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A gap between asthma guidelines and management for adolescents and young adults

Maria Ödling, MSc., Niklas Andersson, MSc., Jenny Hallberg, Ph.D., Catarina Almqvist, MD, Ph.D., Christer Janson, MD, Ph.D., Anna Bergström, Ph.D., Erik Melén, MD, Ph.D., Inger Kull, Ph.D.

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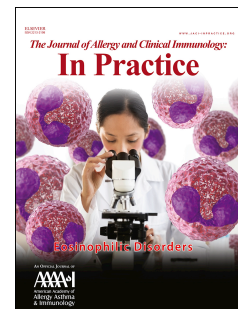
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A gap between asthma guidelines and management for adolescents and young adults

Maria Ödling, MSc.¹, Niklas Andersson, MSc.², Jenny Hallberg, Ph.D.^{1,3}, Catarina Almqvist, MD, Ph.D.^{4,5}, Christer Janson, MD, Ph.D.⁶, Anna Bergström, Ph.D.^{2,7}, Erik Melén, MD, Ph.D.^{1,2,3} & Inger Kull, Ph.D.^{1,3}

1. Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden;
2. Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden;
3. Sachs' Children and Youth Hospital, Stockholm, Sweden;
4. Department of Medical Epidemiology and Biostatistics Karolinska Institutet, Stockholm, Sweden;
5. Paediatric Allergy and Pulmonology Unit at Astrid Lindgren's Children's Hospital, Karolinska University Hospital, Stockholm, Sweden;
6. Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden;
7. Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden.

Corresponding author

Maria Ödling
Forskningscentrum
Södersjukhuset
SE-118 83 Stockholm, Sweden
Telephone: +468 524 800 02
E-mail: Maria.Odling@ki.se

E-mail addresses

Niklas.Andersson@ki.se
Jenny.Hallberg@ki.se
Catarina.Almqvist@ki.se
Christer.Janson@medsci.uu.se

Anna.Bergstrom@ki.se

Erik.Melen@ki.se

Inger.Kull@ki.se

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Abstract

Background: For adolescents, asthma management can be challenging during the transition to adulthood, and changes in healthcare and pharmacological treatment may occur.

Objective: To investigate asthma-related healthcare consumption and pharmacological dispensation during the transition process.

Methods: In a Swedish birth cohort study, questionnaire and clinical data from the 16- and 24-year follow-ups were linked to national and regional registries for asthma-related healthcare consumption and dispensed medications during an eight-year period: four years before and after 18 years of age, respectively.

Results: In the study population ($n = 1,808$), 14% fulfilled the study definition of current asthma at the 16-, respective 24-year follow-up, and 8% ($n = 147$) had persistent asthma. Among them, register data showed that in the four-year period before their 18th birthday, 39% (58/147) had at least one consultation, similar with 37% (55/147) in the following four-year period. The mean number of consultations before 18 years was 1.6, compared with 1.0 after 18 years ($p = 0.02$). At least one dispensation of any inhaled corticosteroids (ICS) before 18 years was found for 73% (107/147), compared with 50% (74/147) after 18 years. The mean number of dispensed any ICS was 3.1 before 18 years, and 2.1 after 18 years ($p < 0.01$). Only 3% (5/147) had a regular dispensation of any ICS once a year during the eight-year period.

Conclusions: Healthcare consultations were fewer than recommended in guidelines and decreased after the transition to adult healthcare. Almost no one had dispensed regular asthma medications during the eight-year period.

Highlights box

1. What is already known about this topic?

Clinical guidelines for management of asthma exists, but adherence to them is generally low. For adolescents, asthma management can be challenging during the transition to adulthood.

2. What does this article add to our knowledge?

Asthma-related healthcare consultations were fewer than recommended in guidelines and decreased after the transition to adult healthcare. Almost no one had regular asthma treatment dispensed during the transition process.

3. How does this study impact current management guidelines?

There is a gap between asthma guidelines and actual management. Increased adherence to current guidelines is required when planning for optimal care of adolescents and young adults, and their process of transition.

Key words

Adolescents,
adult healthcare,
birth cohort,
guidelines,
level of care,
management,
paediatric healthcare,
phenotypes,

101 severity,
102 young adults.

103

104 **Abbreviations**

105 95% CI: Ninety-five percent confidence interval
106 ATC: Anatomical therapeutic chemical
107 BAMSE: Barn/Child, Allergy, Milieu, Stockholm, Epidemiology
108 ERS/ATS: European Respiratory Society and American Thoracic Society
109 FEV₁: Forced expiratory volume in 1 second
110 FVC: Forced vital capacity
111 GINA: Global Initiative for Asthma
112 ICD-10: International statistical Classification of Diseases, version 10
113 ICS: Inhaled corticosteroids
114 IgE: Immunoglobulin E
115 LABA: Long-acting β_2 -agonists
116 LLN: Lower limit of normal
117 LTRA: Leukotriene receptor antagonist
118 MEFV: Maximal expiratory flow volume
119 OR: Odds ratio
120 SABA: Short-acting β_2 -agonists
121 SPDR: Swedish Prescribed Drug Register
122 VAL: Stockholm Regional Healthcare Data Warehouse; Vårdanalysdatabasen

Introduction

Most patients with asthma have mild or moderate disease and can be managed in primary care; with currently available medications, the majority can be treated effectively (1, 2). The long-term goal of asthma treatment is to achieve control of symptoms and maintain normal activity levels (3). It is therefore important to regularly monitor symptom control, risk factors, and response to treatment through follow-up visits performed by an appropriate suitable healthcare provider at an appropriate level of care (3). Swedish recommendations on asthma management are similar to the Global Initiative for Asthma (GINA) guidelines. Depending on level of asthma control and severity, it is recommended, e.g., that adolescents with asthma and controller medications should have 1–2 annual visits, adults with controlled asthma should have a follow-up visit once a year, and that patients with severe asthma should be managed by specialty physicians (allergists or pulmonologists) (3-5). At around 18 years old, management involves a transition from paediatric to adult healthcare (6). Our recent qualitative study showed that young adults with severe asthma felt left out of the system during the transition from paediatric to adult healthcare (7). Moreover, they experienced fewer or no follow-up visits in adult healthcare. Thus, it is relevant to investigate if the transition to adult healthcare influences asthma-related healthcare consumption in a wider group. It is also important to explore how the process of transition affects pharmacological dispensation, since non-adherence to therapy is particularly common during this period (8, 9). Medication adherence is the cornerstone for improving the patient's health-related quality of life, and an improved adherence can lead to decreased asthma morbidity and mortality (10).

The aim of this study was therefore to investigate asthma-related healthcare consumption and pharmacological dispensation during the transition from paediatric to adult healthcare. A longitudinal approach was used to follow different asthma phenotypes during the entire transition process.

Methods

Study design

During 1994–1996, parents to all new-borns living in predefined areas of Stockholm, the capital of Sweden, including inner city, urban, and suburban districts, were asked to participate in the longitudinal population-based birth cohort BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) (11, 12). The ongoing birth cohort includes 4,089 participants, who have been followed since birth with repeated follow-ups. At 2 months of age, a baseline questionnaire was answered. When the participants were approximately ages 1, 2, 4, 8, 12, and 16 years, parents completed follow-up questionnaires to collect information about symptoms related to asthma and other allergic diseases, lifestyle factors and treatment of asthma. At 12, 16, and 24 years, participants were also asked to complete a questionnaire themselves. In addition to the questionnaires, the participants were invited to undergo clinical examinations, including blood sampling and lung function measurement, at approximately ages 4, 8, 16, and 24 years.

The study population consisted of 1,808 participants who responded to the questionnaires and lived in the Stockholm region at both the 16- and 24-year follow-ups (Figure 1). The mean age was 16.5 years at the 16-year follow-up, and 22.4 years at the 24-year follow-up. For analyses related to the clinical examinations, participants with a valid spirometry measure were included.

Lung function exposure assessment

At the clinical examinations carried out at approximately ages 16 and 24 years, lung function was measured through spirometry using a Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA). All subjects performed repeated maximal expiratory flow volume (MEFV) measurements (13). The highest values of forced vital capacity (FVC),

and forced expiratory volume in 1 second (FEV₁) were extracted and used for analysis in accordance with the European Respiratory Society and American Thoracic Society (ERS/ATS) criteria (14). FEV₁/FVC data were converted to z-scores based on GLI-reference values (15).

Asthma phenotypes – exposure definitions

Exposure definitions were based on questionnaire and clinical data from the 16-, and 24-year follow-ups. *Current asthma* was defined as fulfilling at least two of the following three criteria (16): Symptoms of wheeze and/or breathing difficulties in the last 12 months, ever doctor's diagnosis of asthma and/or asthma medication occasionally or regularly in the last 12 months. *Persistent asthma* was defined as fulfilling the definition of current asthma at both the 16-, and 24-year follow-ups.

Allergic asthma was defined as a combination of asthma and immunoglobulin E (IgE) sensitisation to inhalant allergens (cat, dog, horse, and/or house dust mite, timothy grass, birch, mugwort, and/or mould) (17).

Severe asthma was based on ERS/ATS, and GINA guidelines (1, 3, 16), defined as asthma with *high daily doses of inhaled corticosteroids* (ICS). Information on pharmacy-dispensed asthma medication within the 18 months prior to each follow-up was obtained by linkage to the Swedish Prescribed Drug Register (SPDR) (18). High doses were identified when a participant dispensed at least 800 µg budesonide or equivalent, ≥ 500 µg fluticasone, or fixed combinations of ICS and long-acting β₂-agonists (LABA). Plus, dispensed LABA and/or leukotriene receptor antagonists (LTRA) at least once to prevent the asthma from becoming or remaining uncontrolled despite therapy. Uncontrolled asthma was defined as at least one of the following four alternatives based on data from the 16- or 24-year follow-ups:

- 1) *Uncontrolled asthma* based on modified GINA definition (3, 16).
- 2) Taken cortisone

tablets dissolved in water for asthma or respiratory symptoms ≥ 3 days in a row. 3) Sought acute medical care because of respiratory symptoms. 4) FEV₁ below 80% of predicted.

Airflow obstruction was defined as the FEV₁/FVC ratio z-score below the lower limit of normal (LLN), defined as the lower 5th percentile in the never asthmatic population.

Data sources of outcome assessment

A flow chart is shown in Figure 1 and presents how questionnaire and clinical data from the 16-, and 24-year follow-ups were linked to mandatory Swedish health registries between 2008–2018. In total, an eight-year period (based upon individual age, participants born 1994–1996): four years before and four years after age 18 years, respectively. This period is hereafter denoted “before and after 18 years”. A timeline with study periods and data collection is presented in Figure E1 (see the Online Repository). Data on asthma-related healthcare consumption were obtained from Stockholm Regional Healthcare Data Warehouse: VAL (19). The VAL database includes complete data on all healthcare consultations in primary and specialist care, all hospitalisations and medical procedures, and diagnoses based on the International Statistical Classification of Diseases, version 10 (ICD-10) (20). For each healthcare consultation, a maximum of 15 diagnoses based on the ICD-10 can be registered. One diagnosis is assigned as the main condition, while others are secondary (21). We identified participants with physician-diagnosed asthma, ICD-10 codes J45 and/or J46, as main or secondary diagnosis. With data linked to the personal identity number, it is possible to follow each individual over time (22).

Information on dispensed asthma medications was obtained by linkage to the national SPDR using personal identity numbers (18, 22, 23). The medications included were the following, classified in accordance with the Anatomical Therapeutic Chemical (ATC) Classification System (24): short-acting β_2 -agonists, SABA (R03AC02 + R03AC03), LABA

(R03AC12 + R03AC13), ICS (R03BA), fixed combinations of ICS and LABA (R03AK), and LTRAs (R03DC).

Covariates

Information on covariates was obtained from the baseline questionnaire (gender, mother's age at birth, parent born outside Sweden, parental allergic disease, parental education, and parental smoking).

Statistical analysis

Tests of proportions (categorical variables) and Wilcoxon signed-rank test (continuous variables) were used to study differences between groups (background characteristics, consultations, levels of care, medical procedures, and dispensed asthma medications). Two-sample Wilcoxon rank-sum test was used to study gender differences. McNemar's test was used to evaluate differences in asthma control over time. P-values of < 0.05 were considered statistically significant.

The association between having had a consultation after 18 years of age and selected asthma phenotypes (allergic asthma, asthma and airflow obstruction, asthma with high daily doses of ICS, and severe asthma) was analysed using a logistic regression model. Potential confounders were selected a priori from the previous literature: gender and socioeconomic status. Expressed as odds ratios (OR) with 95% confidence intervals (CI).

For the main analyses, we used ICD-10 codes J45 and/or J46. Sensitivity analysis with all ICD-10 codes J – "Diseases of the respiratory system" was performed to assess potential underreporting.

All analyses were performed with the STATA statistical software (release 14.2; College Station, TX, USA).

- 248 The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.
- 249 All participants and parents provided informed consent to participate in the study.

Results

The study population (n = 1,808) had higher proportions of female gender (53% vs. 47%), parental allergic disease (31% vs. 28%), and higher parental education (55% vs. 51%) compared with excluded participants (n = 2,281) (see Table E1 in the Online Repository).

Healthcare consumption

Asthma at the 16-year follow-up

At the 16-year follow-up, 14% (n = 253) of the adolescents fulfilled the study definition of current asthma (Table I). Of these, 62% (n = 157) had allergic asthma, 7% (n = 18) had airflow obstruction (FEV_1/FVC z-score <LLN), 24% (n = 60) were dispensed high daily doses of ICS or fixed combinations of ICS and LABA, and 5% (n = 12) fulfilled the definition of severe asthma (Table II).

In the four-year period before their 18th birthday, 32% (82/253) of the adolescents had at least one asthma-related consultation, compared with 27% (68/253) in the following four-year period (Table I). The mean number of consultations decreased from 1.2 before 18 years to 0.6 after 18 years ($p < 0.01$). This relationship was seen for all asthma phenotypes (Table II). In the sensitivity analyses including consultations for all diagnoses of diseases of the respiratory system, the mean number of consultations before and after 18 years was 3.0 vs. 2.0, $p < 0.01$ (see Table E2 in the Online Repository).

Asthma at the 24-year follow-up

At the 24-year follow-up, 14% (n = 248) of the young adults fulfilled the study definition of current asthma (Table I). Of these, 60% (n = 149) had allergic asthma, 6% (n = 15) had airflow obstruction (FEV_1/FVC z-score <LLN), 11% (n = 27) were dispensed high daily

doses of ICS or fixed combinations of ICS and LABA, and 4% (n = 9) fulfilled the definition of severe asthma.

Persistent asthma

Eight percent fulfilled the criteria for persistent asthma (Table I). Before 18 years, 39% (58/147) of these young adults had one or more asthma-related consultation, similar with 37% (55/147) after 18 years. Only 2% (3/147) had yearly consultations during the entire study period of eight years. The mean number of consultations decreased from 1.6 before 18 years to 1.0 after 18 years ($p = 0.02$).

Figure 2 shows the number of consultations before and after 18 years, respectively, divided by level of care. The most common combination was having no consultation either before or after 18 years, and the second most common was attending specialist care before 18 years but having no consultation after 18 years. After 18 years, the mean number of consultations in primary care increased significantly and the number in specialist care decreased (Table I). The sensitivity analyses showed similar results (see Table E2 in the Online Repository).

Uncontrolled asthma was found among 57% (80/147) at the 16-year follow-up, and among 72% (103/147) at the 24-year follow-up ($p < 0.01$). There were two registered emergency room visits before 18 years, and four after 18 years. During the study period of eight years, there was one registered hospitalisation with asthma as the main diagnosis, while nine of the young adults had hospitalisations where asthma was a secondary diagnosis (eight on one occasion and one on two occasions).

Of all registered consultations during the study period, indirect contacts, for instance by telephone and mail accounted for a total of 4% (17/382).

Factors associated with the odds for respective asthma phenotypes (allergic asthma, asthma and airflow obstruction, asthma with high daily doses of ICS, and severe asthma) and having a consultation after 18 years among those with persistent asthma showed that asthma with high daily doses of ICS was associated with increased odds of having a consultation ($OR_{adj} = 2.6$; 95% CI 1.3–5.6) (Table III). Increased odds were also seen for severe asthma ($OR_{crude} = 3.9$; 95% CI 1.0–16.0), but no significant association was seen in the adjusted model ($OR_{adj} = 3.9$; 95% CI 0.9–16.1). No association was seen for asthma and airflow obstruction.

The mean number of registered spirometry tests in VAL decreased significantly, from 0.27 before 18 years to 0.16 after 18 years ($p < 0.01$). One or more spirometry was registered among 27% (40/147) of the young adults before 18 years, and among 16% (24/147) after 18 years.

Figure 3 shows the prevalence of current asthma, and the mean number of yearly consultations in relation to gender. Males had a higher mean number of consultations before 18 years (male: 2.1, female: 1.2, $p = 0.25$), but after 18 years, no difference was seen (male: 0.9, female: 1.1, $p = 0.90$).

Pharmacological dispensation

For those with current asthma at the 16-year follow-up, SABA and any ICS (combining ICS and fixed combinations of ICS and LABA) dispensations were low and decreased significantly after 18 years for all asthma phenotypes, except severe asthma (Table IV).

Among those with persistent asthma, at least one dispensation of SABA before 18 years was found for 70% (103/147) compared with for 50% (73/147) after 18 years. The average number was 2.8 before 18 years, and 2.1 after 18 years ($p < 0.01$) (Table V). Only 3% (4/147) had a regular dispensation of SABA once a year during the entire study period of eight years.

323 At least one dispensation of any ICS before 18 years was found for 73% (107/147), compared
324 with for 50% (74/147) after 18 years. The mean number of dispensed any ICS was 3.1 before
325 18 years and 2.1 after 18 years ($p < 0.01$) (Table V). Only 3% (5/147) had a regular
326 dispensation of any ICS once a year during the entire eight-year period.

Discussion

This longitudinal population-based birth cohort, investigating different asthma phenotypes in relation to asthma-related healthcare consumption and pharmacological dispensation during the transition from paediatric to adult healthcare, showed that there is a gap between asthma guidelines and actual management. Almost two thirds of the young adults with persistent asthma had not had any follow-up visit after 18 years of age. For all asthma phenotypes, healthcare consultations were fewer than recommended in guidelines, and their frequency decreased after the transition. The dispensations of asthma medications decreased after the transition, even for the participants with severe asthma. For all asthma phenotypes, almost no one had dispensed regular asthma medications during the eight-year period.

Few previous studies have addressed the transition from paediatric to adult healthcare for patients with asthma. However, a recent French observational study characterised changes in asthma care in adult patients with persistent asthma, and found that the number of visits per year to specialist care increased with time during a 10-year period, while the number of visits to primary care decreased (25). In the present study, the opposite was seen regarding level of care. The result was expected, given that Swedish primary care is responsible for providing basic medical treatment (26). However, a large proportion of the participants attending specialist care before age 18 years had no consultation either in primary or specialist care after 18 years. Patients who are managed well in primary care can remain with their primary care physician, ensuring continuity, but the majority of adolescents with asthma requiring a tertiary level of care would be expected to need specialist care as adults (8). One of few published studies examining the impact of randomised referral to either primary or specialist care, and risk factors for deterioration during the transition from paediatric to adult healthcare, showed that mild/moderate asthma was managed equally effectively regardless of level of care (27).

Our results showed that registered consultations were fewer than recommended in international and Swedish guidelines (3-5). A recent U.S. study assessed clinician-reported adherence to asthma guideline recommendations, and found that agreement with and adherence to guidelines was higher for specialty physicians than primary care physicians, and overall low adherence with e.g., use of written asthma action plans and medical procedures, such as spirometry (28). In the present study, the number of registered spirometry tests was very low. A single measure of lung function may not provide a true estimate of an individual's risk of obstructive disease later (29). However, repeated measurements may reveal a persistent reduction or rapid decline in lung function over time, either of which is more likely to be associated with an increased risk of chronic obstructive pulmonary disease in early adulthood. It is therefore important that adolescents and young adults with asthma have regular follow-up visits, even if their asthma is mild (8).

A recent Swedish observational cohort study found that one out of five adult patients with severe asthma had visited specialist care because of asthma during the course of a year (30). Furthermore, they showed that one third of patients with asthma, irrespective of severity, had visited primary care. The authors discussed that many patients probably did not have regular visits but were managed by prolonged prescription of asthma medication through indirect consultations. Our results showed for all asthma phenotypes low numbers of dispensed asthma medications, that very few had dispensed regular asthma medications, and that more than two thirds among those with persistent asthma had uncontrolled asthma at the 24-year follow-up. This is unsatisfactory, as the long-term goal of asthma management is to achieve control of symptoms through, e.g., treatment. Previous studies have shown that adherence to ICS is poor, leaving patients exposed to the risks of SABA-only treatment (31, 32). According to the GINA guidelines' new recommendations, treatment of asthma with SABA alone is no longer suggested for adults and adolescents (33). This supports the

importance of consultation and increased understanding of asthma and asthma management (34).

In the present study, among those with persistent asthma, high daily doses of ICS indicated increased odds of having had a consultation after age 18 years. However, almost two thirds of these young adults had no consultation after 18 years. Severe asthma also indicated increased odds of having had a consultation, but the adjusted model did not show a significant association. Results from a recent cohort showed that the proportion of children with severe asthma decreased steadily with increasing age, and approximately half of those with severe asthma in childhood resolved during adolescence (35). However, a recent cross-sectional study discussed that severe asthma symptoms, poor lung function, and higher airway hypersensitiveness in childhood are predictors of persistence of childhood asthma to adulthood (36). These groups should therefore, as suggested in guidelines, have more frequent monitoring during and post transition to adult healthcare.

Strengths and limitations

Important strengths of the present study include the prospective and population-based design of the BAMSE cohort, and the large and well-characterised study sample. Another strength is the use of solid and unique data through linkage to mandatory Swedish health registries, with high quality and coverage. The national SPDR provides complete data on the number of individuals exposed to dispensed prescribed medications in the Swedish population (23). The regional VAL database has approximately 85% coverage of all diagnoses in primary care, more than 90% coverage of utilisation in specialist care, and more than 99% coverage of hospital care (37).

Information gathered via healthcare registers may theoretically also have limitations. There is a potential bias in over- or under-reporting diagnoses and a risk of variability in data

quality (38). However, the sensitivity analyses with the wider ICD-10 codes showed comparable results with a slightly improved mean number of consultations both before and after 18 years.

The study definition of persistent asthma could be discussed, since symptoms vary over time and in intensity. However, the same results were seen for all asthma phenotypes.

Our results are based on the Swedish population and the generalisability may be questioned since healthcare systems vary between countries; reimbursement systems, modes of payment, and the uses of specialist services also vary (21). However, the transition from paediatric to adult healthcare is an international concern, and we believe that our results can be transferred to other countries and populations.

Conclusions

Almost two thirds of the young adults with persistent asthma had not had a follow-up visit after 18 years of age. For all asthma phenotypes, healthcare consultations were fewer than recommended in guidelines, and decreased after the transition. The dispensations of asthma medications decreased after the transition, even for the participants with severe asthma. For all asthma phenotypes, almost no one had dispensed regular asthma medications during the eight-year period. This study shows that there is a gap between asthma guidelines and actual management. Increased adherence to current guidelines is required when planning for optimal care of adolescents and young adults, including their transition to adult healthcare.

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References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal*. 2014;43(2):343-73.
2. Nyenhuis SM, Akkoyun E, Liu L, Schatz M, Casale TB. Real-World Assessment of Asthma Control and Severity in Children, Adolescents, and Adults with Asthma: Relationships to Care Settings and Comorbidities. *The journal of allergy and clinical immunology In practice*. 2019.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. [cited 2019 June]. Available from: <http://ginasthma.org/>.
4. The Swedish Paediatric Society. [cited 2019 September]. Available from: <http://www.barnallergisektionen.se/>.
5. Guideline recommendations for asthma and COPD. Stockholm: The Swedish National Board of Health and Welfare; 2018.
6. White PH, Cooley WC. Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home. *Pediatrics*. 2018;142(5).
7. Odling M, Jonsson M, Janson C, Melen E, Bergstrom A, Kull I. Lost in the transition from pediatric to adult healthcare? Experiences of young adults with severe asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2019;1-9.
8. Withers AL, Green R. Transition for Adolescents and Young Adults With Asthma. *Frontiers in pediatrics*. 2019;7:301.
9. Murphy J, McSharry J, Hynes L, Matthews S, Van Rhoon L, Molloy GJ. Prevalence and predictors of adherence to inhaled corticosteroids in young adults (15-30 years) with asthma: a systematic review and meta-analysis. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2020;1-23.
10. Burg GT, Covar R, Oland AA, Guilbert TW. The Tempest: Difficult to Control Asthma in Adolescence. *The journal of allergy and clinical immunology In practice*. 2018;6(3):738-48.
11. Westman M, Aberg K, Apostolovic D, Lupinek C, Gattinger P, Mittermann I, et al. Sensitization to grass pollen allergen molecules in a birth cohort - Phl p 4 as early indicator of grass pollen allergy. *The Journal of allergy and clinical immunology*. 2020.
12. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2002;13 Suppl 15:11-3.
13. Hallberg J, Ballardini N, Almqvist C, Westman M, van Hage M, Lilja G, et al. Impact of IgE sensitization and rhinitis on inflammatory biomarkers and lung function in adolescents with and without asthma. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2019;30(1):74-80.
14. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *The European respiratory journal*. 2005;26(2):319-38.
15. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *The European respiratory journal*. 2012;40(6):1324-43.
16. Odling M, Andersson N, Ekstrom S, Melen E, Bergstrom A, Kull I. Characterization of asthma in the adolescent population. *Allergy*. 2018;73(8):1744-6.
17. Schatz M, Rosenwasser L. The allergic asthma phenotype. *The journal of allergy and clinical immunology In practice*. 2014;2(6):645-8; quiz 9.
18. Dahlen E, Wettermark B, Bergstrom A, Jonsson EW, Almqvist C, Kull I. Medicine use and disease control among adolescents with asthma. *European journal of clinical pharmacology*. 2016;72(3):339-47.
19. Dahlen E, Komen J, Jonsson EW, Almqvist C, Kull I, Wettermark B. Eliminated patient fee and changes in dispensing patterns of asthma medication in children-An interrupted time series analysis. *Basic & clinical pharmacology & toxicology*. 2019;125(4):360-9.

20. Ivanova I, Elseviers M, Wettermark B, Schmidt Mende K, Vander Stichele R, Christiaens T. Electronic assessment of cardiovascular potentially inappropriate medications in an administrative population database. *Basic & clinical pharmacology & toxicology*. 2019;124(1):62-73.
21. Wandell P, Carlsson AC, Wettermark B, Lord G, Cars T, Ljunggren G. Most common diseases diagnosed in primary care in Stockholm, Sweden, in 2011. *Family practice*. 2013;30(5):506-13.
22. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology*. 2009;24(11):659-67.
23. Wettermark B, Hammar N, Forel 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.
24. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2016. Oslo, 2016.
25. Belhassen M, Nolin M, Nibber A, Ginoux M, Devouassoux G, Van Ganse E. Changes in Persistent Asthma Care and Outcomes From 2006 to 2016 in France. *The journal of allergy and clinical immunology In practice*. 2019;7(6):1858-67.
26. Anell A, Dackehag M, Dietrichson J. Does risk-adjusted payment influence primary care providers' decision on where to set up practices? *BMC health services research*. 2018;18(1):179.
27. Bergstrom SE, Sundell K, Hedlin G. Adolescents with asthma: consequences of transition from paediatric to adult healthcare. *Respiratory medicine*. 2010;104(2):180-7.
28. Cloutier MM, Salo PM, Akinbami LJ, Cohn RD, Wilkerson JC, Diette GB, et al. Clinician Agreement, Self-Efficacy, and Adherence with the Guidelines for the Diagnosis and Management of Asthma. *The journal of allergy and clinical immunology In practice*. 2018;6(3):886-94.e4.
29. Melen E, Guerra S, Hallberg J, Jarvis D, Stanojevic S. Linking COPD epidemiology with pediatric asthma care: Implications for the patient and the physician. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2019;30(6):589-97.
30. Larsson K, Stallberg B, Lisspers K, Telg G, Johansson G, Thuresson M, et al. Prevalence and management of severe asthma in primary care: an observational cohort study in Sweden (PACEHR). *Respiratory research*. 2018;19(1):12.
31. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clinics in chest medicine*. 2012;33(3):405-17.
32. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *The Journal of allergy and clinical immunology*. 2011;128(6):1185-91.e2.
33. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *The European respiratory journal*. 2019;53(6).
34. Lee JX, Wojtczak HA, Wachter AM, Lee ML, Burns L, Chen D, et al. Understanding asthma medical nonadherence in an adult and pediatric population. *The journal of allergy and clinical immunology In practice*. 2015;3(3):436-7.
35. Ross KR, Gupta R, DeBoer MD, Zein J, Phillips BR, Mauger DT, et al. Severe asthma during childhood and adolescence: A longitudinal study. *The Journal of allergy and clinical immunology*. 2020;145(1):140-6.e9.
36. To M, Tsuzuki R, Katsube O, Yamawaki S, Soeda S, Kono Y, et al. Persistent asthma from childhood to adulthood presents a distinct phenotype of adult asthma. *The journal of allergy and clinical immunology In practice*. 2020.

- 527 37. Carlsson AC, Wandell P, Osby U, Zarrinkoub R, Wettermark B, Ljunggren G. High
528 prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total
529 population of Stockholm, Sweden - a challenge for public health. BMC public health. 2013;13:670.
530 38. Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and Overdiagnosis of
531 Asthma. American journal of respiratory and critical care medicine. 2018;198(8):1012-20.

532

Table I. Number of consultations and level of care, four years before and after 18 years of age, in relation to asthma at the 16-, and 24-year follow-ups.

	Current asthma at the 16-year follow-up^a			Current asthma at the 24-year follow-up^a			Persistent asthma^b		
	n = 253			n = 248			n = 147		
	Before 18	After 18	p-value ^c	Before 18	After 18	p-value ^c	Before 18	After 18	p-value ^c
At least 1 consultation n (%)	82 (32)	68 (27)	0.17	68 (27)	76 (31)	0.43	58 (39)	55 (37)	0.72
Number of consultations Mean (max)	1.2 (23)	0.6 (27)	< 0.01	1.0 (23)	0.8 (27)	0.47	1.6 (23)	1.0 (27)	0.02
Primary care Mean (max)	0.06 (3)	0.3 (5)	< 0.01	0.04 (2)	0.4 (5)	< 0.01	0.05 (2)	0.4 (5)	< 0.01
Specialist care Mean (max)	1.1 (23)	0.4 (27)	< 0.01	1.0 (23)	0.4 (27)	< 0.01	1.6 (23)	0.6 (27)	< 0.01

^aFulfilling at least two of the following three criteria: symptoms of wheeze and/or breathing difficulties in the last 12 months, ever doctor's diagnosis of asthma and/or asthma medicine occasionally or regularly in the last 12 months.

^bFulfilling the definition of current asthma at both the 16-, and 24-year follow-ups.

^cp-values obtained using tests of proportions and Wilcoxon's signed-rank test indicated differences between four years before and after 18 years of age for visits and level of care.

Table II. Number of consultations and level of care, four years before and after 18 years of age, in relation to asthma phenotypes at the 16-year follow-up.

	Allergic asthma^a			Asthma and airflow obstruction^b			Asthma with high daily doses ICS^c			Severe asthma^d		
	n = 157			n = 18			n = 60			n = 12		
	Before 18	After 18	p-value ^e	Before 18	After 18	p-value ^e	Before 18	After 18	p-value ^e	Before 18	After 18	p-value ^e
At least 1 consultation												
n (%)	57 (36)	53 (34)	0.64	8 (44)	5 (28)	0.30	31 (52)	27 (45)	0.47	10 (83)	8 (67)	0.35
Number of consultations												
Mean (max)	1.5 (23)	0.9 (27)	0.01	1.7 (10)	0.6 (4)	0.03	2.4 (23)	1.4 (27)	0.01	5.8 (23)	1.6 (4)	0.02
Primary care												
Mean (max)	0.05 (2)	0.3 (3)	< 0.01	0.1 (1)	0.3 (2)	0.16	0.08 (1)	0.4 (2)	< 0.01	0.08 (1)	0.4 (2)	0.08
Specialist care												
Mean (max)	1.4 (23)	0.6 (27)	< 0.01	1.6 (9)	0.3 (3)	0.01	2.4 (23)	1.1 (27)	< 0.01	5.7 (23)	1.2 (3)	0.01

^aA combination of asthma and immunoglobulin E sensitisation to inhalant allergens (cat, dog, horse, and/or house dust mite, timothy grass, birch, mugwort and/or mould) at the 16-year follow-up.

^bThe forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio z-score below the lower limit of normal, defined as the lower 5th percentile in the never asthmatic population.

^cDispensed at least 800 µg budesonide or equivalent, ≥ 500 µg fluticasone, or fixed combinations of inhaled corticosteroids (ICS) and long-acting β₂-agonists (LABA).

^dAsthma with high daily doses of ICS plus dispensed LABA and/or leukotriene receptor antagonist at least once in the 18 months prior to the 16-year follow-up to prevent the asthma from becoming or remained uncontrolled, defined as at least one of the following four alternatives based on data from the 16-year follow-up: 1. Uncontrolled asthma based on modified GINA definition (3, 16). 2. Taken cortisone tablets dissolved in water for asthma or respiratory symptoms ≥3 days in a row. 3. Sought acute medical care because of respiratory symptoms. 4. Impaired lung function, FEV₁ below 80% of predicted.

^ep-values obtained using tests of proportions and Wilcoxon's signed-rank test indicated differences between four years before and after 18 years of age for visits and level of care.

Table III. Asthma phenotypes at the 16-year follow-up in relation to one consultation after 18 years of age among young adults with persistent asthma (n = 147). Results obtained with logistic regression.

	One consultation after age 18 years of age				
	n	OR _{Crude}	(95% CI)	OR _{Adjusted} ^a	(95% CI)
Allergic asthma ^b	109	1.7	(0.7–4.5)	1.8	(0.7–4.7)
Asthma and airflow obstruction ^c	10	0.4	(0.08–1.8)	0.4	(0.07–1.8)
Asthma with high daily doses inhaled corticosteroids ^d	44	2.4	(1.2–5.0)	2.6	(1.3–5.6)
Severe asthma ^e	10	3.9	(1.0–16.0)	3.9	(0.9–16.1)

^aAdjusted for gender and socio-economic status.

^bA combination of asthma and immunoglobulin E sensitisation to inhalant allergens (cat, dog, horse, and/or house dust mite, timothy grass, birch, mugwort and/or mould).

^cThe forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio z-score below the lower limit of normal, defined as the lower 5th percentile in the never asthmatic population.

^dDispensed at least 800 µg budesonide or equivalent, ≥ 500 µg fluticasone, or fixed combinations of inhaled corticosteroids (ICS) and long-acting β₂-agonists (LABA).

^eAsthma with high daily doses of ICS plus dispensed LABA and/or leukotriene receptor antagonist at least once in the 18 months prior to the 16-year follow-up to prevent the asthma from becoming or remained uncontrolled, defined as at least one of the following four alternatives based on data from the 16-year follow-up: 1. Uncontrolled asthma based on modified GINA definition (3, 16). 2. Taken cortisone tablets dissolved in water for asthma or respiratory symptoms ≥3 days in a row. 3. Sought acute medical care because of respiratory symptoms. 4. Impaired lung function, FEV₁ below 80% of predicted.

Table IV. Number of dispensed asthma medicines, four years before and after 18 years of age, in relation to asthma phenotypes at the 16-year follow-up.

	Allergic asthma ^a			Asthma and airflow obstruction ^b			Asthma with high daily doses ICS ^c			Severe asthma ^d		
	n = 157			n = 18			n = 60			n = 12		
	Before 18	After 18	p-value ^e	Before 18	After 18	p-value ^e	Before 18	After 18	p-value ^e	Before 18	After 18	p-value ^e
Number of dispensed:												
Short-acting β_2-agonists (SABA)												
Mean (max)	2.6 (39)	1.8 (52)	< 0.01	3.3 (17)	1.1 (8)	< 0.01	3.8 (39)	2.6 (42)	< 0.01	3.1 (7)	3.5 (11)	0.69
Long-acting β_2-agonists (LABA)												
Mean (max)	0.2 (5)	0.2 (11)	0.71	0.6 (7)	0.6 (10)	0.61	0.2 (5)	0.2 (7)	0.56	1.0 (5)	0.8 (7)	0.53
Inhaled corticosteroids (ICS)												
Mean (max)	1.2 (16)	0.7 (9)	< 0.01	2.0 (12)	0.1 (1)	< 0.01	1.8 (22)	0.9 (16)	< 0.01	3.6 (22)	2.3 (16)	0.24
Fixed combinations of ICS and LABA												
Mean (max)	1.9 (18)	1.1 (24)	< 0.01	1.6 (8)	0.9 (11)	0.07	3.9 (18)	2.4 (16)	< 0.01	5.7 (18)	4.1 (11)	0.11
Any inhaled corticosteroids (ICS)												
Mean (max)	3.1 (20)	1.8 (24)	< 0.01	3.6 (20)	0.9 (11)	< 0.01	5.7 (23)	3.2 (17)	< 0.01	9.3 (23)	6.3 (16)	0.22
Leukotriene receptor antagonists (LTRA)												
Mean (max)	0.7 (14)	0.4 (17)	0.22	1.9 (13)	0.7 (9)	0.05	1.7 (13)	1.0 (11)	0.02	5.9 (13)	2.7 (11)	0.01

^aA combination of asthma and immunoglobulin E sensitisation to inhalant allergens (cat, dog, horse, and/or house dust mite, timothy grass, birch, mugwort and/or mould).

^bThe forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio z-score below the lower limit of normal, defined as the lower 5th percentile in the never asthmatic population.

^cDispensed at least 800 µg budesonide or equivalent, ≥ 500 µg fluticasone, or fixed combinations of inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA).

^dAsthma with high daily doses of ICS plus dispensed LABA and/or leukotriene receptor antagonist at least once in the 18 months prior to the 16-year follow-up to prevent the asthma from becoming or remained uncontrolled, defined as at least one of the following four alternatives based on data from the 16-year follow-up: 1. Uncontrolled asthma based on modified GINA definition (3, 16). 2. Taken cortisone tablets dissolved in water for asthma or respiratory symptoms ≥3 days in a row. 3. Sought acute medical care because of respiratory symptoms. 4. Impaired lung function, FEV₁ below 80% of predicted.

^ep-values obtained using Wilcoxon's signed-rank test indicated differences between four years before and after 18 years of age for respective dispensed asthma medicines.

Table V. Number of dispensed asthma medicines, four years before and after 18 years of age, in relation to asthma at the 16-, and 24-year follow-ups.

	Current asthma at the 16-year follow-up^a			Current asthma at the 24-year follow-up^a			Persistent asthma^b		
	n = 253			n = 248			n = 147		
	Before 18	After 18	p-value ^c	Before 18	After 18	p-value ^c	Before 18	After 18	p-value ^c
Number of dispensed:									
Short-acting β_2-agonists (SABA)									
Mean (max)	2.3 (39)	1.4 (52)	< 0.01	1.9 (39)	1.6 (52)	< 0.01	2.8 (39)	2.1 (52)	< 0.01
Long-acting β_2-agonists (LABA)									
Mean (max)	0.2 (12)	0.2 (11)	0.80	0.2 (7)	0.2 (11)	0.61	0.2 (7)	0.3 (11)	0.25
Inhaled corticosteroids (ICS)									
Mean (max)	1.1 (22)	0.6 (16)	< 0.01	0.9 (22)	0.7 (16)	0.18	1.2 (22)	0.9 (16)	< 0.01
Fixed combinations of ICS and LABA									
Mean (max)	1.5 (18)	0.8 (24)	< 0.01	1.2 (18)	1.0 (24)	0.02	1.9 (18)	1.3 (24)	< 0.01
Any inhaled corticosteroids (ICS)									
Mean (max)	2.6 (23)	1.4 (24)	< 0.01	2.0 (23)	1.7 (24)	0.03	3.1 (23)	2.1 (24)	< 0.01
Leukotriene receptor antagonists (LTRA)									
Mean (max)	0.7 (14)	0.4 (17)	0.01	0.5 (14)	0.4 (17)	0.47	0.7 (14)	0.5 (17)	0.14

^aFulfilling at least two of the following three criteria: symptoms of wheeze and/or breathing difficulties in the last 12 months, ever doctor's diagnosis of asthma, and/or asthma medicine occasionally or regularly in the last 12 months.

^bFulfilling the definition of current asthma at both the 16-, and 24-year follow-ups.

^cp-values obtained from Wilcoxon's signed-rank test indicated differences between four years before and after 18 years of age for respective dispensed asthma medicines.

Figure captions and footnotes

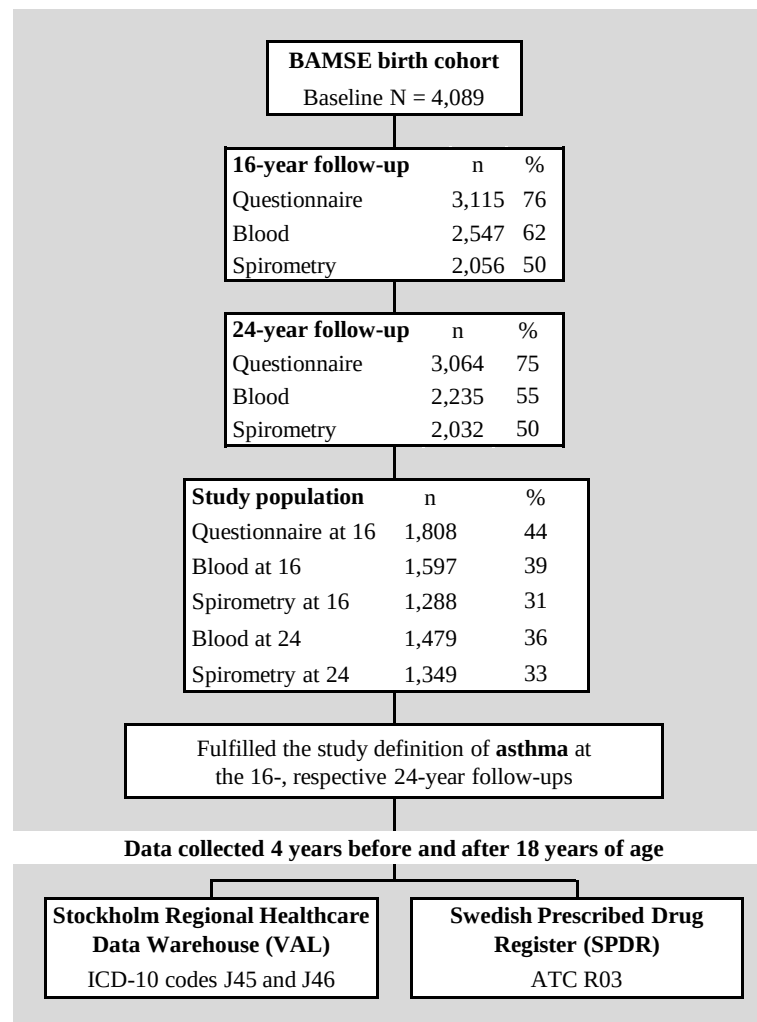
Figure 1. Study flow chart of the study population (n = 1,808) linked to data sources for asthma-related healthcare consumption and pharmacological dispensation.

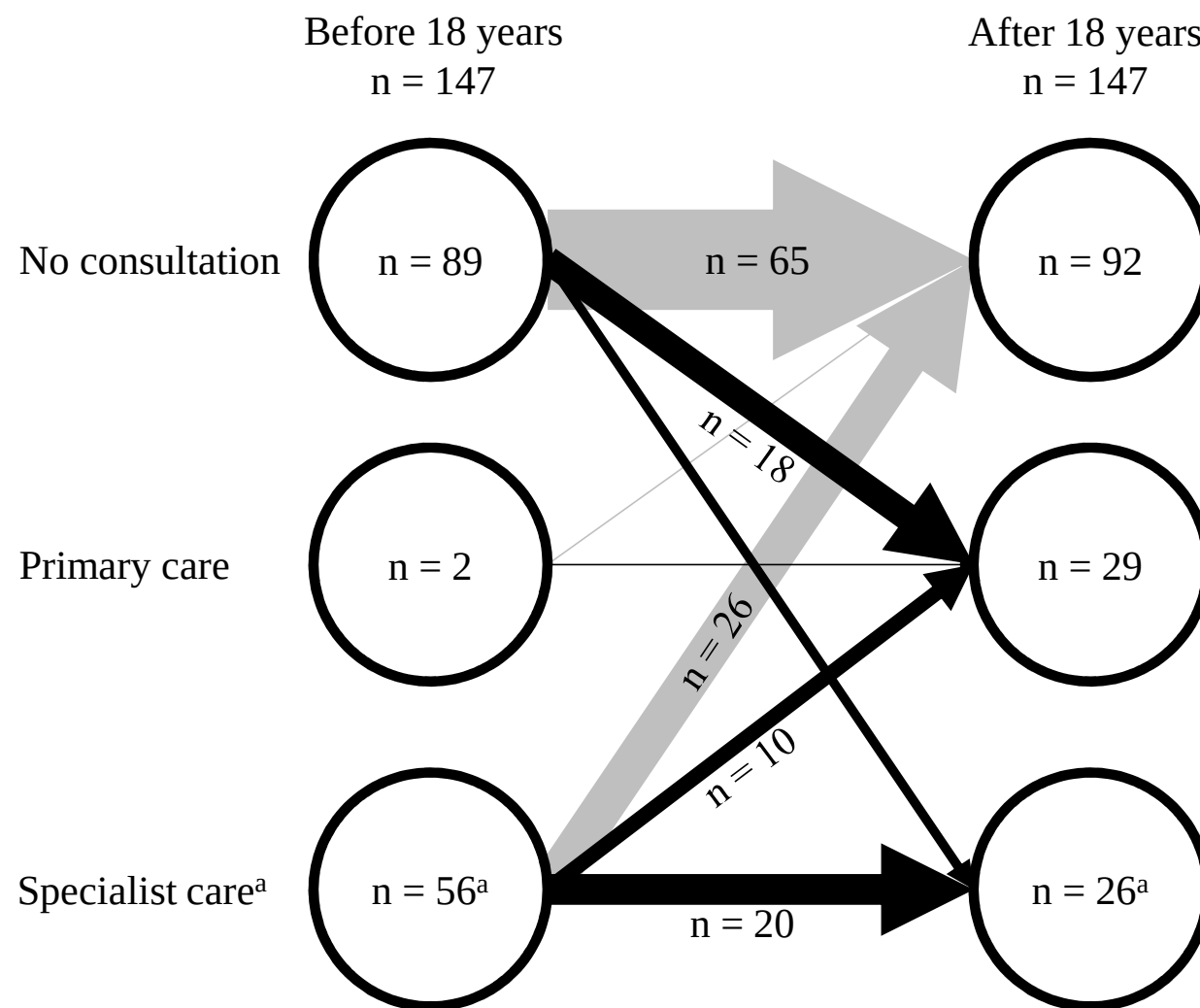
Figure 2. Number of consultations four years before and after 18 years of age, divided by level of care, among young adults with persistent asthma (n = 147).

^aConsultations in both primary and specialist care were merged into specialist care (n = 4).

Figure 3. The mean number of yearly consultations among young females (n = 79) and males (n = 68) with persistent asthma and the prevalence of asthma during this time period^a.

^aThe prevalence of current asthma is plotted based on the prevalence at the 12-, 16-, and 24-year follow-ups.





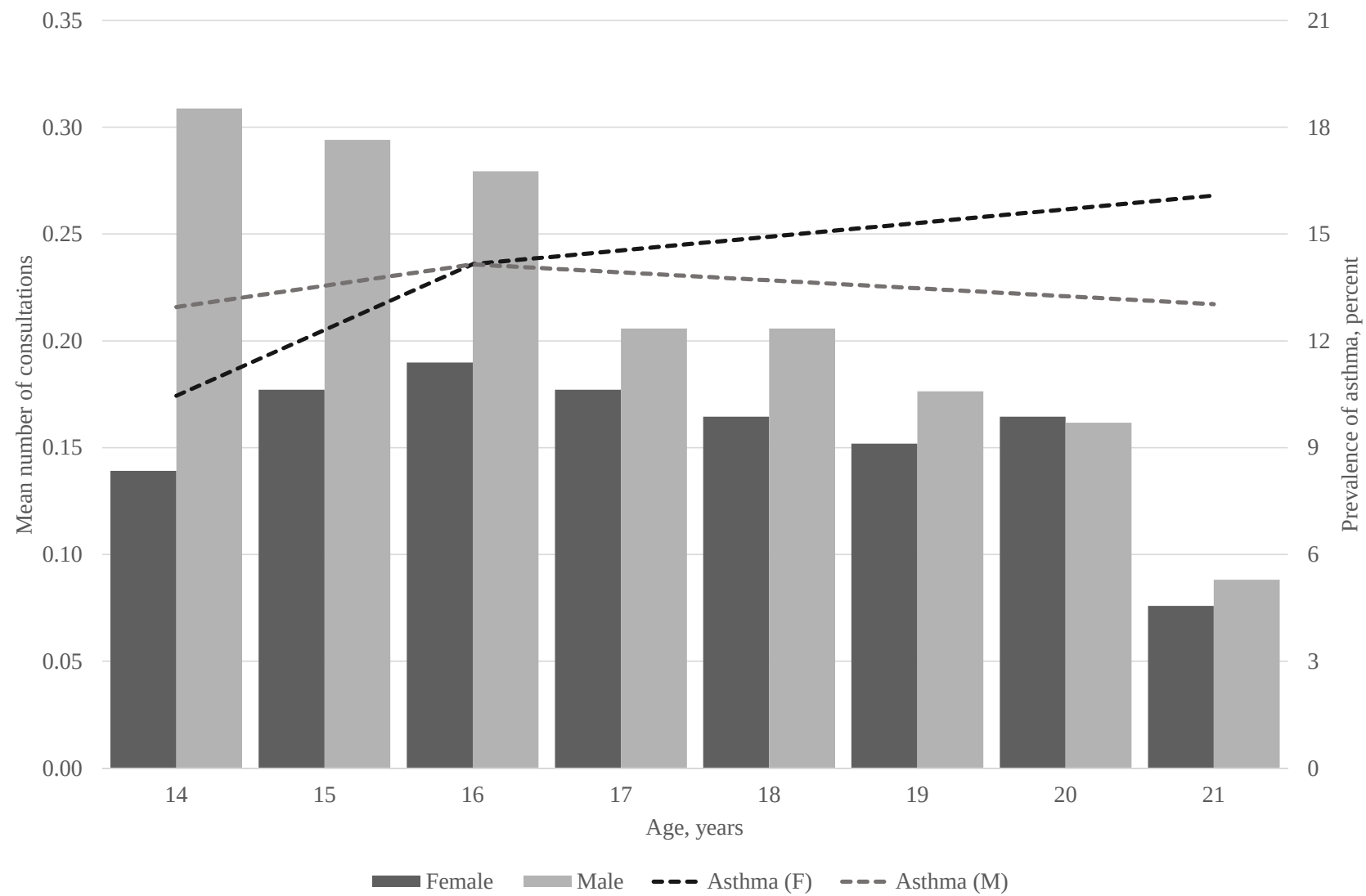


Table E1. Distribution of selected background characteristics among included and not included participants in the present study ($N_{\text{tot}} = 4,089$).

Background characteristics	Included n = 1,808			Not included n = 2,281			p-value ^d
	n	%	(95% CI)	n	%	(95% CI)	
Gender							
Female	951	53	(50.3–54.9)	1,073	47	(45.0–49.1)	< 0.01
Mother's age at birth							
< 25 years	133	7	(6.2–8.7)	186	8	(7.1–9.3)	0.34
Parent born outside Sweden							
Yes	370	21	(19.6–23.5)	348	21	(18.8–22.6)	0.55
Parental allergic disease^a							
Yes	563	31	(29.3–33.6)	637	28	(26.5–30.2)	0.03
Parental education^b							
University	998	55	(52.9–57.5)	1,163	51	(48.9–53.0)	< 0.01
Parental smoking at baseline^c							
Yes	382	21	(19.4–23.2)	473	21	(19.2–22.6)	0.76

^aMother and/or father with doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hay fever in combination with reported allergy to furred pets and/or pollen at the time of baseline questionnaire.

^bAt least university or college degree/other education.

^cAny of the parents smoked at least one cigarette per day at the time of baseline questionnaire.

^dp-values obtained using tests of proportions indicated differences between included and excluded participants.

Table E2. Consultations and level of care for ICD-10 J00–J99, four years before and after 18 years of age, in relation to asthma at the 16-, and 24-year follow-ups.

	ICD-10 J00–J99: diseases of the respiratory system								
	Asthma at the 16-year follow-up ^a			Asthma at the 24-year follow-up ^a			Persistent asthma ^b		
	n = 253			n = 248			n = 147		
	Before 18	After 18	p-value ^c	Before 18	After 18	p-value ^c	Before 18	After 18	p-value ^c
At least 1 consultation n (%)	185 (73)	162 (64)	0.03	172 (69)	174 (70)	0.85	109 (74)	105 (71)	0.60
Number of consultations Mean (max)	3.0 (40)	2.0 (33)	< 0.01	2.9 (40)	2.3 (33)	0.06	3.5 (40)	2.4 (33)	< 0.01
Primary care Mean (max)	1.6 (12)	1.2 (8)	0.01	1.4 (12)	1.4 (11)	0.82	1.5 (12)	1.3 (8)	0.43
Specialist care Mean (max)	1.5 (37)	0.8 (27)	< 0.01	1.4 (37)	0.9 (27)	0.01	2.0 (37)	1.1 (27)	< 0.01

^aFulfilling at least two of the following three criteria: Symptoms of wheeze and/or breathing difficulties in the last 12 months, ever doctor's diagnosis of asthma and/or asthma medicine occasionally or regularly in the last 12 months.

^bFulfilling the definition of asthma at both the 16-, and 24-year follow-ups.

^cp-values obtained using tests of proportions and Wilcoxon's signed-rank test indicated differences between four years before and after 18 years of age for visits and level of care.

17 **Figure caption**

18

19 **Figure E1.** Timeline with study periods and data collection.

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