



**Karolinska
Institutet**

This is the peer reviewed version of the following article:
Pharmacoepidemiol Drug Saf. 2019 Jul;28(8):1109-1116.

**Sibship and dispensing patterns of asthma medication
in young children-a population-based study.**

**Elin Dahlén, Sara Ekberg, Cecilia Lundholm, Eva
Wikström Jonsson, Inger Kull, Björn Wettermark and
Catarina Almqvist.**

which has been published in final form at

<https://doi.org/10.1002/pds.4802>

This article may be used for non-commercial purposes in
accordance with Wiley Terms and Conditions for Self-
Archiving.

Access to the published version may require subscription.
Published with permission from: **Wiley**

Sibship and dispensing patterns of asthma medication in young children- a population based study

Running title: Sibship and asthma medication in young children

Elin Dahlén^{1,2}, Sara Ekberg¹, Cecilia Lundholm¹, Eva Wikström Jonsson³, Inger Kull⁴, Björn Wettermark², Catarina Almqvist^{1,5}.

¹Dept of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

²Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institute, Stockholm, Sweden

³Clinical epidemiology, Department of Medicine Solna, Karolinska Institutet, and Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden

⁴Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden and Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden

⁵Pediatric Allergy and Pulmonology Unit at Astrid Lindgren Children's Hospital, Karolinska University Hospital

Corresponding author

Elin Dahlén

Centre for Pharmacoepidemiology, Department of Medicine

Karolinska University Hospital Solna, T2

S-171 76 Stockholm, Sweden

E-mail: elin.dahlen@ki.se

Key words: Asthma, Drug utilization, Medication, Persistence, Sharing, Sibship.

Key points:

- Sibship affects dispensing patterns, measured as incidence and persistence, of asthma medication in young children regardless of asthma diagnoses.
- The estimated proportion of children with persistent asthma medication was lower for children with siblings compared with singletons, and there was no difference in effect between older, younger, full, half, or number of siblings.
- When including the siblings' dispensed asthma medication in the analysis and comparing with unrelated control children, the estimated proportion of children with persistent medication increased, suggesting that siblings may share asthma medications.

Word count: 3,529

Abstract

Purpose

Our aim was to study the association between sibship and dispensing patterns of asthma medication in young children, focusing on incidence and persistence, and taking sibship status, asthma diagnoses, and siblings' medication into account.

Methods

A register-based cohort study including all children (n=50,546) born in Stockholm, Sweden 2006–2007, followed up during 2006–2014. Exposure was sibling status; outcome was incidence of dispensed asthma medication and persistence over time. A Cox-model was used to study the association between sibship and asthma medication. Persistence was defined using two different time windows (4- and 18-months) in a refill sequence model including siblings' and unrelated control children's medication.

Results

After one year of age, the adjusted hazard ratio of dispensed asthma medication was 0.85 (95%CI 0.80–0.90) among children with siblings compared to singletons. The estimated proportion of children with persistent controller medication was 7.2% (4-month model) and 64.5% (18-month model). When including the siblings' controller medication, the estimated proportion was 8.8% (4-months) and 7.8% for control children (relative risk, RR 0.89, 95%CI 0.81-0.98). The persistence was lower for those with siblings compared to singletons (adj. RR 0.72, 95%CI 0.62-0.85 for 4-months) with similar estimates for older, younger, and full siblings and regardless of asthma diagnoses.

Conclusions

Siblings have different dispensing patterns of asthma medications compared to singletons regardless of asthma diagnoses. After including the siblings' asthma medication and compared with control children, the proportion of children with persistent medication increased which may indicate that siblings share asthma medications.

Introduction

Asthma is one of the most common chronic diseases among children worldwide, and as many as one out of five children have experienced asthma symptoms up to age 12 (1, 2). Pharmacological treatment is a cornerstone in asthma management and many studies have shown room for improvement in adherence to medication and guidelines (3-5), although some have limitations such as cross-sectional design or small samples of patients collected through surveys, sometimes with poor response-rates (e.g., (6-11)). To achieve asthma control, continuous use of controller medication is required for many children with asthma (1). However, the need for asthma medication can vary over time, due to viral infections or exposure to allergens, which in turn leads to irregular dispensing patterns of asthma medications.

Having an older sibling is associated with a lower risk of asthma (12-14). This may be due to an increased risk of infections during childhood which may reduce the risk of asthma and allergic disease (15). It may also be explained by differences in parental health-seeking behavior in first-born children compared to younger siblings (14). Sibling status, i.e., being singleton, full- or half sibling, can also be associated with differences in children's medication dispensing and use, such as sharing medication, i.e. the lending or borrowing of prescribed medications (16). In a systematic review by Beyene et al., it was found that sharing of medication was common (17), with a prevalence of 6-23% for lending medication and 5-52% for borrowing. Sharing of asthma medication has been addressed in a few studies (18-22), but only two studies have addressed sharing among children and adolescents (21, 22) or the effect on family income (21). In a previous study, we found that 13% of the adolescents with asthma claimed that they used someone else's medication (23). However, it is still unknown to what extent sibship influences

dispensing patterns of medications and if there is any difference among children with older, younger, and full- and half siblings.

In registers, continuous medication use is often measured as persistence (24-26), i.e., time from initiation to discontinuation of treatment (26). Although registers are considered as the golden standard when measuring persistence, there is no standard method on how to measure persistence in children with asthma since the need for asthma medication can vary over time due to infections or allergen exposure. We previously showed that different time windows in a register influenced the prevalence of asthma medication (7) but the impact of different time windows on the estimated persistence has not been studied. Using a time window of 12 months, Øymar et al. found that the prevalence of inhaled corticosteroids (ICS) among pre-school children was high, but the persistence was low. (27). Furthermore, no study has, to the best of our knowledge, included the siblings' medication in a persistence model, or accounted for sibship status (older, younger, full, half and number of siblings). Better understanding may inform healthcare professionals seeing children with asthma and improve clinical care. Based on clinical experience and previous studies (12-14, 16, 23) on medication sharing, our hypothesis is that siblings have different dispensing patterns of asthma medications compared to singletons, and that this also depends on sibship status, and diagnoses.

The aim of this study was to assess the association between sibship and dispensing patterns of asthma medications in young children. Focus was on a) initiation of asthma medication, and b) differences in persistence of the drug therapy, taking sibship status, diagnoses, and siblings' asthma medications into account.

Methods

Study design and study population

This was a population-based cohort study including all children born in Stockholm County, Sweden, between January 1, 2006 and December 31, 2007. This period was selected since the Swedish Prescribed Drug Register (SPDR) started on July 1, 2005, and we wanted to include information on all dispensed medications from birth onwards. Information on siblings was included, and those born in 2006 or 2007 contributed as study participants as well as siblings. The study period ranged from January 1, 2006 to December 31, 2014.

The children were identified from the Medical Birth Register (MBR) (28) and linked to the Multi Generation Register (MGR) (29), using each child's personal identity number (PIN). The full- and half siblings were identified from their biological mothers and fathers in the MGR, as well as older and younger siblings. Area of residence from Statistics Sweden provided information about emigration from the Stockholm County. The date of death from the Cause of Death register was also collected. The SPDR was added to the data to obtain information on dispensed prescription medications for each child and his or her siblings (30). The children's diagnoses were retrieved from the National Patient Register (NPR) (31) and the administrative healthcare databases VAL held by the Stockholm County Council (32). Finally, the socioeconomic status (family income) was collected from the longitudinal integration database for health insurance and labor market studies (LISA by Swedish acronym), held by Statistics Sweden (29). All data was linked using the children's personal identity number.

Exposure

Each child's sibling status was used as the exposure and defined in five different ways; a) no sibling/sibling, b) no sibling/older/younger/both older and younger, c) no sibling/full/half/both

full and half, d) no sibling/one sibling/at least two siblings, and e) no sibling/sibling without an asthma diagnosis/sibling with an asthma diagnosis. The sibling status was updated yearly during the follow-up.

Siblings' asthma diagnosis was denoted if at least one of the siblings had a recorded diagnosis of ICD-10 J45 or J46 from inpatient care, specialized ambulatory care, or primary care.

Outcome

Dispensed asthma medication was used as the outcome, identified by ATC-codes as: Short-acting β_2 -agonists, SABA (ATC-codes R03AC02, R03AC03); Inhaled corticosteroids, ICS (R03BA); Leukotriene receptor antagonists, LTRAs (R03DC); Long-acting β_2 -agonists, LABA (R03AC12, R03AC13); Fixed combination of ICS + LABA (R03AK); at least one of SABA, ICS, LTRAs, LABA, or fixed combination was denoted as 'any asthma medication.'

Persistence after 1.5 years was defined as refill of a prescription with a controller medication (either ICS, LTRAs, or fixed combination) within a defined time window (4- or 18-months). In the sibling persistence model, the child was classified as being persistent to controller medication if the child or his/her sibling refilled the prescription within the defined time window (Figure 1).

Potential confounders

The child's sex was collected from the MBR. Family income was collected from the LISA database and defined as disposable income at the household level during 2006. Disposable income includes individual net benefits after deduction of debits such as taxes, repaid study allowance, and paid maintenance support. The family income was divided into quartiles.

Asthma diagnosis among index children was defined as any recorded diagnosis (main or contributing diagnosis) of ICD-10 J45 or J46 from inpatient care, specialized ambulatory care, or primary care (33).

Parental diagnosis of asthma was denoted if at least one of the parents had a recorded diagnosis of ICD-10 J45 or J46 from inpatient care, specialized ambulatory care, or primary care.

Statistical analyses

Descriptive statistics including frequencies, proportions, and quartiles were used to describe the study population. The prevalence of asthma medication and asthma diagnosis was calculated as the number of children with dispensed medication/recorded diagnosis during the follow-up, divided by all the children in the study population. We calculated unadjusted incidence rates for first asthma medication dispensed as the number of first dispenses per 1000 person-years with 95% confidence intervals (CIs) based on the Poisson distribution.

A Cox-model, with age as time scale, was used to study the association between sibship and initiation of asthma medication. Hazard ratios (HR) with 95% CIs were estimated. Sibship was used as a time-varying exposure. The Cox-model was adjusted for family income. A child was censored when moving from Stockholm County, death, or end of follow-up (December 31, 2014), whichever occurred first. Due to non-proportional hazards, an interaction term with age was included (below/above age 1 year).

Persistence was defined with two different time windows, 4- and 18-months, using a refill sequence model (25). The 4-month time window was selected based on the Swedish reimbursement system, where a prescription for medication for a chronic disease is normally refilled after 3 months. The 18-month time window was used based on our previous findings (7).

To be classified as being persistent to asthma controller medication, the prescription had to be refilled within the defined time window (4- or 18-months), see Figure 1. Sibship was assessed at the time of initiation of controller medication. The estimated proportion of children with persistent asthma controller medication was measured as percentage with 95% CI. In addition, siblings' controller medication was added to a sibling persistence model, in which the child was classified as being persistent if the child or his/her sibling refilled the prescription within the defined time window. However, adding another child's medication to the persistence evaluation would automatically increase the persistence. Therefore, for comparison, we added controller medication from randomly selected siblings in the cohort to an unrelated control child's persistence model, in which the index child and the assigned control child's controller medication was included. Only children who live together (at least part time) i.e. siblings, would have the chance to share medication. Thus, the persistence model including asthma medication from the unrelated control children was compared to the sibling persistence model to test the difference in persistence. A significant higher persistence in the sibling model compared to the unrelated control children model would suggest that siblings share medications. A log-binomial regression model was used to estimate the relative risk (RR) with 95% CIs for the association between sibship and persistence of asthma medication after 1.5 years, using both the 4-month and 18-month models. The models were adjusted for family income. Asthma diagnosis and parental asthma diagnosis were added to the model as interaction terms with sibship and tested for with the Likelihood ratio test.

>>>Insert Figure 1 here<<<

Results

The study population consisted of 50 546 children with 9% censored during follow-up, due to moving from Stockholm County (n=4501) or death (n=48). At birth, 59% of the children had an older sibling (43% full sibling, 10% half sibling, and 6% both full and half siblings) in the whole study population. Among children in the persistence analysis, the proportion of children with older siblings at birth was 72% (n=8567); Table 1.

<<<Insert Table 1 here<<<

In total, 23% of the study population was dispensed asthma medication (27% of the boys and 20% of the girls). Controller medication was dispensed to 19% of the study population, and 15% of the study population had both an asthma diagnosis and a controller medication. The mean age of the first dispensed asthma controller medication was 2.13 years (CI 2.10-2.17) and the mean age of recorded asthma diagnosis was 2.39 years (CI 2.34-2.43) among children in the 4-months persistence model.

Incidence of asthma medication

The incidence rate of dispensed asthma medication in the first year of life was higher for children with siblings (81.2 per 1000 person-years) than for those without siblings (34.1 per 1000 person-years) (Table 2). The incidence rate was higher regardless of whether the sibling was older, younger, full or half. The adjusted hazard ratio for being dispensed asthma medication was 2.37 (95% CI 2.15–2.60) in the first year of life for children with siblings compared to children without siblings. After one year of age, the incidence rate of being dispensed asthma medication was lower for children with siblings (27.2 per 1000 person-years) than for singletons (49.5). The adjusted hazard ratio for dispensed asthma medication was 0.85 (95% CI 0.80–0.90) for those

with siblings compared to those without. The hazard ratios were similar for children with older, younger, and full siblings but not for those with half siblings.

>>>Insert Table 2 here<<<

Persistence of asthma medication

The estimated proportion of children with persistent asthma controller medication differed between the time windows. The estimated proportion after 1.5 years was 7.2% (95% CI 6.6–7.7) for the 4-month time window and 64.5% (95% CI 63.5–65.4) for the 18-month time window (Table 3). Among index children with a doctor’s diagnosis of asthma, the estimated proportion of children with persistent asthma controller medication was 8.2% (95% CI 7.5–9.0) and 72.1% (95% CI 71.3–73.1), respectively. After including their siblings’ controller medication dispensing data in the analysis, the estimated proportion was 8.8% (95% CI 8.2–9.4) with the 4-month time window and 73.6% (95% CI 72.6–74.5) with the 18-month time window. In the sibling persistence model, a total of 80,536 controller medication prescriptions were included of which 16,897 (21%) originated from the siblings. In the persistence model including controller medication from unrelated control children, the corresponding proportion of persistence was 7.8% (95% CI 7.3–8.4) and 72.6 (95% CI 71.7–73.6) respectively.

>>>Insert Table 3<<<

The estimated proportion of children with persistent asthma controller medication after 1.5 years was lower among those with siblings compared to those without (adj. RR 0.72, 95%CI 0.62-0.85 with the 4-month model; Table 4). Children with younger siblings had the lowest proportion of persistence to asthma controller medication. There was no significant difference in the proportion between children with half-siblings and singletons, when using the 4-month time window. Furthermore, the estimated proportion was not affected by the number of sibling or if the siblings

had an asthma diagnosis. The estimated proportion of children with persistent controller medication was lower for the model including medication from an unrelated control child than that including medication of siblings, RR 0.89 (95% CI 0.81–0.98) with the 4-month time window but there was no statistical difference for the 18-month time window, RR 0.99 (95% CI 0.97–1.00).

>>>Insert Table 4 here<<<

The association between sibling status and persistence medication was not affected by sex, asthma diagnosis of the index child, and parental asthma ($p>0.1$; data not shown).

Discussion

In this population-based cohort study of all children born in Stockholm County during 2006-2007, the incidence of dispensed asthma medication was lower among children with siblings compared to singletons after the first year of life. In general, the estimated proportion of children with persistent asthma controller medication was lower among children with siblings compared to singletons.

Children with siblings, in particular older and full siblings, were more likely to be dispensed asthma medication in the first year of life compared to singletons. The reason for this may be that older siblings transmit respiratory tract infections, which, in turn, increases the risk of viral-induced asthma. After the first year, children with siblings received less asthma medication. One explanation could be that older children are more likely to develop asthma, whereas having an older sibling decreases the risk of developing asthma (12-14, 34). Another explanation could be that in families with several children, parents have less time to dispense and administer the child's medication (35). On the other hand, parents' positive attitude toward their child's asthma

medication has been found to be associated with good adherence (36), which in turn would increase the dispensing of asthma medication. Children with only half siblings had a risk similar to singletons of having had asthma medication dispensed. This might be because half siblings live in separate homes, at least part time, and are therefore less exposed to each other, or they do not have full access to their half siblings' supply of asthma medication (37).

The estimated proportion of children with persistent controller medication differed largely with different time windows. The reason for this is most likely the irregular dispensing patterns for children with asthma, which has also been seen in other studies (27). Few children had their prescriptions refilled after four months, which is not surprising since asthma in young children is often an intermittent disease (10). The estimated proportion of children with persistent medication after 18-months was quite high, which is in accordance with one of our previous studies (7). One explanation for the lower proportion of children with persistent medication among those with siblings could be that siblings share medications. Also, when including the siblings' controller medication in the model, the estimated proportion after 1.5 years was slightly higher and statistically different from the estimated proportion when including medication of an unrelated control child using the 4-month time window. Only children who live together (at least part time) i.e. siblings, would have the chance to share medication. However, when using the 18-month model, the differences were smaller and non-significant. Furthermore, the estimated proportion of children with persistent medications was lower among children with younger siblings compared to older siblings. Having a younger sibling may change the family situation at home including having less time to refill prescriptions of asthma medications.

To our knowledge, this is the first study on incidence and persistence of asthma medications in relation to sibship, diagnoses and siblings' medications. Øymar et al. calculated the incidence of

ICS each year (27) and found that the incidence was highest the second year of life and decreased each year up to year 5. They also found a low proportion of pre-school children with persistent ICS; only 9–18% refilled a prescription of ICS every 12 months after 5 years. In a review by Desai and Oppenheimer, it was concluded that non-adherence (not taking medication as agreed) among children with asthma was alarmingly high (35). Among children with intermittent asthma, admitted to the Children’s Hospital of Michigan, Detroit, 25% lacked asthma medication (38). That corresponds to our estimated proportion of children with persistent medication of 72% among those with an asthma diagnosis, using the 18-month time window. In a Dutch study, 88% of the children (aged 7–17 years) were dispensed at least one ICS prescription during a 12-month period. However, only half of them used more than one inhalation of ICS per day (36), indicating non-adherence. This can also be an explanation for our results with a low proportion of children with persistent medication using the 4-month time window and a substantial increase in the proportion with the 18-month time window. We also found that the number of siblings and diagnosis of asthma in the index child, sibling or parent did not affect the estimated proportion of children with persistent medication. A potential explanation could be that sharing asthma medications can be mutual, i.e. the index children could either lend or borrow medication from their sibling, although this would not be the case for parents due to different devices used for inhalation in different age-groups. In a previous study, we found that 10% of the adolescents with asthma reported use of someone else’s medication (23). The lack of impact of asthma diagnosis may be due to treatment with asthma medication without getting a diagnosis (32, 33).

Our main findings remained after adjusting for family income. However, Gong et al., found the lowest incidence of dispensed asthma medication among young children in Sweden from the lowest income families (39).

As far as we know, no other study has included both the children and their siblings' asthma medication in the same persistence model. The sibling model might be more complete and may suggest that the proportion of children with persistent controller medication is not as low as previously shown (27, 35). Excluding siblings' asthma medications from persistence models when using dispensing data from pharmacies may underestimate the actual persistence among children with siblings. However, more research is needed to explore the association between sibship and dispensing patterns. Healthcare professionals seeing children with asthma should be aware of the possibility of sharing medications among siblings and be sure to take a thorough medical history. Furthermore, it is important for healthcare professionals meeting families with asthmatic children, to stress that treatment and choice of devices needs to be individualized. Every child should have an individual treatment plan and a sufficient medical supply tailored for his/her need.

Strengths and limitation

This was a register-based cohort study including all children born in an entire region. The high quality of the data made it possible to follow all children's and their siblings' medication, allowing for a complete persistence model. We also had full information on recorded diagnoses from inpatient, specialized and ambulatory care over time.

The main limitations are those associated with registries. Even though we had data on all dispensed prescriptions both for the children in the study population and their siblings, we do not know if the siblings actually shared medications. Longitudinal analyses of dispensing data are considered the golden standard when measuring persistence of medication (26), still it is important to emphasize that dispensing a prescription is not necessarily equal to use of

medication. Also, children classified as being non-persistent may have grown out of their asthma and is it not possible to distinguish different types of asthma. However, when using the 18-month time window the persistence increased substantially, suggesting that the majority of children needs asthma controller medication i.e., either still has asthma symptoms at least intermittently or use medication to avoid them.

In conclusion, we confirm our hypothesis that siblings compared to singletons have different dispensing patterns of asthma medications. These differences were seen regardless of asthma diagnoses. Also, after taking the siblings' asthma medication into account, and comparing with unrelated control children, the proportion of children with persistent medication increased, which may indicate that siblings share asthma medications.

Ethics statement

Permission for this study was obtained from the Regional Ethical Review board in Stockholm, Sweden. In accordance with their decision, we did not obtain informed consent from participants involved in the study. All data were de-identified prior to analyses.

Acknowledgments

We would like to direct our great appreciation to Christina Norrby and Marcus Boman who contributed with excellent data collection and management. We would also like to acknowledge Dr. Bronwyn K Brew for professional language edits.

This work was supported by the Swedish Research Council through the Swedish initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework grant no. 340-

2013-5867, the Swedish Heart Lung Foundation, grants provided by the Stockholm County Council (ALF projects), the Strategic Research Program in Epidemiology at Karolinska Institutet and the Swedish Research Council for Health, Working Life and Welfare (FORTE) grant no. 2015-00289.

Conflict of Interest

The authors have no conflict of interest to disclose pertaining to this work.

References

1. Globale Initiative for Asthma G. Global Strategy For Asthma Management and Prevention. 2017.
2. Ballardini N, Kull I, Lind T, Hallner E, Almqvist C, Ostblom E, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy*. 2012;67(4):537-44.
3. Breekveldt-Postma NS, Koerselman J, Erkens JA, van der Molen T, Lammers JW, Herings RM, et al. Treatment with inhaled corticosteroids in asthma is too often discontinued. *Pharmacoepidemiol Drug Saf*. 2008;17(4):411-22.
4. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest*. 2000;117(2):542-50.
5. Ingemansson M, Wettermark B, Jonsson EW, Bredgard M, Jonsson M, Hedlin G, et al. Adherence to guidelines for drug treatment of asthma in children: potential for improvement in Swedish primary care. *Qual Prim Care*. 2012;20(2):131-9.
6. Furu K, Karlstad O, Skurtveit S, Haberg SE, Nafstad P, London SJ, et al. High validity of mother-reported use of antiasthmatics among children: a comparison with a population-based prescription database. *J Clin Epidemiol*. 2011;64(8):878-84.
7. Dahlen E, Almqvist C, Bergstrom A, Wettermark B, Kull I. Factors associated with concordance between parental-reported use and dispensed asthma drugs in adolescents: findings from the BAMSE birth cohort. *Pharmacoepidemiol Drug Saf*. 2014;23(9):942-9.
8. Nwaru BI, Lumia M, Kaila M, Luukkainen P, Tapanainen H, Erkkola M, et al. Validation of the Finnish ISAAC questionnaire on asthma against anti-asthmatic medication reimbursement database in 5-year-old children. *Clin Respir J*. 2011;5(4):211-8.
9. Makela MJ, Virta L, Kaila M, Gronlund J, Vanto T, Klaukka T. Medication use in children with asthma in Finland from 1995 to 2006. *J Allergy Clin Immunol*. 2008;122(3):648-9.
10. Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. *J Allergy Clin Immunol*. 2012;130(2):287-96; quiz 97-8.
11. Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol*. 2007;42(5):407-20.
12. Strachan DP, Ait-Khaled N, Foliaki S, Malloy J, Odhiambo J, Pearce N, et al. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clin Exp Allergy*. 2015;45(1):126-36.

13. Bernsen RM, de Jongste JC, van der Wouden JC. Birth order and sibship size as independent risk factors for asthma, allergy, and eczema. *Pediatr Allergy Immunol.* 2003;14(6):464-9.
14. Almqvist C, Olsson H, Fall T, Lundholm C. Sibship and risk of asthma in a total population: A disease comparative approach. *J Allergy Clin Immunol.* 2016;138(4):1219-22 e3.
15. Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299(6710):1259-60.
16. Goldsworthy RC, Schwartz NC, Mayhorn CB. Beyond abuse and exposure: framing the impact of prescription-medication sharing. *Am J Public Health.* 2008;98(6):1115-21.
17. Beyene KA, Sheridan J, Aspden T. Prescription medication sharing: a systematic review of the literature. *Am J Public Health.* 2014;104(4):e15-26.
18. Thompson S SK. Prescription medication use practices among non-institutionalised older persons. *Int J Pharm Pract.* 2001;9(3):141-51.
19. Sorensen L, King MA, Ientile CS, Roberts MS. Has drug therapy gone to the dogs? *Age Ageing.* 2003;32(4):460-1.
20. Kheir N, Hajj ME, Wilbur K, Kaissi R, Yousif A. An exploratory study on medications in Qatar homes. *Drug Healthc Patient Saf.* 2011;3:99-106.
21. Daniel KL, Honein MA, Moore CA. Sharing prescription medication among teenage girls: potential danger to unplanned/undiagnosed pregnancies. *Pediatrics.* 2003;111(5 Pt 2):1167-70.
22. Goldsworthy RC, Mayhorn CB. Prescription medication sharing among adolescents: prevalence, risks, and outcomes. *J Adolesc Health.* 2009;45(6):634-7.
23. Dahlen E, Wettermark B, Bergstrom A, Jonsson EW, Almqvist C, Kull I. Medicine use and disease control among adolescents with asthma. *Eur J Clin Pharmacol.* 2016;72(3):339-47.
24. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* 2008;11(1):44-7.
25. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. *Clin Ther.* 2006;28(9):1411-24; discussion 0.
26. Vrijens B, Dima AL, Van Ganse E, van Boven JF, Eakin MN, Foster JM, et al. What We Mean When We Talk About Adherence in Respiratory Medicine. *The journal of allergy and clinical immunology In practice.* 2016;4(5):802-12.
27. Oymar K, Mikalsen IB, Furu K, Nystad W, Karlstad O. Prescription patterns of inhaled corticosteroids for preschool children--A Norwegian register study. *Pediatr Allergy Immunol.* 2015;26(7):655-61.
28. Centre for Epidemiology TNBoHaW. The Swedish Medical Birth Register- A Summary of content and quality. 2003.
29. Statistics Sweden. SCB:s data för forskning. 2013.
30. 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. *Pharmacoepidemiol Drug Saf.* 2007;16(7):726-35.
31. Ludvigsson JF, Andersson E, Ekblom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* 2011;11:450.
32. Carlsson AC, Wandell P, Osby U, Zarrinkoub R, Wettermark B, Ljunggren G. High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden - a challenge for public health. *BMC Public Health.* 2013;13:670.
33. Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf.* 2013;22(8):850-60.

34. Wu P, Feldman AS, Rosas-Salazar C, James K, Escobar G, Gebretsadik T, et al. Relative Importance and Additive Effects of Maternal and Infant Risk Factors on Childhood Asthma. *PLoS One*. 2016;11(3):e0151705.
35. Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. *Current allergy and asthma reports*. 2011;11(6):454-64.
36. van Dellen QM, Stronks K, Bindels PJ, Ory FG, van Aalderen WM, Group PS. Adherence to inhaled corticosteroids in children with asthma and their parents. *Respir Med*. 2008;102(5):755-63.
37. Manning WD, Brown SL, Stykes JB. Family Complexity among Children in the United States. *Ann Am Acad Pol Soc Sci*. 2014;654(1):48-65.
38. Poowuttikul P, Hart B, Thomas R, Secord E. Poor Adherence With Medication Refill and Medical Supplies Maintenance as Risk Factors for Inpatient Asthma Admission in Children. *Glob Pediatr Health*. 2017;4:2333794X17710588.
39. Gong T, Lundholm C, Rejno G, Mood C, Langstrom N, Almqvist C. Parental socioeconomic status, childhood asthma and medication use--a population-based study. *PLoS One*. 2014;9(9):e106579.

Figure legends

Figure 1: Persistence model for hypothetical children with two different time windows (4- and 18-months). Persistence was defined as refilling the prescription of controller medication (ICS, LTRA, or fixed combination) within the defined time window.

Table 1: Characteristics of the study population and the children in the persistence analysis.

Characteristics	All children in the study population (N=50,546)	Children in the persistence analysis (n=8,567)¹
Boys	51% (26,014)	59% (5,091)
<i>Sibship status at birth</i>		
No siblings	41% (20,675)	28% (2,378)
Older siblings	59% (29,857)	56% (4,758)
Younger siblings	0	11% (955)
Both older and younger siblings	0	6% (476)
Full sibling	43% (21,685)	54% (4,588)
Half sibling	10% (5,060)	9% (804)
Both full and half sibling	6% (3,126)	9% (797)
<i>Family income²</i>		
Q1	SEK ³ 0 – 211,800	SEK 0 – 213,100
Q2	SEK 211,801 – 345,900	SEK 213,001 – 343,000
Q3	SEK 345,901 – 474,700	SEK 343,001 – 466,600
Q4	SEK 474,701 – 7.18*10 ⁷	SEK 466,601 – 7.18 *10 ⁷

1. Children with a dispensed controller medication (ICS, fixed combination of ICS and LABA or LTRA).

2. Disposable income (individual net benefits after deduction of debits such as taxes, repaid study allowance and paid maintenance support) at household level during 2006.

3. Foreign exchange rate: 100 SEK = 11.85 USD.

Table 2: Incidence rates and hazard ratio (HR) with 95% confidence intervals (CI) of dispensed asthma medication and sibship status using a cox model.

Sibship	Incidence rates/ 1000 person-years (CI)	Person-years	Crude HR (CI)	Adj.* HR (CI)
Age 0-1				
No sibling (ref)	34.1 (31.6-36.7)	19 895	1	1
Sibling	81.2 (77.9-84.5)	28 896	2.39 (2.20-2.61)	2.37 (2.15-2.60)
Older sibling	80.9 (77.7-84.3)	28 277	2.39 (2.19-2.60)	2.36 (2.14-2.59)
Younger sibling	61.8 (38.4-99.4)	275	1.77 (1.10-2.87)	2.25 (1.29-3.93)
Both older & younger sibling	113.4 (82.9-155.2)	343	3.34 (2.43-4.60)	3.43 (2.31-5.09)
Full sibling	85.2 (81.3-89.3)	20 521	2.51 (2.30-2.75)	2.48 (2.24-2.74)
Half sibling	50.4 (44.5-57.2)	4 838	1.48 (1.28-1.71)	1.52 (1.30-1.79)
Both full & half sibling	99.1 (89.3-110.1)	3 551	2.92 (2.56-3.32)	3.21 (2.77-3.72)
Age 1-6				
No sibling (ref)	49.5 (47.5-51.5))	46 896	1	1
Sibling	27.2 (26.5-27.9)	225 073	0.85 (0.81-0.90)	0.85 (0.80-0.90)
Older sibling	31.3 (30.4-32.3)	127 560	0.84 (0.80-0.89)	0.84 (0.79-0.89)
Younger sibling	22.5 (21.3-23.7)	64 956	0.91 (0.85-0.98)	0.90 (0.83-0.98)
Both older & younger sibling	20.3 (18.8-21.9)	32 558	0.82 (0.75-0.90)	0.80 (0.73-0.89)
Full sibling	29.3 (28.2-30.4)	96 279	0.80 (0.75-0.84)	0.79 (0.74-0.84)
Half sibling	41.7 (38.8-44.8)	17 889	1.05 (0.97-1.14)	1.04 (0.95-1.14)
Both full & half sibling	23.0 (22.1-23.9)	110 966	0.88 (0.83-0.93)	0.87 (0.81-0.93)

*Adjusted for family income i.e. disposable income (individual net benefits after deduction of debits such as taxes, repaid study allowance and paid maintenance support) at household level during 2006.

Table 3: The estimated proportion of children with persistent asthma controller medication after 1.5 years in the different persistence models measured as % with 95% confidence intervals (CI), n=8,567.

Persistence models	4-month model, % (CI)	18-month model, % (CI)
Index child's controller medication	7.2 (6.6-7.7)	64.5 (63.5-65.4)
Index child's controller medication + asthma diagnosis	8.2 (7.5-9.0)	72.1 (71.3-73.1)
Index child's + siblings' controller medication	8.8 (8.2-9.4)	73.6 (72.6-74.5)
Index child's + unrelated control child's controller medication	7.8 (7.3-8.4)	72.6 (71.7-73.6)

Table 4: Association between sibship status and controller medication persistence after 1.5 years with the 4 and 18 months' models measured as proportions (%), relative risks (RR), and 95% confidence intervals (CI), n=8,567.

Sibship	4m % Persistent (CI)	4m Crude RR (CI)	4m Adj.* RR CI	18m % Persistent (CI)	18m Crude RR (CI)	18m Adj.* RR (CI)
No sibling (ref)	8.7 (7.6-9.9)	1	1	71.1 (69.3-72.9)	1	1
Sibling	6.6 (6.0-7.2)	0.76 (0.65-0.89)	0.72 (0.62-0.85)	62.1 (60.9-63.2)	0.87 (0.85-0.90)	0.87 (0.84-0.90)
Older sibling	7.0 (6.3-7.8)	0.81 (0.69-0.96)	0.77 (0.65-0.92)	65.9 (64.6-67.2)	0.93 (0.90-0.96)	0.92 (0.89-0.95)
Younger sibling	4.7 (3.5-6.3)	0.54 (0.40-0.74)	0.53 (0.39-0.73)	51.1 (48.2-54.0)	0.72 (0.68-0.76)	0.72 (0.67-0.76)
Both older & younger sibling	5.7 (3.8-8.2)	0.65 (0.44-0.97)	0.63 (0.43-0.93)	50.5 (46.4-54.6)	0.71 (0.65-0.77)	0.71 (0.65-0.77)
Full sibling	6.5 (5.8-7.3)	0.75 (0.64-0.89)	0.71 (0.59-0.84)	61.3 (59.9-62.6)	0.86 (0.83-0.89)	0.85 (0.83-0.88)
Half sibling	7.8 (6.1-9.9)	0.90 (0.69-1.19)	0.93 (0.71-1.22)	64.4 (61.1-67.6)	0.91 (0.86-0.96)	0.91 (0.86-0.96)
Both full & half sibling	5.5 (4.0-7.3)	0.64 (0.46-0.87)	0.62 (0.45-0.84)	64.1 (60.9-67.3)	0.90 (0.85-0.95)	0.90 (0.85-0.95)
Number of siblings 1	6.9 (6.1-7.7)	0.79 (0.66-0.94)	0.75 (0.63-0.90)	62.3 (60.8-63.8)	0.88 (0.85-0.91)	0.87 (0.84-0.90)
2	6.2 (5.3-7.2)	0.71 (0.58-0.87)	0.68 (0.56-0.83)	61.7 (59.8-63.5)	0.87 (0.83-0.90)	0.86 (0.83-0.90)
Siblings no asthma diagnosis	6.5 (5.9-7.3)	0.76 (0.64-0.90)	0.72 (0.61-0.86)	62.0 (60.6-63.3)	0.87 (0.84-0.90)	0.87 (0.84-0.90)
Siblings with asthma diagnosis	6.7 (5.5-8.0)	0.77 (0.61-0.96)	0.73 (0.58-0.92)	62.3 (60.1-64.4)	0.88 (0.84-0.91)	0.87 (0.83-0.91)

* Adjusted for family income i.e. disposable income (individual net benefits after deduction of debits such as taxes, repaid study allowance and paid maintenance support) at household level during 2006.

4-month model



Persistence



Persistence *only*
in sibling model



Non-persistence

Persistence after
1.5 years

18-month model



Persistence



Persistence *only*
in sibling model



Non-persistence

X = Dispensed controller medication; Y = Siblings' dispensed controller medication