006 to 2017, including by sex⁴ or geographic region.⁵ We hypothesized that, following the

removal of co-payments, EAI dispensings would increase and related hospitalizations would decrease.

We used data from Sweden's National Board of Health and Welfare's open, searchable statistical database. Herein, aggregate data from the Swedish Prescribed Drug Register are available based on dispensed prescription drugs from all Swedish pharmacies from 2006, and thus virtually all dispensed prescribed drugs in Sweden.⁶ We searched on the ATC code for epinephrine (C01CA24). Although other drugs are prescribed for allergy, this is often for concomitant allergic diseases and was therefore excluded. Physician density (physicians/100 000 inhabitants) was only available through 2015. Data on inpatient stays, in days, per 100 000 individuals, coded per ICD-10 code T78+, captured anaphylaxis and other allergic reactions.

Data are presented annual dispensed EAI/1000 inhabitants; annual hospitalizations/100 000 individuals; and dispensings/1000

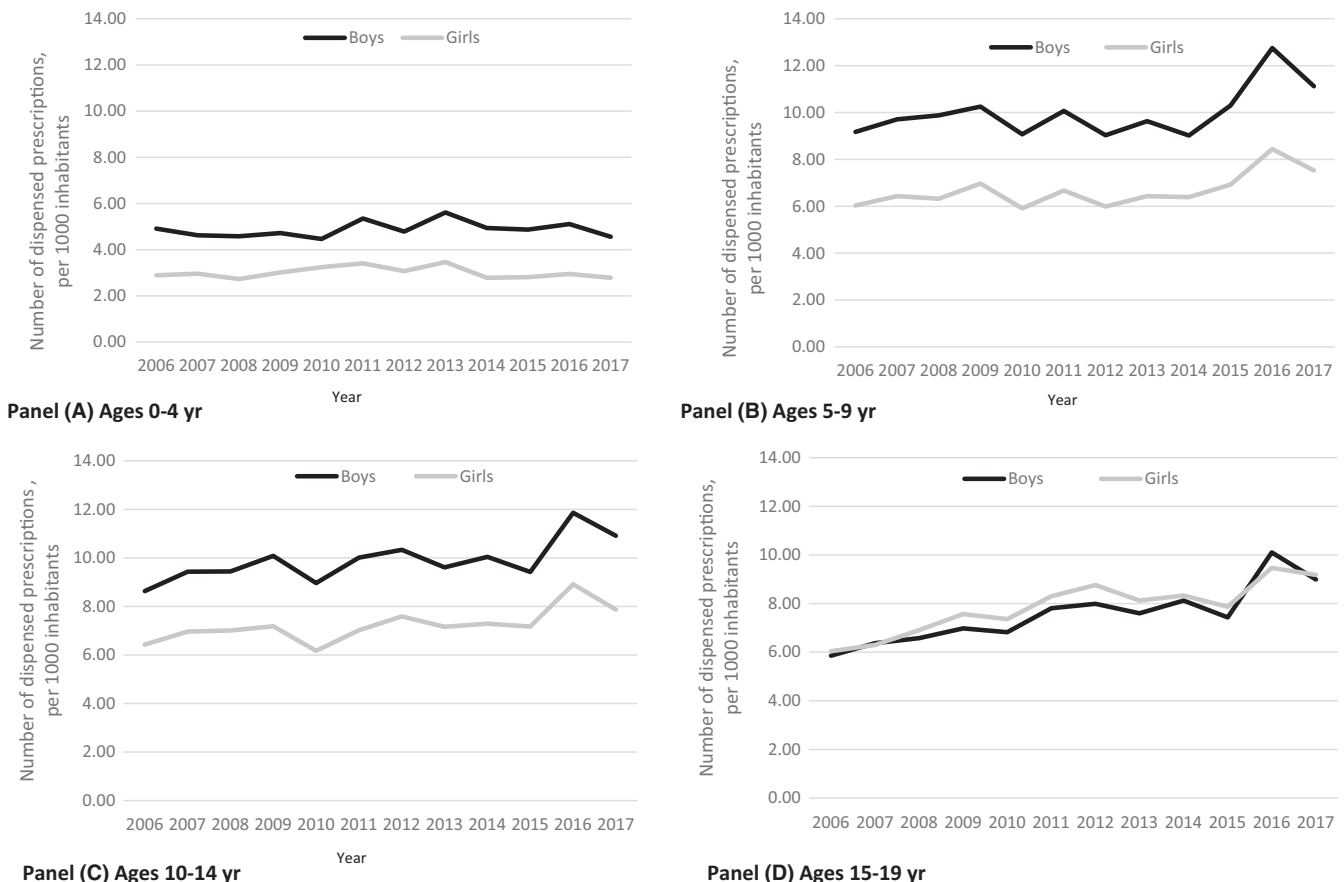


FIGURE 1 Annual dispensed prescriptions of epinephrine autoinjectors to paediatric patients, ages 0-19 years, in Sweden from 2006 to 2017, by sex-stratified age groups

inhabitants, by sex, age group (0-4 years, 5-9 years, 10-14 years and 15-19 years) and county. To strengthen the interpretation of the findings, we also provide comparable data in adults, for whom co-payments were not removed.

As data were retrieved from an open, aggregate database from Swedish authorities, informed consent was neither possible nor necessary.

Amongst children, annual mean EAI dispensings remained stable from 2006 to 2015, then increased, on average, by 24% in 2016-2017 ($P < 0.001$; Figure S1A) to 8.26/1000 inhabitants in 2016-2017 (Figure S1B). During the same period, adult dispensings also increased by 29% (Figure S2A), to 5.04/1000 inhabitants (Figure S2B). In contrast, inpatient hospitalizations in days started to decrease in 2013-2014. Following the elimination of co-payments for paediatric medications, inpatient hospitalizations were 27% lower amongst children (2006-2015: 20.6%; 2016-2017: 15.0%; Figure S3). Amongst adults, inpatient hospitalizations were also lower (2006-2015: 24.3%; 2016-2017: 21.2%, excluding data from 2011; Figure S4A and B), albeit 13% lower or approximately half of the decrease seen amongst children.

With respect to EAI dispensed between 2006 and 2015 by sex, boys averaged 7.74 EAI/1000 inhabitants annually, compared to 6.01/1000 amongst girls. This corresponds to 29% more dispensings annually amongst boys than girls (Figure S5A). A predominance towards boys was also seen in 2016-2017 (boys: 9.39/1000 vs. girls: 7.05/

1000, or 33% more prescriptions to boys). In contrast, compared to 2006-2015, in 2016-2017, more substantial decreases in hospitalizations were seen for girls than boys (33% vs. 22%, respectively; Figure S6A).

Children aged 0-4 years were consistently dispensed fewer EAI, but had more annual inpatient stays than older children (Figures S5B, S6B). An upward trend from 2015 to 2016 seen in the age groups 5-9 years, 10-14 years and 15-19 years (Figure S5B). Children aged 0-4 years had half the EAI dispensings and approximately 1.5 times as many hospitalizations compared to children aged 5-9 years (Figures 1A,B and 2A,B). Within the younger age groups, 0-4 and 5-9, boys were consistently dispensed EAI and hospitalized, on average, 30% to 50% more often than girls (Figures 1, 2). This difference was seen both from 2006 to 2015 and in 2016 to 2017. Less clear patterns were seen for older groups. We previously reported that hospitalizations for allergic reactions doubled in the years preceding the removal of co-payments, including a predominance of 23% more hospitalizations for boys compared to girls.¹ Likewise, boys are more likely than girls to have persistent food allergy.⁷ Yet, no sex differences in EAI dispensings per 1000 inhabitants ages 15-19 years were identified herein (Figure 1D). This period of late adolescence may be the age at which the shift from male to female predominance begins.⁴

EAI dispensings increased in almost all Swedish counties during the study period, but with substantial variation across the nation. For

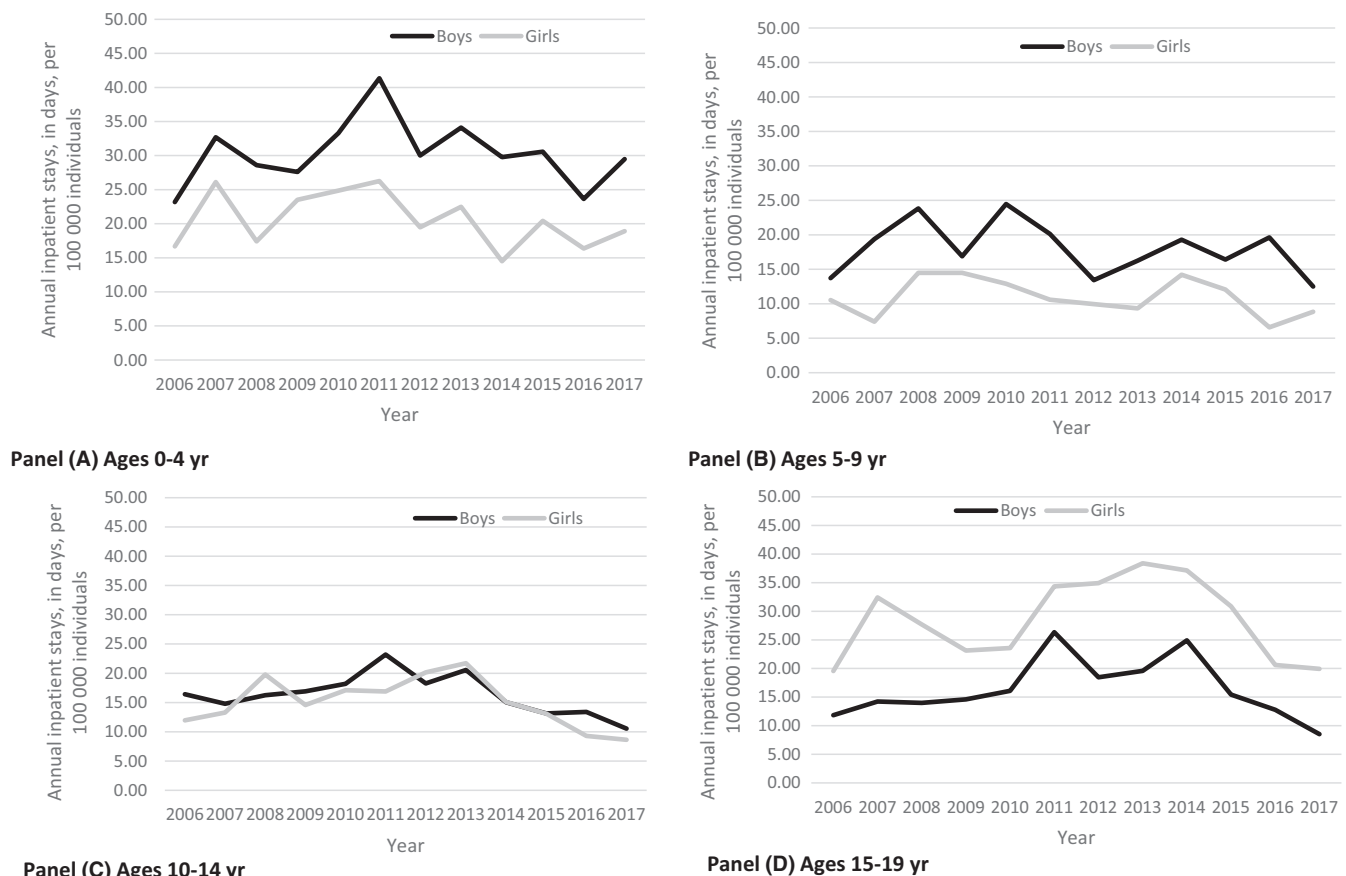


FIGURE 2 Annual inpatient stays, in days, per 100 000 individuals, ages 0-19 years, in Sweden from 2006 to 2017, by sex-stratified age groups

example, in 2006, the national average dispensed EAI for children was 5.31/1000 inhabitants, but ranged from 2.43/1000, in a partly rural county located in central Sweden, to 9.47/1000, in a county which includes Sweden's second largest city. In 2017, the corresponding figures were 6.66/1000 inhabitants overall and ranged from 4.10/1000 in the same partly rural county as which had the lowest rates in 2006, to 11.37/1000, in the most populated county that also includes the national capital (Figure S7). The highest dispensings were in counties with large urban centres. Physician density in the regions with highest dispensings was slightly lower than the national average (2006: 293/100.000 vs. 359/100.000; 2015: 379/100.000 vs. 425/100.000, respectively). This reinforces the discrepancy in dispensings by region, even in countries such as Sweden, where health care is organized by county, but in which all individuals with a personal identification number have low to no cost health care.

Notably, following the removal of co-payments, paediatric EAI dispensings nearly doubled in northern counties, to a rate comparable to that seen in counties with large, urban centres. Yet, food allergy prevalence in northern Sweden is comparable with those in Stockholm, and, more broadly, in Europe.^{7,8} In Sweden, those living in the north—much like those in rural counties—have more restricted access to health care compared to those in urban centres. Similarly, Australian children ≤ 14 years in major cities were prescribed EAI significantly more frequently than those living in remote/rural regions.⁵ We speculate that the doubling of EAI dispensings following the elimination of co-payments may be a response to provide additional EAI for emergency treatment given the more challenging access to emergency care. Alternatively, increased dispensings could be partly due to increased awareness of the need for EAI, as supported by an increase in, albeit not a doubling of, adult EAI dispensings, in northern Sweden (data not shown).

Our study is based on dispensed drugs.⁶ Thus, we cannot conclude if EAI prescribing practices changed, or simply if more EAI prescriptions were filled following the removal of co-payments. Further, although triggers of anaphylaxis shift from foods in early childhood, to insect venom and drugs by age 10 years, those with anaphylaxis to food vs. venom are less likely to be prescribed an EAI.⁹ Furthermore, our results report on EAI dispensings, not usage.

In conclusion, substantial age, sex and geographic variation in EAI dispensing and hospitalizations exist in Sweden, both prior to, and following the removal of co-payments for these devices for children.

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CONFLICT OF INTEREST

All authors declare that they have no real or perceived conflicts of interest in relation to this manuscript.

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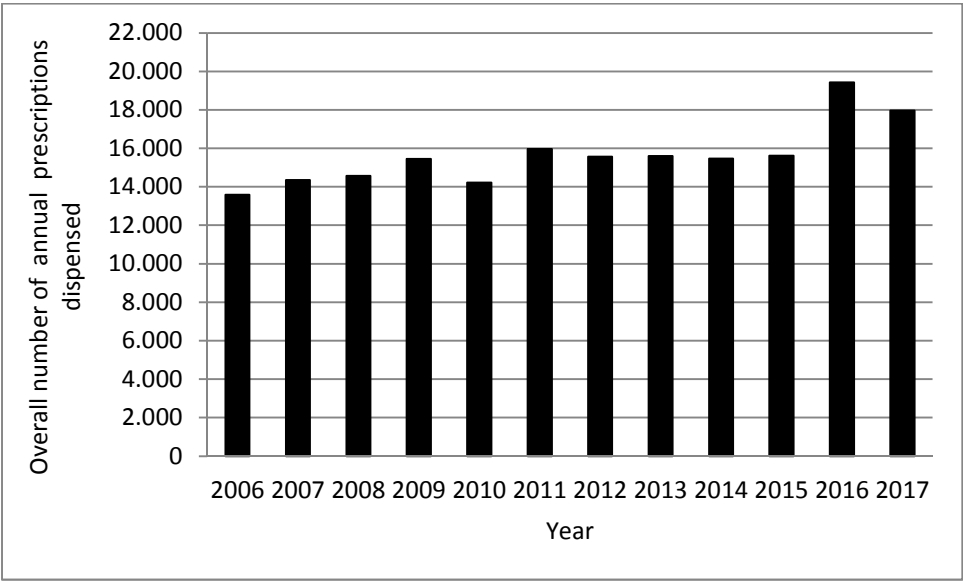
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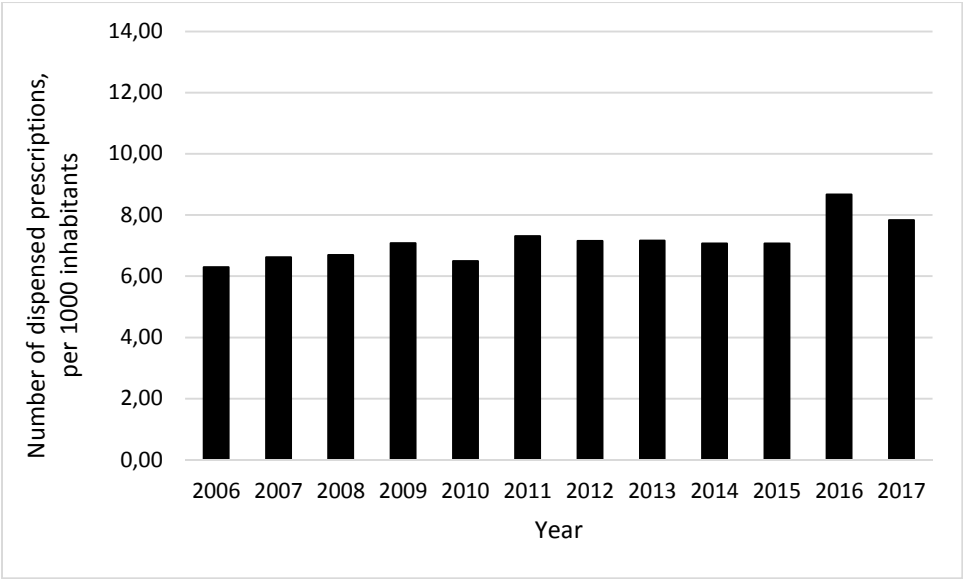
SUPPORTING INFORMATION

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

Supplementary Figure 1. Annual dispensed prescriptions of epinephrine autoinjectors (EAI) to pediatric patients, ages 0-19 years, in Sweden from 2006 to 2017

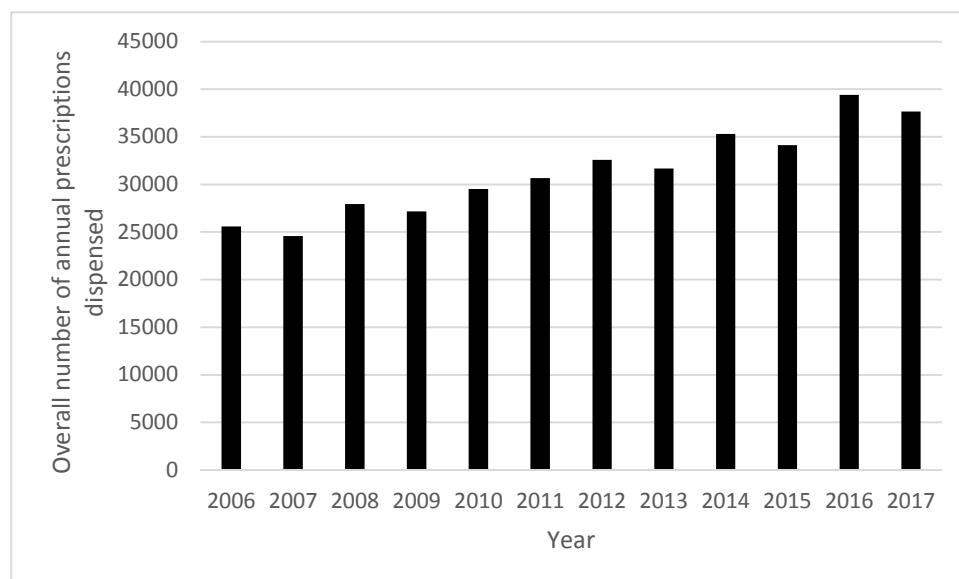


Panel A. Annual dispensed number of EAI prescriptions, overall

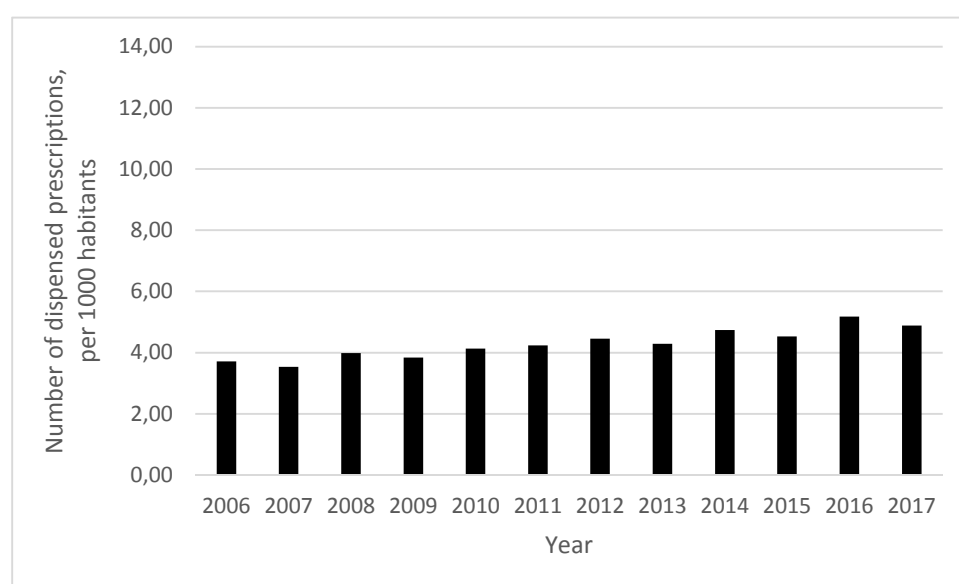


Panel B. Annual number of dispensed EAI prescriptions, per 1000 inhabitants

Supplementary Figure 2. Annual dispensed prescriptions of epinephrine autoinjectors (EAI) to adult patients, ages 20+ years, in Sweden from 2006 to 2017

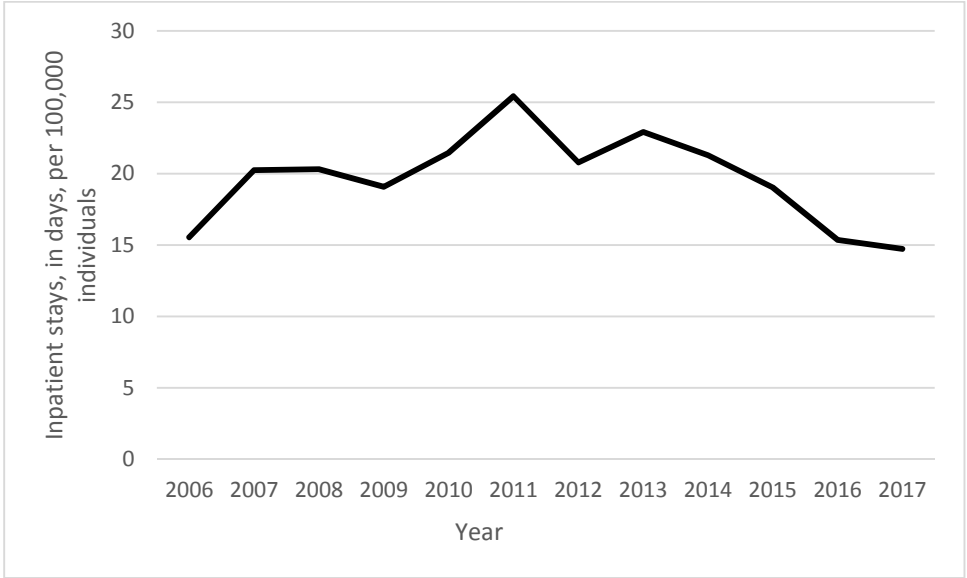


Panel A. Annual dispensed number of EAI prescriptions, overall

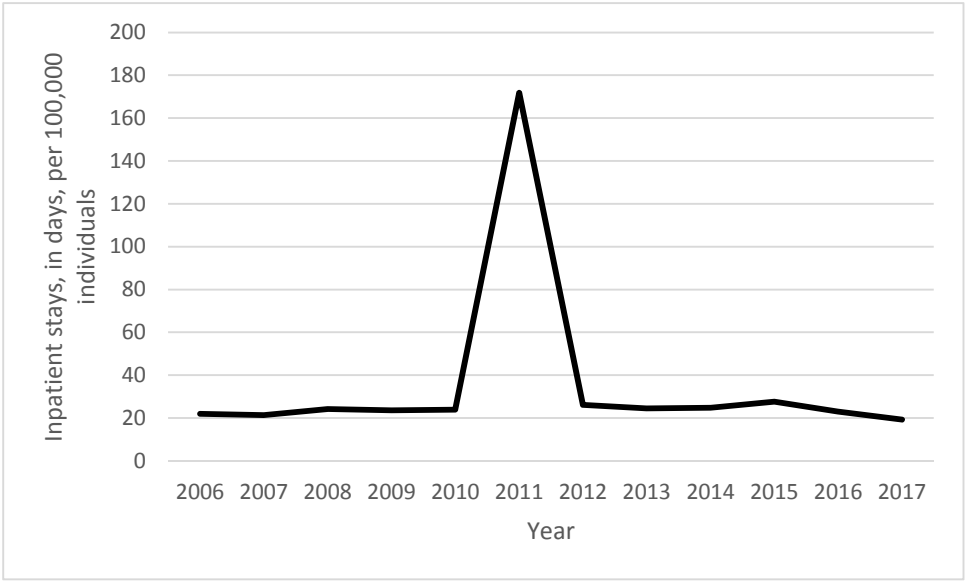


Panel B. Annual number of dispensed EAI prescriptions, per 1000 inhabitants

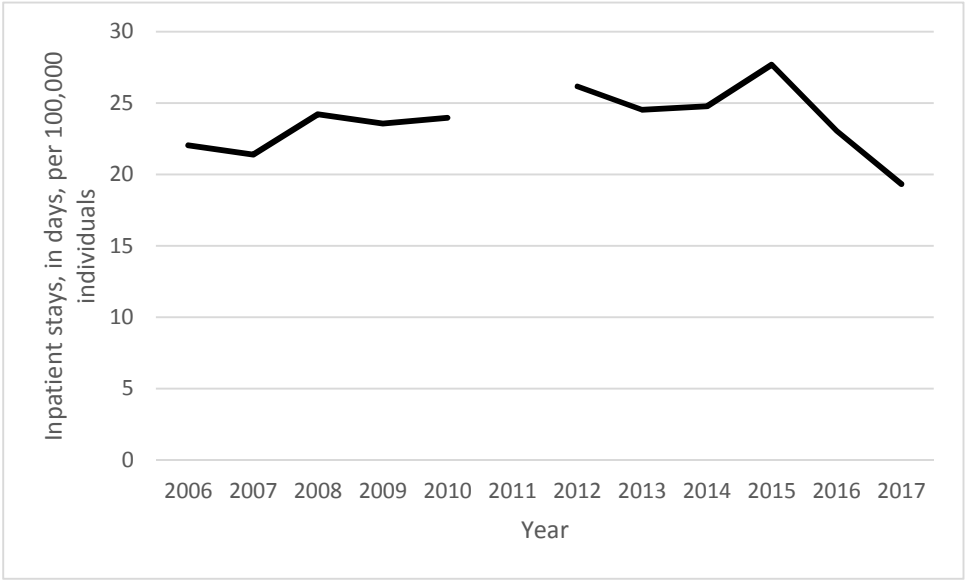
Supplementary Figure 3. Annual pediatric inpatient stays, in days, per 100,000 individuals, ages 0-19 years, in Sweden from 2006 to 2017



Supplementary Figure 4. Annual adult inpatient stays, in days, per 100,000 individuals, ages 20+ years, in Sweden from 2006 to 2017

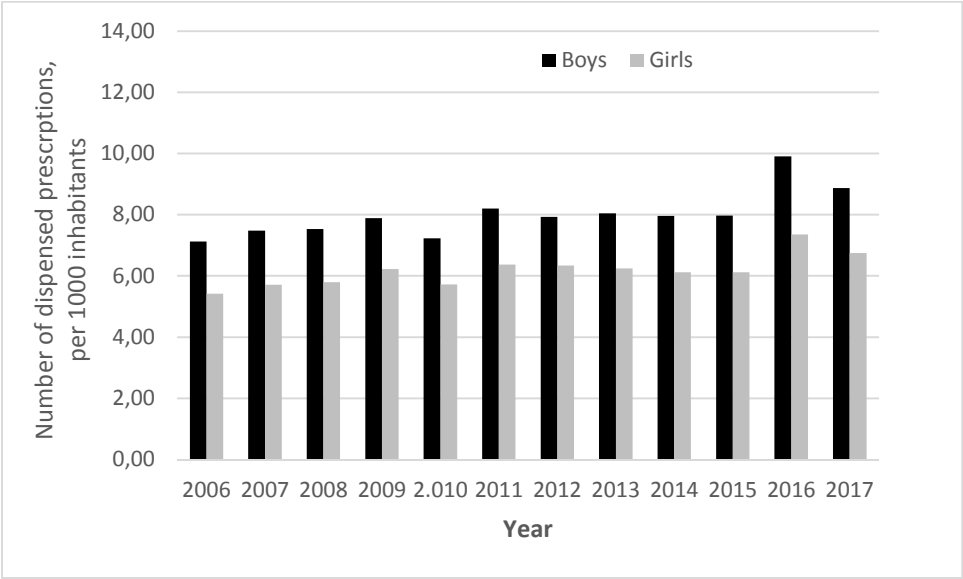


Panel A. Including data from 2011

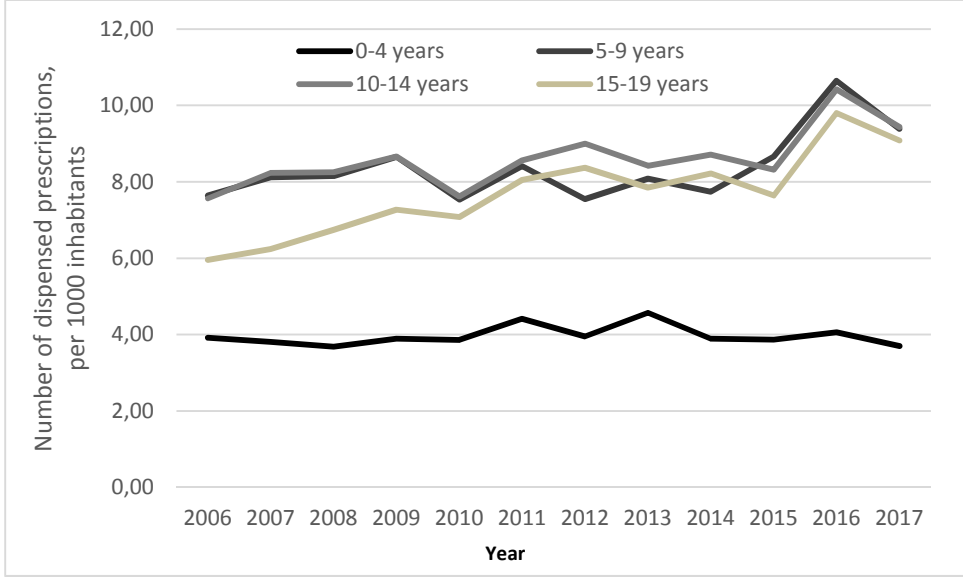


Panel B. Excluding data from 2011

Supplementary Figure 5. Annual dispensed prescriptions of epinephrine autoinjectors to pediatric patients, ages 0-19 years, per 1000 inhabitants in Sweden from 2006 to 2017, by sex and by age group

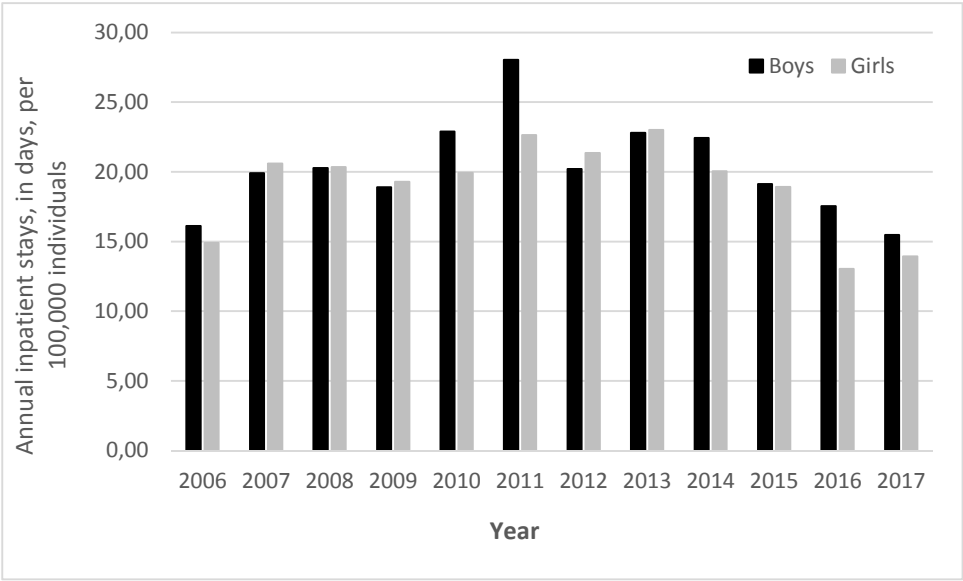


Panel A. Number of dispensed prescriptions per 1000 inhabitants, by sex

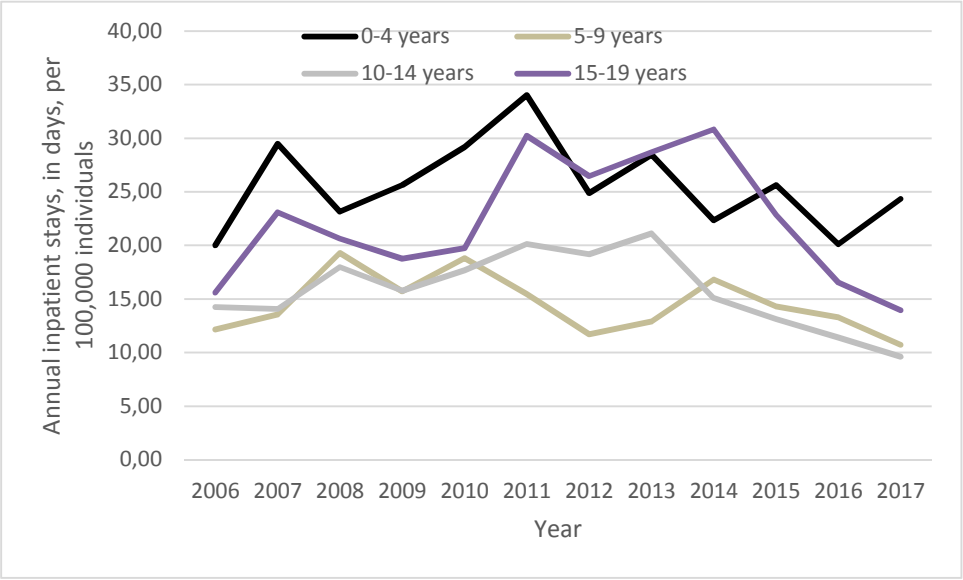


Panel B. Number of dispensed prescriptions per 1000 inhabitants, by age group

Supplementary Figure 6. Annual inpatient stays, in days, per 100,000 individuals, ages 0-19 years, in Sweden from 2006 to 2017, by sex and by age group



Panel A. Annual inpatient stays, in days, per 100,000 individuals, by sex



Panel B. Annual inpatient stays, in days, per 100,000 individuals, by age group

Supplementary Figure 7. Number of dispensed epinephrine autoinjectors per 1000 pediatric patients, ages 0-19 years, in Sweden in 2006 and in 2017, by county

