The use of short-acting Beta 2 adrenergic receptor agonists for asthma increased among Finnish and Swedish children from 2006-2017

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Short title: Asthma medication trends in Sweden and Finland

Abstract

Aim: Paediatric asthma hospitalisation has decreased in Finland, but has remained stable in Sweden. The reasons for these intercountry differences are unclear. The aim of this study was to explore the trend of dispensed asthma medication, including inhaled corticosteroids (ICS), among paediatric populations in the two countries.

Methods: We explored trends in dispensed asthma medication among paediatric populations aged 0-19 in Finland and Sweden from 2006-2017. The Finnish Statistics on Reimbursements for Prescription Medicines and The Swedish Prescribed Drug Register provided data on all dispensed asthma prescriptions.

Results: During the study period, the prevalence of dispensed ICS in paediatric populations was fairly stable in Finland and Sweden. Among children aged 0-4, ICS were 1.5 times more commonly dispensed in Sweden than Finland. The prevalence of children dispensed short-acting Beta 2 adrenergic receptor agonists (SABA) increased in both countries, but rose more in Finland (51%) than in Sweden (27%).

Conclusion: ICS were more commonly dispensed for children aged 0-4 in Sweden than Finland during the study period. This study showed an increasing prevalence of children dispensed SABA in Finland and Sweden, particularly Finland. Differences and trends in asthma medication may effect asthma hospitalisation and asthma deaths.

Key notes

- This study explored dispensing trends for asthma medication in paediatric populations in Sweden and Finland from 2006-2017.
- The Finnish Statistics on Reimbursements for Prescription Medicines and The Swedish Prescribed Drug Register provided data on all collected prescribed drugs.

- Inhaled corticosteroid dispensing was fairly stable and the use of short-acting Beta 2 adrenergic receptor agonists increased in both Finland (51%) and Sweden (27%).

Key words: asthma, child, inhaled corticosteroids, medication, short-acting Beta 2 adrenergic receptor agonists

INTRODUCTION

Asthma is a global health concern that affects approximately 300 million individuals worldwide and it is the most common chronic disease of childhood (1). The Global Initiative for Asthma recommends the use of low dose inhaled corticosteroids (ICS) as the basic treatment for children with asthma (1). Despite international guidelines and advances in treatment, implementing such guidelines remains a challenge (2). Thus, national guidelines are also needed to improve asthma care for children (3).

Although the worldwide burden of asthma and allergic diseases is notable, there have been reports of decreasing trends in hospitalisation, mostly due to improved treatment (4,5). We previously reported a decreasing incidence for paediatric asthma-related hospitalisation in Finland, but relatively stable rates in Sweden (6). However, the reasons for these intercountry differences were unclear. One possible reason could be differences in asthma treatment, as that may have some effect on hospitalisation rates.

The absence of anaphylaxis-related deaths among children in Finland between 1996 and 2013 has been partly attributed to good asthma care among the paediatric population in the country (7,8). Similarly, studies have reported that the incidence of asthma deaths among Finnish and Swedish children is also very low (9,10). Comprehensive asthma care in Finland and Sweden may be one reason that fatalities are rare among children with asthma. Although these studies are encouraging, large, multicentre and international studies on the secular trend for paediatric asthma medications are rare and needed.

The aim of this study was to explore the trend of dispensed asthma medication among paediatric populations in Finland and Sweden between 2006 and 2017 by using national register data.

METHODS

This study was based on the prescription drug registry based databases, The Finnish Statistics on Reimbursements for Prescription Medicines and The Swedish Prescribed Drug Register. These registries were used to report the prevalence of dispensed asthma medication for children 0-19 years, coded for pharmaceutical agents according to Anatomical Therapeutic Chemical Classification System. These registries included data on dispensed medication, namely the amount of drugs that had been collected from pharmacies by patients. The Finnish and Swedish registers provided data on all asthma prescriptions dispensed between 2006-2017.

The Anatomical Therapeutic Chemical Classification System codes and agents of interest in this study were: short-acting Beta 2 adrenergic receptor agonists (SABA) R03AC02 salbutamol and R03AC03 terbutaline, long-acting beta-agonists (LABA) R03AC12 salmeterol and R03AC13 formoterol. Between 2006 and 2017, the ICS on the market in Finland and Sweden were R03BA01 beclomethasone, R03BA02 budesonide, R03BA05 fluticasone, R03BA07 mometasone and R03BA08 ciclesonide.

Fixed combination therapy refers to asthma treatment with inhaled corticosteroids and long-acting beta-agonists, namely ICS plus LABA in the same inhaler. ICS plus LABA products on the market during 2006-2017 were R03AK06 fluticasone plus salmeterol, R03AK07 budesonide plus formoterol, R03AK08 beclomethasone plus formoterol, R03AK10 vilanterol plus fluticasone furoate and R03AK11 fluticasone plus formoterol.

The ICS group in analyses were any drug containing ICS or ICS plus LABA products.

Leukotriene receptor antagonists used to treat asthma were R03DC01 zafirlukast and R03DC03 montelukast.

Data were available from 2006 onward in both countries (11). Both registries provided valuable data on exposure to prescribed drugs and were useful to the study patterns (12). As the data were retrieved from aggregate databases from Finnish and Swedish authorities, ethical approval was not possible or necessary.

In order to compute the prevalence per 1,000 children dispensed asthma medications, the annual age-specific mid-populations were obtained from the Official Statistics of Finland and Statistics Sweden, which are both computer-based national population registers. The prevalence proportion ratio (PPR) and 95% confidence interval (CIs) was calculated using Poisson regression. Line plots were used to illustrate the association between Finland and Sweden and the yearly number of asthma prescriptions dispensed. The statistical analysis was performed using Stata 15.1 (StatCorp LP, Texas, USA).

RESULTS

The prevalence of children dispensed any drug containing ICS showed similar, fairly stable, trends in both countries between 2006 and 2017 (Figures 1 and 2). In Finland, the prevalence of children dispensed any drug containing ICS was 46.4 per 1,000 in 2006 and 47.8 in 2017. The prevalence in Sweden was comparable to those noted in Finland, with corresponding numbers of 47.2 per 1,000 in 2006 and 55.7 in 2017. The prevalence of children dispensed any drug containing ICS was higher in Sweden, where the PPR was 1.12 (95% CI 1.12-1.13).

The prevalence of children dispensed ICS - beclomethasone, budesonide, fluticasone, mometasone or ciclesonide - was very similar during 2006-2014. Between 2015 and 2017, these numbers decreased slightly in Finland and increased slightly in Sweden (Figure 1).

During 2006-2017, the prevalence of children dispensed combination therapy with ICS and long-acting beta-agonists (ICS plus LABA) was rather low and stable in both countries (Figure 1). In Finland, the prevalence of children dispensed ICS plus LABA was 13.5 per 1,000 in 2006, and 11.1 in 2017. The prevalence was comparable in Sweden, where the corresponding numbers were 11.4 per 1,000 in 2006, and 8.2 in 2017. The prevalence of children dispensed combination therapy was lower in Sweden than in Finland, with a PPR of 0.87 (95% CI 0.87- 0.87).

The prevalence of children dispensed leukotriene receptor antagonists increased slightly in both countries during the first half of the study period and these were more commonly dispensed in Finland (Figure 1).

Between 2006 and 2017, the prevalence of children dispensed SABA increased in both countries, but this rise was higher in Finland (51%) than in Sweden (27%). In

2006, the prevalence of children dispensed SABA was 49.7 per 1,000 and 75.3 in 2017. In Sweden, the prevalence was 51.9 per 1,000 in 2006 and 65.8 in 2017, respectively (Figure 1). The prevalence of children dispensed SABA was lower in Sweden than in Finland, with a PPR of 0.89 (95% CI 0.89-0.89).

Compared to the use of SABA, the prevalence of children dispensed LABA as a separate inhaler was low in both countries. In 2006, the prevalence was 0.48 per 1,000 and it was 0.08 in 2017 in Finland. In Sweden, the prevalence was 3.3 per 1,000 in 2006 and it was 1.3 in 2017. The prevalence of children dispensed LABA as a separate inhaler was 6.8 higher in Sweden than in Finland in 2006 and 16.5 higher in 2017. Salmeterol comprised 34.2% and formoterol 65.8% of all dispensed LABA in Finland. The corresponding figures in Sweden were 11.5% for salmeterol and 88.5% for formoterol, respectively. The prevalence was markedly higher in Sweden than in Finland, with a PPR of 9.2 (95% CI 8.8-9.5).

Age group analysis

The increase in SABA was seen in all age groups, but most markedly in children aged 0-4 (Figure 3). This rise was more rapid in Finland than Sweden among children aged 0-4. In 2006, the prevalence of Finnish children aged 0-4 dispensed SABA was 42.9 per 1,000 and it was 102.7 in 2017. In Sweden, the respective figures for this age group were 60.4 per 1,000 in 2006 and 85.7 in 2017 (Figure 3A). The prevalence of SABA use in this age group was lower in Sweden than Finland, with a PPR of 0.89 (95% CI 0.89-0.89).

The prevalence of Finnish children aged 0-4 who were dispensed any drug containing ICS was 37.7 per 1,000 in 2006 and 37.1 in 2017. The prevalence in Sweden was markedly higher, with corresponding numbers of 54.7 per 1,000 in 2006 and 67.2 in 2017 (Figure 3a). The prevalence of children dispensed any drug

containing ICS was higher in Sweden than in Finland in this age group, with a PPR 1.50 (95% CI 1.49-1.51). (Figure 3a).

The prevalence of children aged 5-9 dispensed SABA was lower in Sweden than in Finland, with a PPR of 0.83 (95% CI 0.82-0.83). The prevalence of children dispensed any drug containing ICS in this age group was also lower in Sweden than in Finland, with a PPR of 0.90 (95% 0.90, 0.91). (Figure 3b).

The prevalence of children aged 10-14 dispensed SABA was lower in Sweden than in Finland, with a PPR of 0.91 (95% CI 0.91-0.92). Meanwhile, the prevalence of children dispensed any drug containing ICS in this age groups had a PPR of 0.89 (95% CI 0.89-0.90) (Figure 3c).

The prevalence of children aged 15-19 dispensed SABA was lower in Sweden than in Finland, with a PPR of 0.85 (95% CI 0.85-0.86). So was the prevalence of children dispensed any drug containing ICS, with a PPR of 0.88 (95% CI 0.87-0.88) (Figure 3d).

Most of the drugs that only contained LABA, namely salmeterol and formoterol - were dispensed to children over five years of age. This age group accounted for 97.1% in Finland and 99.3% in Sweden.

DISCUSSION

This study showed an increasing prevalence of children dispensed SABA in Finland and Sweden, particularly in Finland. This increased prevalence was most clearly seen among children aged 0-4. The prevalence of ICS dispensing was very similar in Finland and Sweden, with one exception. ICS dispensing to children aged 0-4 was 1.5 times higher in Sweden than in Finland. The prevalence of combination therapy ICS plus LABA decreased slightly in both countries. The use of combination therapy and leukotriene antagonists was slightly more common in Finland than in Sweden. LABA dispensing of formoterol and salmeterol were not common in either country, but were dispensed 9.2 times more often in Sweden than Finland.

In many countries, childhood asthma control remains suboptimal (13). Despite national and international guidelines and advances in treatment, implementation has been reported to be a real challenge and some paediatric patients may not receive necessary treatment for their asthma (3). Undertreatment of asthma may lead to hospitalisation (14) or even death (10). It is well-recognised that asthma should not be treated with just SABA (15). However, the efficient use of SABA, when needed, combined with exhaustive asthma care with ICS may decrease asthma-related excacerbation, hospitalisation and even death among children with asthma.

Previously, we reported a decreasing incidence of paediatric asthma-related hospitalisation among children aged 0-4 in Finland and Sweden between 2005-2014. The results were more pronounced in Finland than Sweden (6). The changes in the use of ICS and SABA may have had some effect on hospitalisation rates. Earlier Swedish studies reported decreasing hospital days due asthma among Swedish children until year 2000 (16,17). The most probable reason for the decrease in asthma hospitalisation has been anti-inflammatory treatment with ICS (17). It is possible that efficient use of SABA, when needed, along with exhaustive

asthma care with ICS may have decreased the asthma-related hospitalisation of young children. The excessive use of ICS is not likely to prevent excacerbation (18). Moreover, an association has been found between ICS and growth reduction (19,20). These findings support the use of the minimal effective ICS dose for children with asthma (21).

Inhaled SABA was the first-line treatment for asthma for 50 years. However, this treatment dates from an era when asthma was thought to be a disease of bronchoconstriction. The Global Initiative for Asthma guidelines that were in place during the study period recommended using low dose ICS for basic treatment for children with asthma (1). This should be combined with SABA when needed. It should be noted that lower doses of salbutamol are also effective, but higher doses are also safe (22). Salbutamol is used with metered dose inhalers with spacers at homes. This is an effective way to treat children, even in emergency departments, and performs well when compared to salbutamol given via nebulisers (23).

Between 1996 and 2006, the use of combination therapy with ICS and LABA increased in Finland (24). This study shows a rather slow and slightly decreasing prevalence of combination therapy in both Finland and Sweden. The prevalence of ICS dispensed from pharmacies was comparable in both countries, except among children aged 0-4. In this age group, the prevalence was 1.5 higher in Sweden than in Finland.

The reasons for the changes and differences between these two high-income neighbouring countries are not totally clear. The prevalence of paediatric asthma is very similar and national asthma care guidelines are not likely to explain the differences (25,26). Some changes in Finland may be explained by the actions of Finnish Asthma and Allergy Programmes, that have focused on early intervention

and disease control (8,27). Some rise in Swedish prescriptions can be explained by political changes in the country. In 2016, the Swedish Government eliminated co-payments, also described as out-of-pocket costs, for most paediatric medication, including asthma medications, to children under the age of 18 years with a national identification number. This has increased the levels of some medicines dispensed from pharmacies (28). However, this change is not likely to explain all the differences between the two countries. In addition, the changes in the national guidelines for asthma during the study period are not likely to explain the rise in SABA use (26). However, changes in guidelines for cough medicine for young children may have had some effect on the rise of SABA prescriptions (29). Since cough medicines should be avoided, SABA may have been prescribed instead for common colds. It is also possible that using peak flow meters as a diagnostic tool was more common in Finland than in Sweden. This may explain the higher prevalence of dispensed SABA among children in Finland. However, this does not explain differences among children aged 0-9, since peak flow meters have mainly been used among children who are 12 years or older (26).

Products that just contained LABA were dispensed 9.2 times as much in Sweden as Finland. It is possible that there were national differences in whether physicians prescribed LABAs as needed. It may well be that formoterol, as needed, has been used as a reliever among Swedish asthma patients along with regular ICS. External factors, such as marketing, may also have had an effect on these figures. However, the prevalence of LABA dispensing was so limited in both of these countries that they were not likely to explain, for example, differences in paediatric asthma hospitalisation (6).

Asthma is diagnosed on the basis of respiratory symptoms of wheeze, cough, chest tightness, and, or, dyspnoea, together with physiological evidence of variable

expiratory airflow limitation. The prevalence of asthma varies widely around the world (30). Asthma is both under-diagnosed and over-diagnosed. Population-based studies suggest that 20 to 70% of people with asthma remain undiagnosed and untreated (30). Meanwhile, other studies suggest that 30-35% of children and adults with an asthma diagnosis do not have current asthma (30,31). Thus, reliable international figures for asthma prevalence are scarce. There are even fewer comparable studies concerning the prevalence of prescribed asthma drugs for children or asthma drug consumption at a national level.

This novel study describes the national trends of asthma medication over a period of 12 years among children in two well-defined populations. The major strength of this study was that the data were obtained at the national level using validated and well-established registers. To our knowledge, similar national level secular trends over time have not been previously described. This study included all inhaled drugs used in asthma care for children. Finally, cromones were excluded in the study as they have no effect on paediatric asthma and their use been ceased in Nordic countries prior to the study period (24).

The study also had some limitations. First, we were unable to determine whether for example, the increase of SABA dispensing explained the decline in hospitalisation or if the increase was the result of guideline changes to prescribe SABA, rather than traditional cough medicine, for children with respiratory infections. Second, the number of prescriptions does not necessarily equate to the numbers of drugs used. The prescription data only included medicine that had actually been dispensed from pharmacies and not the number of prescriptions issued by doctors. Another point worth making is that it is unlikely that the proportion of medicines that were used by the children, compared to those bought from pharmacies, changed during the study period.

Over the course of the study period, biological treatments such as omalizumab came onto the market (32). It is possible that the use of omalizumab has decreased asthma exacerbation, hospitalisation and even deaths. The prevalence of children who were prescribed omalizumab were not included in the prescribed registers. These drugs are only administered in hospitals and not dispensed from pharmacies to paediatric patients in Finland or Sweden (26). However, the number of patients treated with omalizumab would have been very limited and it is unlikely that it would have caused bias with regard to the prevalence of children prescribed asthma drugs.

CONCLUSION

This study showed an increasing prevalence of children SABA dispensing in Finland and Sweden, particularly Finland. The clearest change in both countries during the 2006-2017 study period was the rise in SABA dispensing among children aged 0-4. The prevalence of ICS dispensing was very similar and fairly stable in both countries. However, ICS were more commonly dispensed to children aged 0-4 in Sweden than in Finland. Differences and trends in asthma medication may have an effect on asthma exacerbation among children. It is possible that the efficient use of SABA, when needed, along with exhaustive asthma care with ICS may have decreased asthma-related hospitalisation among young children.

ABBREVIATIONS

CI	confidence interval
ICS	inhaled corticosteroids
GINA	Global Initiative for Asthma
LABA	long-acting beta-agonists
PPR	prevalence proportion ratio
SABA	short-acting Beta 2 adrenergic receptor agonists

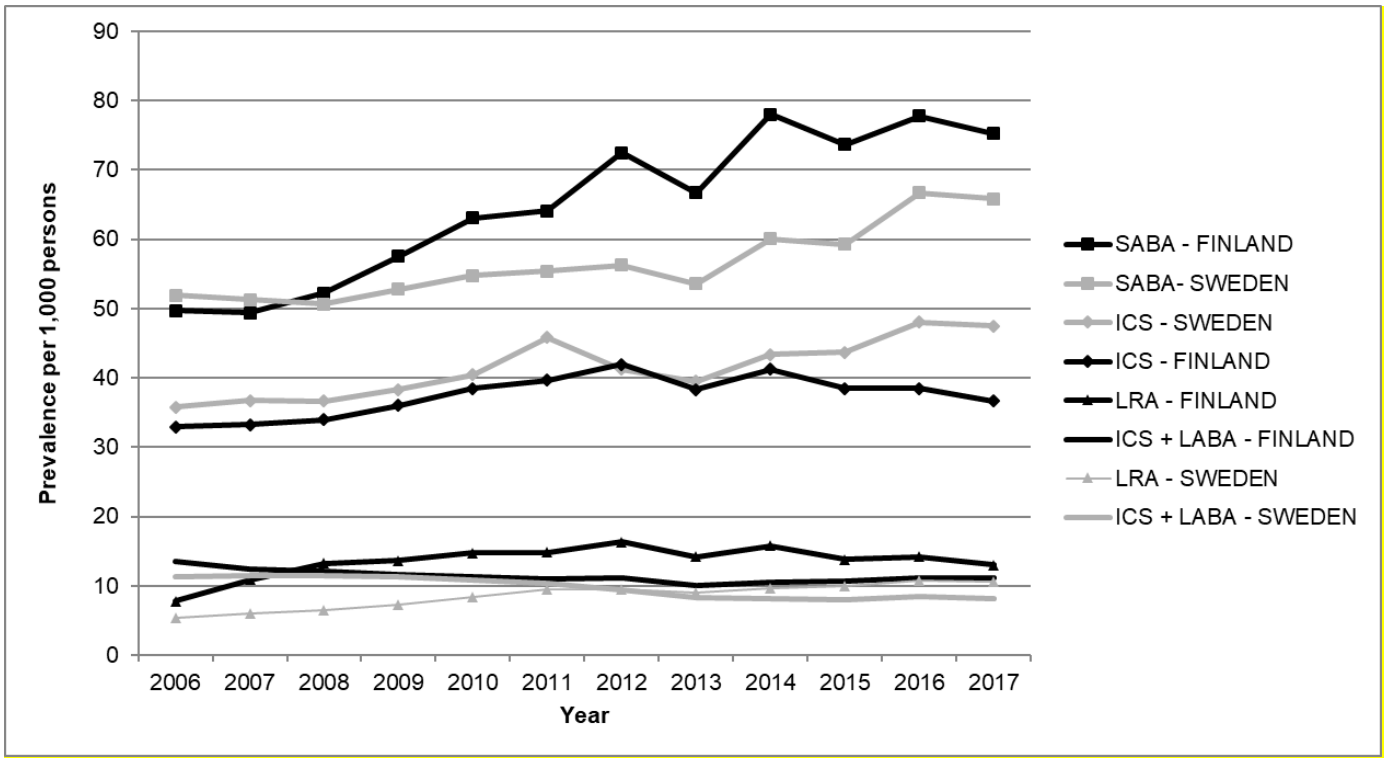
References

1. "Global strategy for asthma management and prevention: GINA executive summary." E.D. Bateman, S.S. Hurd, P.J. Barnes, J. Bousquet, J.M. Drazen, J.M. FitzGerald, P. Gibson, K. Ohta, P. O'Byrne, S.E. Pedersen, E. Pizzichini, S.D. Sullivan, S.E. Wenzel and H.J. Zar. Eur Respir J 2008; 31: 143-178. *The European respiratory journal* 2018; 51 2.
2. Zhou X, Hong J. Pediatric Asthma Management in China: Current and Future Challenges. *Paediatric drugs* 2018; 20 2:105-10.
3. Becker AB, Abrams EM. Asthma guidelines: the Global Initiative for Asthma in relation to national guidelines. *Current opinion in allergy and clinical immunology* 2017; 17 2:99-103.
4. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 351 9111:1225-32.
5. de Miguel-Diez J, Jimenez-Garcia R, Hernandez-Barrera V, Lopez de Andres A, Villa-Asensi JR, Plaza V, et al. National trends in hospital admissions for asthma exacerbations among pediatric and young adult population in Spain (2002-2010). *Respiratory medicine* 2014; 108 7:983-91.
6. Kivisto JE, Protudjer JLP, Karjalainen J, Bergstrom A, Korppi M. Trends in paediatric asthma hospitalisations - differences between neighbouring countries. *Thorax* 2018; 73 2:185-7.
7. Kivisto JE, Dunder T, Protudjer JL, Karjalainen J, Huhtala H, Makela MJ. Adult but no pediatric anaphylaxis-related deaths in the Finnish population from 1996 to 2013. *The Journal of allergy and clinical immunology* 2016; 138 2:630-2.
8. Kauppi P, Linna M, Martikainen J, Makela MJ, Haahtela T. Follow-up of the Finnish Asthma Programme 2000-2010: reduction of hospital burden needs risk group rethinking. *Thorax* 2013; 68 3:292-3.
9. Kivisto JE, Karjalainen J, Kivela L, Huhtala H, Protudjer JLP. Very low asthma death incidence among Finnish children from 1999 to 2015. *Pediatric pulmonology* 2018; 53 8:1009-13.
10. Bergstrom SE, Boman G, Eriksson L, Formgren H, Foucard T, Horte LG, et al. Asthma mortality among Swedish children and young adults, a 10-year study. *Respiratory medicine* 2008; 102 9:1335-41.
11. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and drug safety* 2007; 16 7:726-35.
12. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic & clinical pharmacology & toxicology* 2009; 106 2:86-94.
13. Hossny E, Rosario N, Lee BW, Singh M, El-Ghoneimy D, Soh JY, et al. The use of inhaled corticosteroids in pediatric asthma: update. *The World Allergy Organization journal* 2016; 9:26.
14. Kocevar VS, Bisgaard H, Jonsson L, Valovirta E, Kristensen F, Yin DD, et al. Variations in pediatric asthma hospitalization rates and costs between and within Nordic countries. *Chest* 2004; 125 5:1680-4.

15. Boulet LP, Reddel HK, Bateman E, Pedersen S, FitzGerald JM, O'Byrne PM. The Global Initiative for Asthma (GINA): 25 years later. *The European respiratory journal* 2019; 54 2.
16. Wennergren G, Strannegard IL. Asthma hospitalizations continue to decrease in schoolchildren but hospitalization rates for wheezing illnesses remain high in young children. *Acta paediatrica* 2002; 91 11:1239-45.
17. Wennergren G, Kristjansson S, Strannegard IL. Decrease in hospitalization for treatment of childhood asthma with increased use of antiinflammatory treatment, despite an increase in prevalence of asthma. *The Journal of allergy and clinical immunology* 1996; 97 3:742-8.
18. Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. *The New England journal of medicine* 2018; 378 10:891-901.
19. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. *The Cochrane database of systematic reviews* 2014; 7:CD009878.
20. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of inhaled glucocorticoids in childhood on adult height. *The New England journal of medicine* 2012; 367 10:904-12.
21. Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. *The Cochrane database of systematic reviews* 2014; 7:CD009471.
22. Muchao FP, Souza JM, Torres HC, De Lalibera IB, de Souza AV, Rodrigues JC, et al. Albuterol via metered-dose inhaler in children: Lower doses are effective, and higher doses are safe. *Pediatric pulmonology* 2016; 51 11:1122-30.
23. Mecklin M, Paassilta M, Korppi M. Salbutamol with metered dose inhalers with spacers - an established emergency treatment for preschool wheeze. *Acta paediatrica* 2012; 101 11:1161-3.
24. Makela MJ, Virta L, Kaila M, Gronlund J, Vanto T, Klaukka T. Medication use in children with asthma in Finland from 1995 to 2006. *The Journal of allergy and clinical immunology* 2008; 122 3:648-9.
25. Bjorksten B, Dumitrascu D, Foucard T, Khetsuriani N, Khaitov R, Leja M, et al. Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. *The European respiratory journal* 1998; 12 2:432-7.
26. Haahtela T, Lehtimaki L, Ahonen E, Harju T, Jartti T, Kankaanranta H, et al. [Update on current care guidelines: asthma]. *Duodecim; laaketieteellinen aikakauskirja* 2013; 129 9:994-5.
27. Pelkonen AS, Kuitunen M, Dunder T, Reijonen T, Valovirta E, Makela MJ, et al. Allergy in children: practical recommendations of the Finnish Allergy Programme 2008-2018 for prevention, diagnosis, and treatment. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2012; 23 2:103-16.
28. Protudjer JLP, Middelveld R, Ballardini N, Wai HM, Ahlstedt S, Nilsson L, et al. Epinephrine dispensings, allergy hospitalizations and the elimination of co-payments in Sweden. *Allergy* 2019; 74 6:1197-200.
29. Tapiainen T, Aittoniemi J, Immonen J, Jylkka H, Meinander T, Nuolivirta K, et al. Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children. *Acta paediatrica* 2016; 105 1:44-9.

30. Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and Overdiagnosis of Asthma. *American journal of respiratory and critical care medicine* 2018; 198 8:1012-20.
31. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemiere C, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. *Jama* 2017; 317 3:269-79.
32. Tortajada-Girbes M, Bousquet R, Bosque M, Carrera Martinez JJ, Ibanez MD, Moreira A, et al. Efficacy and effectiveness of omalizumab in the treatment of childhood asthma. *Expert review of respiratory medicine* 2018; 12 9:745-54.

Figure 1. Prevalence of asthma medication dispensed for children aged 0-19 years in Finland and Sweden.



Abbreviations: ICS, Inhaled corticosteroids; LRA, Leukotriene Receptor Antagonists; SABA, Short-Acting Beta-2 adrenergic receptor agonists.

Figure 2. Prevalence of any ICS dispensed to children aged 0-19 years in Finland and Sweden.

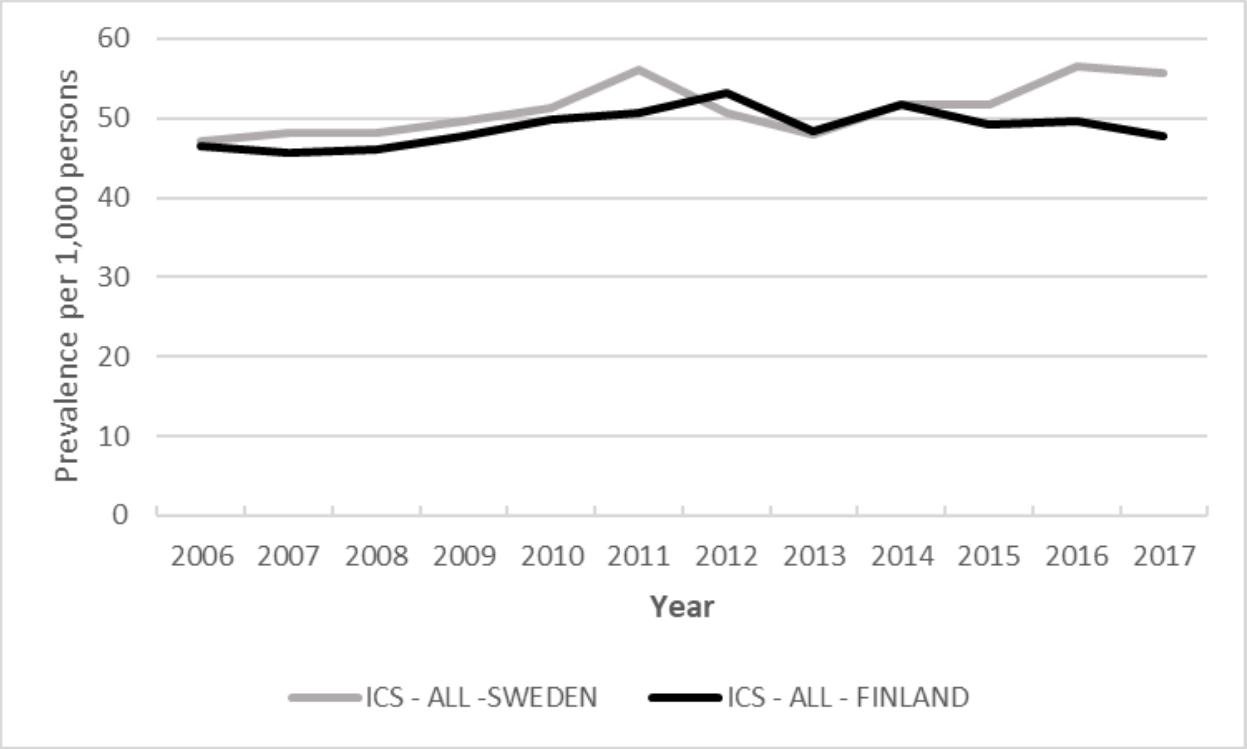
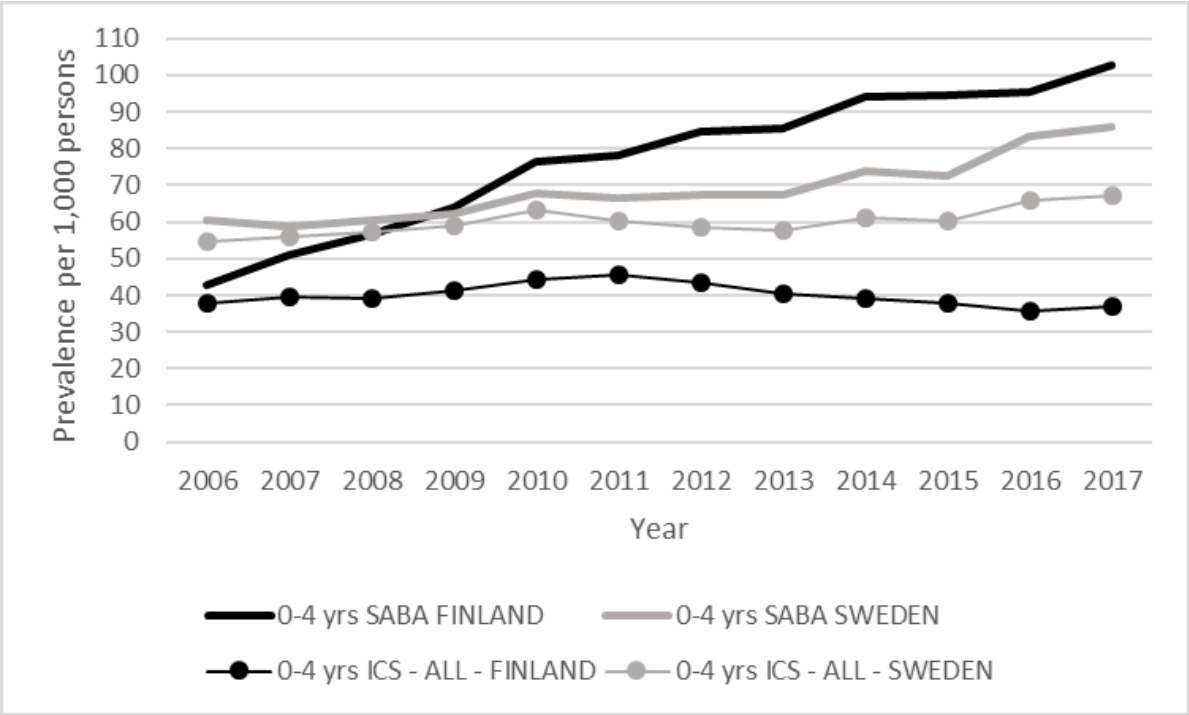
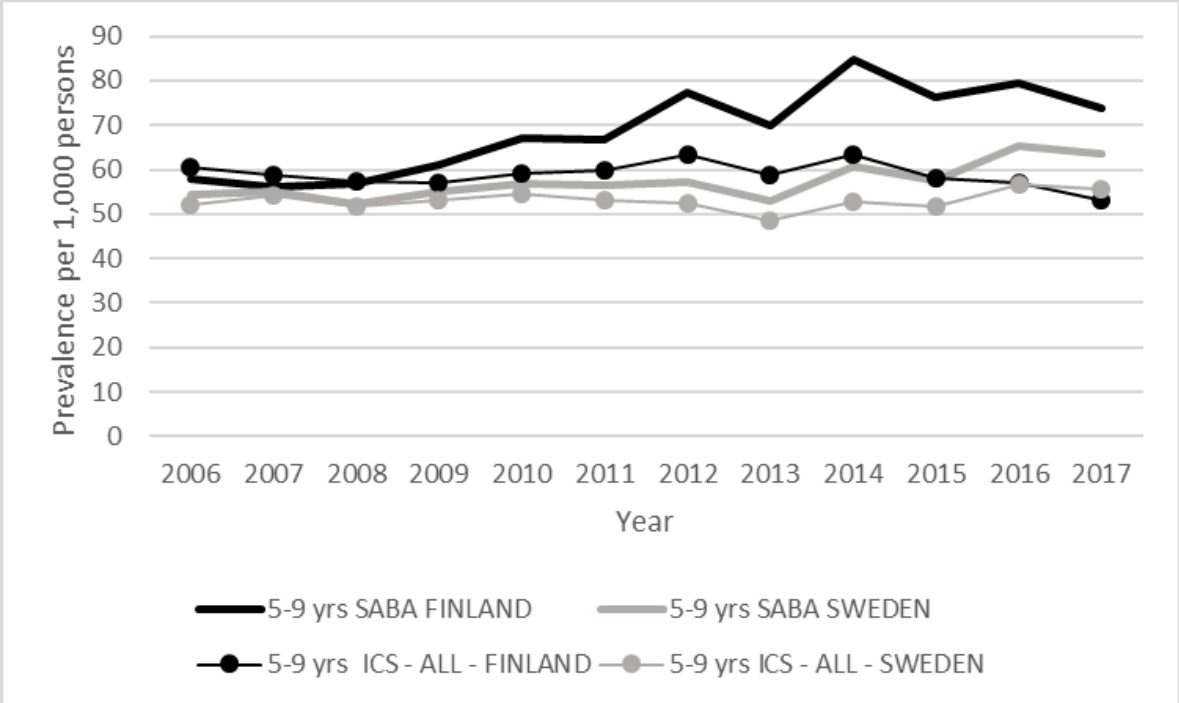


Figure 3. Prevalence per 1,000 of dispensed SABA and any inhaled corticosteroids among children aged 0-19 years in Finland and Sweden.

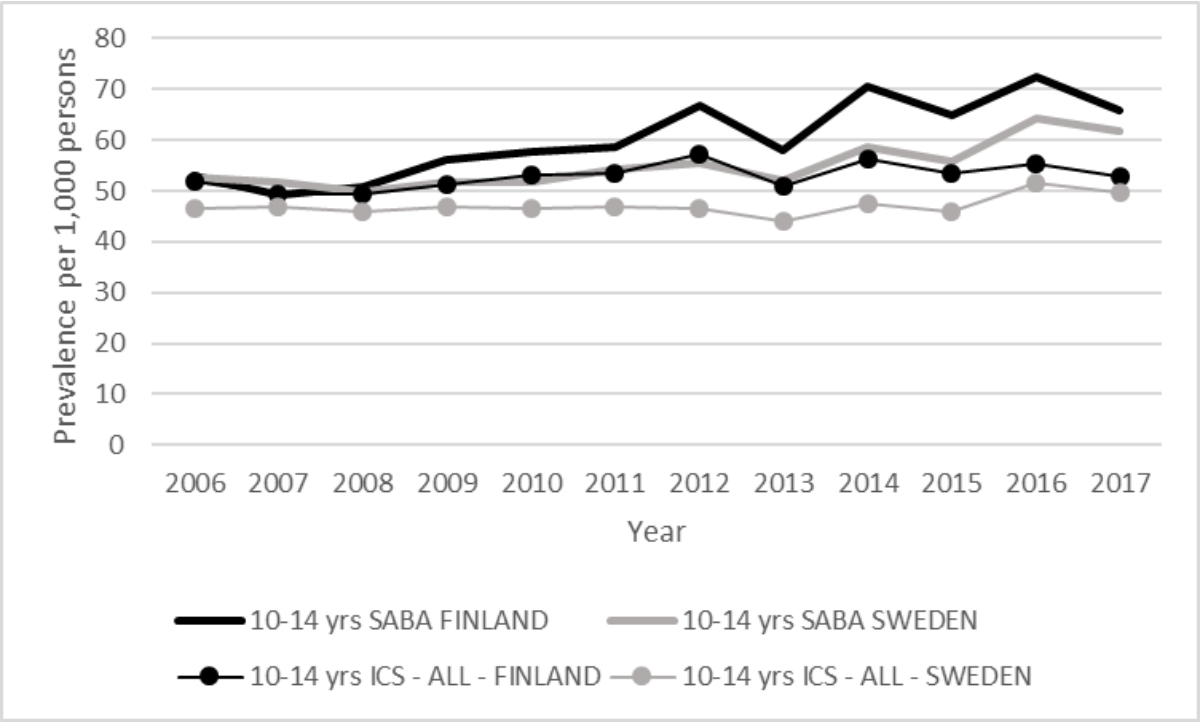
A. 0-4 years old



B. 5-9 years old



C. 10-14 years old



D. 15-19 years old