INHALED CORTICOSTEROIDS IN INFANTS AND TODDLERS ATTENUATE LINEAR GROWTH

ANTTI SAARI, PHD[1,2] *, LAURI J. VIRTA, PHD[3] *, LEO DUNKEL, PHD[4], AND ULLA SANKILAMPI, PHD[2]

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CAPSULE SUMMARY:

Inhaled corticosteroid exposure prior to 24 months of age is associated with attenuated linear growth. , our results highlight, in addition to careful growth monitoring, the importance of judicious use of inhaled corticosteroids in infants and toddlers with recurrent wheezing.

KEYWORDS:

Anti-asthmatic drugs; asthma; budesonide; corticosteroids; fluticasone propionate; growth; infant; inhaled corticosteroids; wheezing

ABBREVIATIONS:

BUD: budesonide; FP: fluticasone propionate; ICS: inhaled corticosteroid; PEAK: Prevention of Early Asthma in Kids; zTH^{DEV} height-for-age z-score deviation from target height z-score

FUNDING SOURCE:

This study was supported by The Päivikki and Sakari Sohlberg Foundation (AS, US), The Foundation for Pediatric Research (AS, US), Kuopio University Hospital State Research Funding (AS, US), and The Finnish Medical Foundation (US).

FINANCIAL DISCLOSURE:

The authors have nothing to disclose.

CONFLICT OF INTEREST:

The authors have nothing to disclose.

To the Editor,

Wheezing is a common symptom during viral respiratory tract infections in children aged less than 24 months, but the distinction between wheezing and asthma is difficult, because diagnostic tests are not available.[1] Empiric drug therapy with inhaled corticosteroids (ICS) has been recommended, particularly if the symptom pattern is consistent with asthma or if there is a considerable burden of symptoms.[1]

Treatment with an ICS has potential adverse effects such as impaired linear growth.[1-3] Several studies of children older than 2 years have shown that these growth effects are dose-dependent albeit relatively small.[2,3] In addition, only one study has reported compromised adult height after ICS exposure.[4] Studies for children aged less than 24 months remain scarce.[2-3] In a small study Bisgaard et al. reported no adverse growth effects.[5] However, further studies are clearly needed as the Prevention of Early Asthma in Kids (PEAK) Study and its post hoc analysis reported significant growth reduction without catch-up after medication discontinuation in a subgroup of children aged 2 years at the initiation of fluticasone propionate (FP).[6,7]

We evaluated the effects of ICS exposure prior to 24 months of age on linear growth in a Finnish population-based cohort of 12,482 children, who were carefully screened for chronic conditions and other factors that could affect growth (see **Fig E1** and **Table E2~~1~~** in this article's Online Repository at www.jacionline.org). The first height and weight measurements at or after 24 months of age were used as primary end-points (median age 25 months [interquartile range 24 to 26 months]). Our hypothesis was that ICS use during the first 24 months of life compromises linear growth, and the effect varies by the dose and the duration of ICS treatment.

Based on information from the Drug Purchase Register covering all prescribed and reimbursed drug purchases in Finland, 562 of 12,482 (4.5%) children had been exposed to ICS (2.0% to budesonide [BUD], 2.3% to FP and 0.2% to both) and 424 (3.4%) to other anti-asthmatic drugs (montelukast, inhaled β-sympathomimetic drugs, or oral corticosteroids) before the age of 24 months. Children with ICS exposure were classified into nine groups according to the daily ICS doses (a minimal, a low or a medium/high dose in comparison to the recommended daily dose)[1] and the duration of the treatment (< 3 months, 3 - 6 months and > 6 months) (**Table E1**). Linear growth was compared between the exposed and unexposed groups using two growth parameters: height-for-age z-score (zHFA)[9] and zHFA deviation from target height z-score based on parental heights (zTH^{DEV}).[9] Statistical comparison was performed using covariance analysis with random effects (See Method's in the Online Repository at www.jacionline.org.)

Children exposed to ICS were significantly shorter than unexposed children at the median age of 25 months The mean adjusted differences in zHFA and zTH^{DEV} were -0.13 (95% CI -0.18 to -0.08) and -0.15 (95% CI -0.20 to -0.10) as compared to unexposed children **(Table 1**).

Daily low dose ICS consumption was associated with a growth-suppressing effect at or after 24 months of age if the medication was used more than 6 months (**Fig 1**). The mean zTH^{DEV} difference from the unexposed children was -0.25 (95% CI -0.41 to -0.09). However, after treatment with medium/high dose ICS for 3 - 6 months, or > 6 months, reduction in average height was even more pronounced. The mean zTH^{DEV} differences between exposed and unexposed children were -0.53 (95% CI -0.79 to -0.26) and -0.25 (95% CI -0.46 to -0.03), respectively, equaling to up to 1 cm loss in height at or after 24 months of age in both sexes.

In this population-based study, we show that ICS exposure during the infancy is independently associated with poor linear growth at or after 24 months of age. Young children that were exposed to daily low dose ICS therapy for >6 months had significant reduction in height in comparison to unexposed children. However, neither daily minimal dose nor short term (< 3 months) use of ICS even at a medium/high dose were not associated with attenuated growth. Nevertheless, individual responses to ICSs may vary considerably.

Our observations confirm and complement the findings of Guilbert et al,[7] indicating that infants are more susceptible to growth-impairing effects of ICSs than children after 24 months of age. Infancy is characterized by rapid linear growth, which is vulnerable to suboptimal environmental effects. A positive secular change in adult height has been attributed primarily to improved environmental conditions in infancy, which facilitates the use of full growth potential during that period.[9] Factors interfering with physical development during infancy likely cause long-term effects on later growth.[9] Growth attenuation in early life is not always followed by catch-up, as shown in the PEAK-Study[7] wherein children aged 2 years did not exhibit catch-up growth after cessation of the medication, although older children did. In this study we could not access longitudinal growth data beyond the age of 25 months and therefore catch-up growth in our cohort of exposed children remains unknown.

The major strength of our study was the large, carefully examined population-based cohort of infants and their longitudinal growth data sets, as well as parental height data. These data enabled the comparison of the linear growth against the individual genetic growth potential. We also utilized the national drug purchase register as a source of medication data, which likely is a more reliable source than prescription data or information based on self-reported use. Due to the retrospective nature of our data we cannot, however, provide conclusive causality between ICS and growth.

In summary, ICS exposure before 24 months of age is associated with attenuated linear growth. Careful considerations should be given to developing treatment modalities that are safe including formulations of ICS and devices for their administration for young children. Further studies on efficacy and safety of ICS in infants are clearly needed.[6,7] Meanwhile, judicious use of ICS in infants is warranted, and during ICS treatment linear growth of children should be frequently and carefully monitored.

Yours sincerely,

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REFERENCES

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LEGEND OF THE FIGURE

Figure 1 Association of the dose of inhaled corticosteroid (ICS) and duration of ICS treatment with the height-for-age z-score deviation from target height (zTH^{DEV}) at or after 24 months of age. Bars indicate the adjusted mean differences with 95% confidence intervals in comparison to unexposed children (the zero line).

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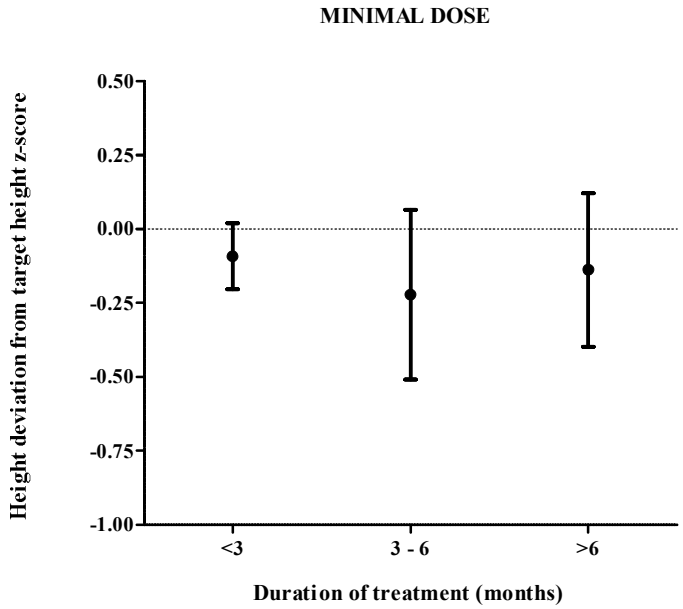
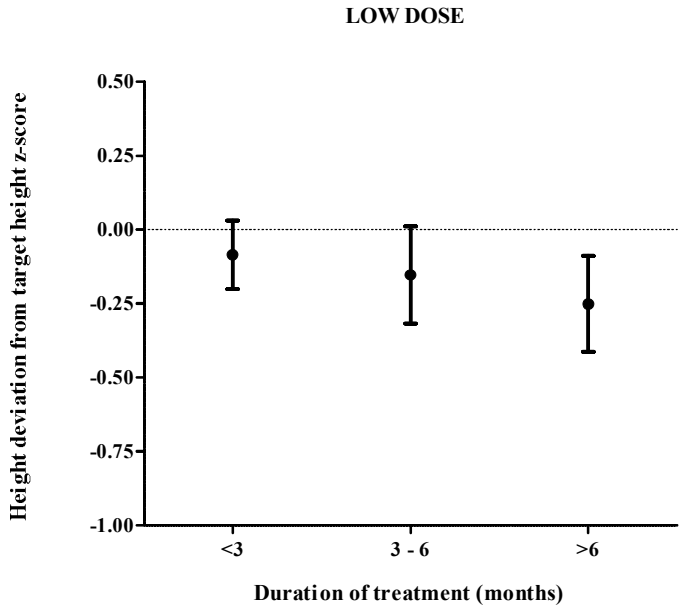
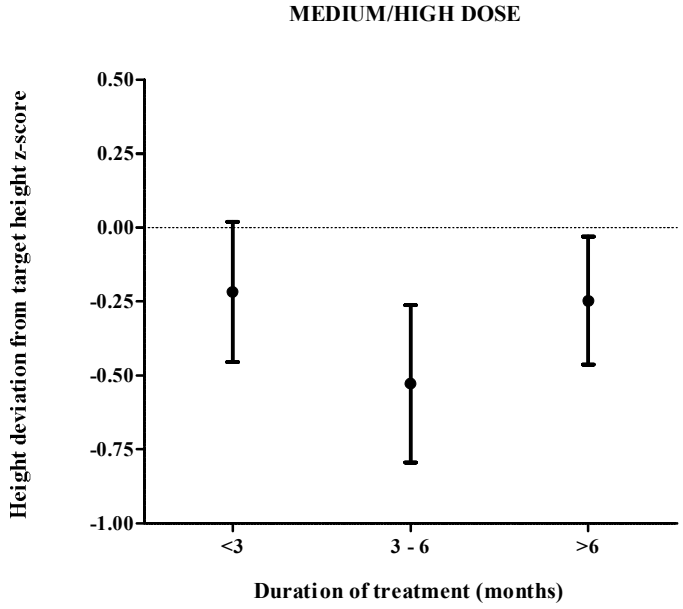
Figure No. 1 - Marked







Statistical adjustments: antibiotic exposure, birth weight and length z-score, gestational age, maternal age, parity, season at birth, weight status and heigh t-for-age deviation from target height z-score before the initiation of medication

Figure No. 1 - Unmarked

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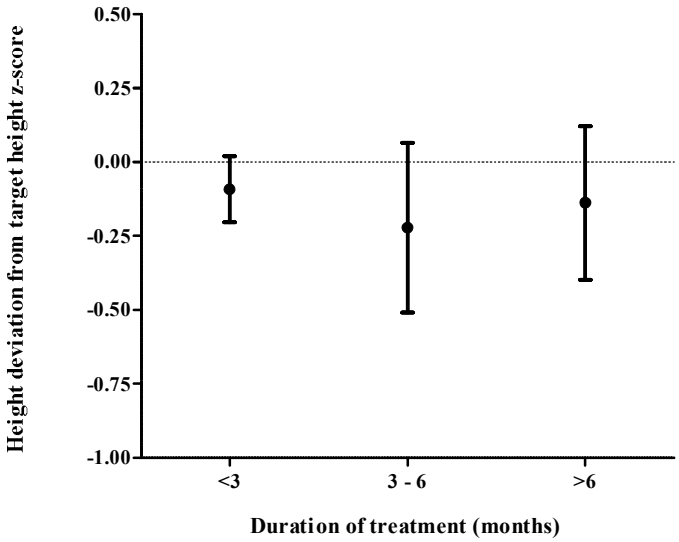

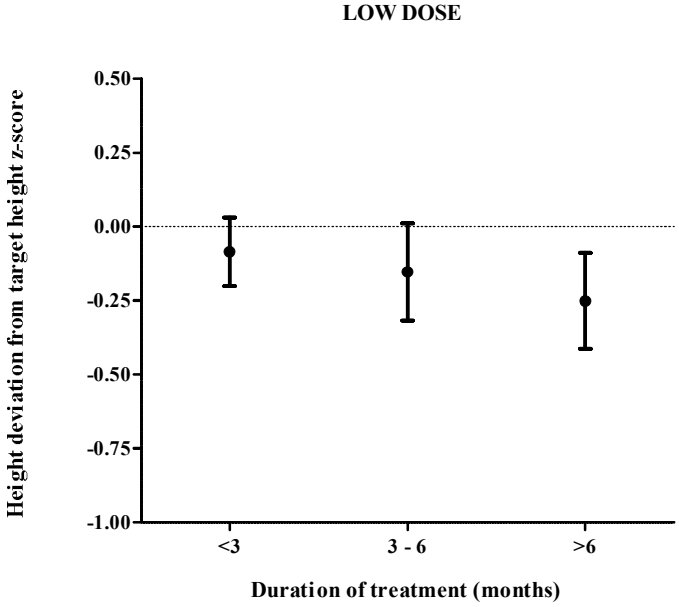

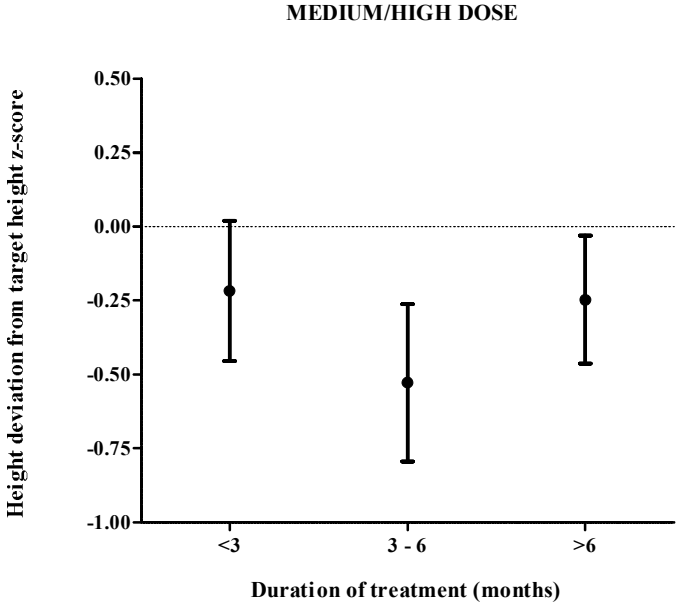

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Table 1 Growth in children exposed to inhaled corticosteroids in infancy compared to the unexposed reference population (n = 11,496) at the median age of 25 months.

	Mean difference in the unexposed children (95% CI)							
	Any inhaled corticosteroid (N = 562)		Budesonide only[a] (N = 244)		Fluticasone propionate only[a] (N = 283)		Other asthma medications[b] (N = 424)	
	Adjusted[c]	*p*-value	Adjusted[c]	*p*-value	Adjusted[c]	*p*-value	Adjusted[c]	*p*-value
Height-for-age z-score[d]	-0.13 (-0.18 – -0.08)	<0.001	-0.16 (-0.23 – -0.09)	<0.001	-0.08 (-0.15 – -0.01)	0.02	-0.03 (-0.08 – 0.03)	0.36
Height-for-age z-score deviation from target height	-0.15 (-0.20 – -0.10)	<0.001	-0.19 (-0.27 – -0.11)	<0.001	-0.08 (-0.15 – -0.00)	0.04	-0.05 (-0.12 – 0.01)	0.08

[a]Medication was delivered by a spacer (budesonide [93%], fluticasone propionate [100%]) or by a nebulizer (budesonide [7%])
[b]Oral corticosteroids, montelukast and/or inhaled β-sympathomimetic drugs
[c]Adjusted for antibiotic exposure, birth weight and length z-score, gestational age, maternal age, parity, season at birth, and baseline height z-score at the initiation of ICS therapy; see Tables E1 and E2 in the Online Repository at www.jacionline.org
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E-MATERIAL

METHODS

Ethics

Permission for the study was obtained from Espoo Municipality Institutional Review Board, The Social Insurance Institution of Finland (SII), and the National Institutes of Health and Welfare (THL). Analyses were performed with encrypted register data.

Study Population

The Finnish child welfare clinics in primary care provide pre-scheduled visits (monthly from birth to 6 months, 8, 12, 18, and 24 months of age, then annually) to all children living in Finland, with a coverage of nearly 100% of the child population.[E1,E2] These visits include auxological evaluation (length/height, and weight) by specially trained nurses with standardized equipment.[E1,E2] For this study, we initially included all 14,764 children born between January 1, 2003, and April 30th 2007 (51% boys) who attended child welfare clinics in the city of Espoo, Finland, and had at least one visit at or after 24 months (**Figure E1**).[E3]

To exclude children with prenatal conditions affecting growth, and to control for possible confounding perinatal factors statistically, we obtained the Medical Birth Register data from the Finnish National Institute of Health and Welfare.[E4] These data included maternal age, smoking during pregnancy, parental relationship, gestational age, mode of delivery, parity, plurality, birth weight and length, season at birth, and congenital syndromes or anomalies. First, we excluded 1,381 children with any of the following: preterm birth at <37 gestational weeks, congenital anomaly or syndrome, and a lack of perinatal data. Second, we excluded children with postnatally diagnosed growth disorders or regular medication possibly affecting

growth (not ICS or other anti-asthmatic drugs) (N = 901). The final study population was comprised of 12,482 children, while 6,391 (51%) of them were boys (**Figure E1**).

Auxological data and growth outcomes

All of the available growth data from birth to the age over 24 months, as well as data on parental heights were collected from the electronic health records of child welfare clinics in primary care. Potentially false measurements or typing errors were evaluated by scatter plots, and either corrected or excluded. Birth size, length and weight measurements, and body mass indices (BMI, calculated as weight [kg]/height $[m]^2$)] were transformed into z-scores (BMI-for-age, weight-for-length, and height-for-age) according to contemporary Finnish growth references.[E3,E5] Target height (TH) was calculated by using parental heights,[E6] and height-for-age z-score deviation from TH z-score was expressed as zTH^{DEV}.

Exposure to inhaled corticosteroids

In Finland, ICS and other medications for recurrent wheezing/asthma are available only by prescription and sold in registered pharmacies. Two types of ICS, budesonide (BUD) and fluticasone propionate (FP) are licensed by the Finish Medicines Agency (Fimea) for daily use in infancy from the age of 6 months (BUD) and 12 months (FP). In the case of recurrent wheezing, off-label ICS have been prescribed for patients younger than 6 months. Formulations applicable for infants included metered-dose inhalers delivered by a spacer (BUD, FP) or inhaled suspension delivered by a nebulizer (BUD).[E7]

The Drug Purchase Register covers all drug purchases prescribed by physicians and reimbursed by the National Sickness Insurance Scheme in Finland. The register data include information on drug class, quantity, and date of dispense.[E8] Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System, developed by the World Health Organization (WHO) for drug consumption statistics.[E9] Information about the

purchase of drugs for asthma (ATC-code R03 including ICS, β-sympathomimetics, montelukast), systemic corticosteroids (H02AB), and systemic antibiotics (J01) was merged to the growth data. According to the annual wholesale survey conducted by the Fimea, the Drug Purchase Register of SII has a coverage of about 93% of all outpatient consumption of drugs for obstructive airway diseases (R03). Medications administrated in hospitals were not collected.

Altogether 562 (4.5%) children of the study population had been exposed to ICS before the age of 24 months (**Table E1**). ICS was delivered by a spacer (BUD [N=227, 93%], FP [N=283, 100%]) or by a nebulizer (BUD [N=17, 7%]). Detailed information of the spacer devices was not available in The Drug Purchase Register. In addition, 424 children (3.4%) had been exposed to anti-asthmatic drugs other than ICS (montelukast, inhaled β-sympathomimetic drugs, or oral corticosteroids). The reference population without exposure to any of these drugs consisted of 11,496 children (**Fig E1**).

Duration of the treatment and the average daily dose of ICS for each individual child was calculated using the Drug purchase register data on the type and number of ICS purchases before the age of 24 months. The Finnish regulations allow for the purchase of reimbursed medication for the period of 3 months. Duration of the ICS treatment for an individual child was calculated using the total number of the purchases prior to 24 months of age (one purchase = treatment < 3 months, two purchases = treatment 3 - 6 months, three or more purchases = treatment >6 months). In addition, the purchased doses of ICSs were divided by the number of days between the first and the following purchases stepwise until the growth visit at or after 24 months of age resulting into the average daily dose of a child. The average daily dose of ICS was then categorized as a medium/high dose (equal or more than daily BUD 400 µg or FP 200 µg via spacer, or BUD 1000 µg via nebulizer), a low-dose (half of

the medium dose), and a minimal dose (equal or less than one quarter of the medium dose), according to the Global Initiative for Asthma report.[E10]

Statistical analyses

Frequency of perinatal factors and postnatal factors possibly interfering with growth in infancy, or affecting exposure to ICS (**Table E2**) was compared with the chi square test. Baseline growth data (height-for-age, weight-for-length z-score and zTH^{DEV}) of the ICS exposed and unexposed infants (closest measurements to ICS initiation in the unexposed infants at median age of ICS initiation, i.e., at 12 months) were compared using independent sample t-tests for normally distributed parameters (**Table E3**). Variables achieving statistical significance ($p < 0.05$) in the model were selected for adjusted growth analyses.

The linear growth at 24 months or closest to that age; median age at measurement, 25 months, (IQR from 24 to 26 months) was compared between children exposed to ICS, exposed to other anti-asthmatic medications, and unexposed children using covariance analysis with random effects for subjects. Mean differences of zTH^{DEV} between the exposure groups were assessed in relation to exposure to any ICS (yes/no), or to the average daily dose of ICS (minimal, low or medium/high dose) and duration of treatment (< 3 months, 3 - 6 months, > 6 months) (**Table E3**) .

Data were analyzed using SPSS software (version 21, IBM Corporation, Armonk, NY, USA). *P* values less than 0.05 were considered statistically significant.

REFERENCES

E1. Primary Healthcare Act 66/1972, Government Degree on Primary Health Care 380/2009.

E2. Mäki P, Laatikainen T, Koponen P, Hakulinen-Viitanen T, LATE work group, editors. Lasten ja nuorten terveysseurannan kehittäminen, LATE-hanke (The development of health monitoring among children and the young, LATE-project, in Finnish). Helsinki: Finnish National Institute for Health and Welfare; 2008.

E3. Saari A, Sankilampi U, Hannila ML, Kiviniemi V, Kesseli K, Dunkel L. New finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. Ann Med 2011; 43:235-48.

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E5. Sankilampi U, Hannila ML, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. Ann Med 2013; 45:446-54.

E6. Saari A, Sankilampi U, Hannila ML, Saha MT, Makitie O, Dunkel L. Screening of turner syndrome with novel auxological criteria facilitates early diagnosis. J Clin Endocrinol Metab 2012; 97:E2125-32.

E7. Finnish Pharmaceutical Information Centre. Pharmaca Fennica. Helsinki, Finland: Lääketietokeskus; 2015.

E8. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 2010; 106:86-94.

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E10. Global initiative for asthma. Diagnosis and management of asthma in children 5 years and younger. Available at: http://ginasthma.org/. Accessed Jan. 6, 2018.

E-MATERIAL

METHODS

Ethics

Permission for the study was obtained from Espoo Municipality Institutional Review Board, The Social Insurance Institution of Finland (SII), and the National Institutes of Health and Welfare (THL). Analyses were performed with encrypted register data.

Study Population

The Finnish child welfare clinics in primary care provide pre-scheduled visits (monthly from birth to 6 months, 8, 12, 18, and 24 months of age, then annually) to all children living in Finland, with a coverage of nearly 100% of the child population.[E1,E2] These visits include auxological evaluation (length/height, and weight) by specially trained nurses with standardized equipment.[E1,E2] For this study, we initially included all 14,764 children born between January 1, 2003, and April 30th 2007 (51% boys) who attended child welfare clinics in the city of Espoo, Finland, and had at least one visit at or after 24 months (**Fig E1**).[E3]

To exclude children with prenatal conditions affecting growth, and to control for possible confounding perinatal factors statistically, we obtained the Medical Birth Register data from the Finnish National Institute of Health and Welfare.[E4] These data included maternal age, smoking during pregnancy, parental relationship, gestational age, mode of delivery, parity, plurality, birth weight and length, season at birth, and congenital syndromes or anomalies. First, we excluded 1,381 children with any of the following: preterm birth at <37 gestational weeks, congenital anomaly or syndrome, and a lack of perinatal data. Second, we excluded children with postnatally diagnosed growth disorders or regular medication possibly affecting

growth (not ICS or other anti-asthmatic drugs) (N = 901). The final study population was comprised of 12,482 children, while 6,391 (51%) of them were boys (**Figure E1**).

Auxological data and growth outcomes

All of the available growth data from birth to the age over 24 months, as well as data on parental heights were collected from the electronic health records of child welfare clinics in primary care. Potentially false measurements or typing errors were evaluated by scatter plots, and either corrected or excluded. Birth size, length and weight measurements, and body mass indices (BMI, calculated as weight [kg]/height $[m]^2$)] were transformed into z-scores (BMI-for-age, weight-for-length, and height-for-age) according to contemporary Finnish growth references.[E3,E5] Target height (TH) was calculated by using parental heights,[E6] and height-for-age z-score deviation from TH z-score was expressed as zTH^{DEV}.

Exposure to inhaled corticosteroids

In Finland, ICS and other medications for recurrent wheezing/asthma are available only by prescription and sold in registered pharmacies. Two types of ICS, budesonide (BUD) and fluticasone propionate (FP) are licensed by the Finish Medicines Agency (Fimea) for daily use in infancy from the age of 6 months (BUD) and 12 months (FP). In the case of recurrent wheezing, off-label ICS have been prescribed for patients younger than 6 months. Formulations applicable for infants included metered-dose inhalers delivered by a spacer (BUD, FP) or inhaled suspension delivered by a nebulizer (BUD).[E7]

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Duration of the treatment and the average daily dose of ICS for each individual child was calculated using the Drug purchase register data on the type and number of ICS purchases before the age of 24 months. The Finnish regulations allow for the purchase of reimbursed medication for the period of 3 months. Duration of the ICS treatment for an individual child was calculated using the total number of the purchases prior to 24 months of age (one purchase = treatment < 3 months, two purchases = treatment 3 - 6 months, three or more purchases = treatment >6 months). In addition, the purchased doses of ICSs were divided by the number of days between the first and the following purchases stepwise until the growth visit at or after 24 months of age resulting into the average daily dose of a child. The average daily dose of ICS was then categorized as a medium/high dose (equal or more than daily BUD 400 µg or FP 200 µg via spacer, or BUD 1000 µg via nebulizer), a low-dose (half of

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Statistical analyses

Frequency of perinatal factors and postnatal factors possibly interfering with growth in infancy, or affecting exposure to ICS (**Table E2**) was compared with the chi square test. Baseline growth data (height-for-age, weight-for-length z-score and zTH^{DEV}) of the ICS exposed and unexposed infants (closest measurements to ICS initiation in the unexposed infants at median age of ICS initiation, i.e., at 12 months) were compared using independent sample t-tests for normally distributed parameters (**Table E3**). Variables achieving statistical significance ($p < 0.05$) in the model were selected for adjusted growth analyses.

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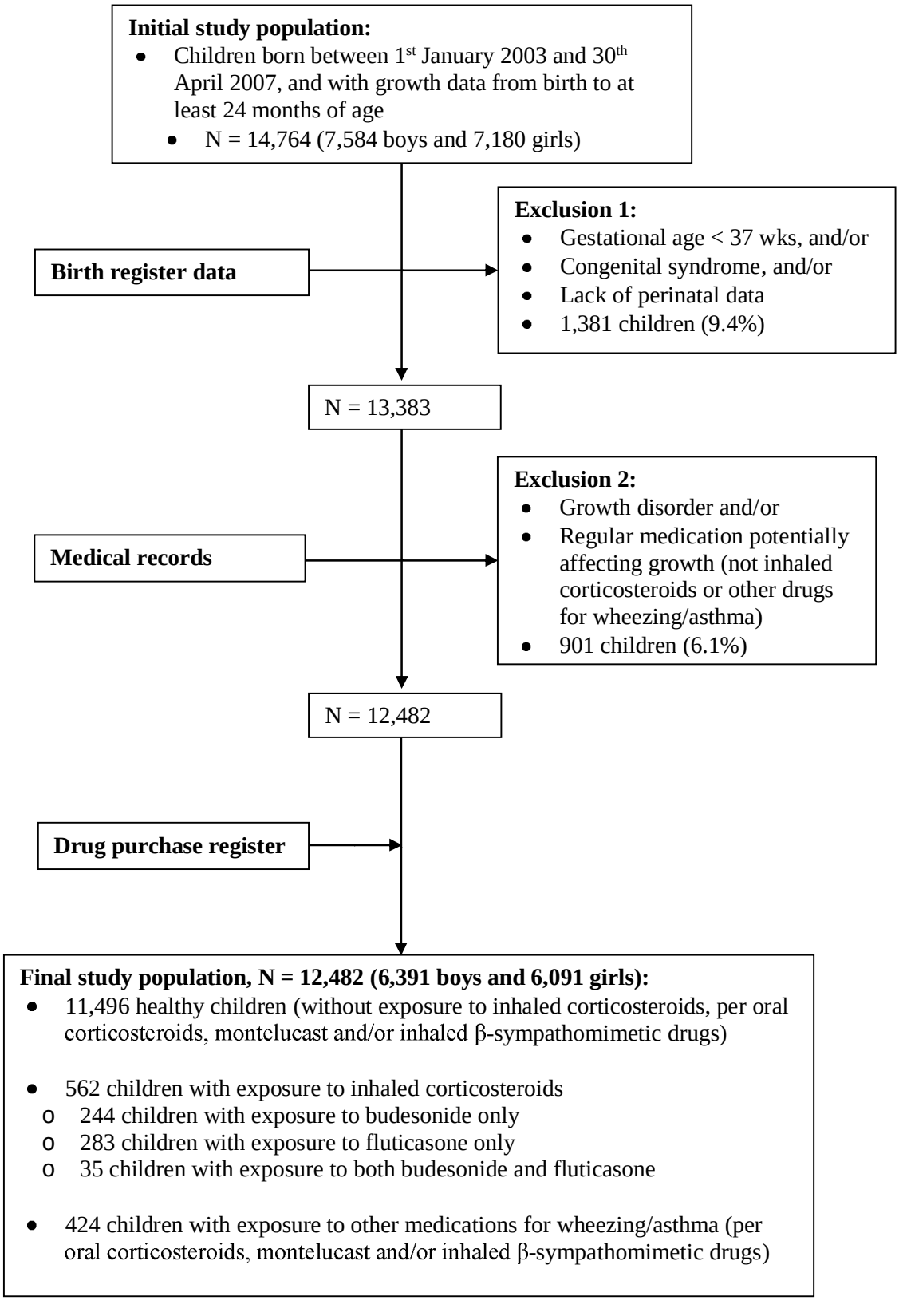
Initial study population:
Children born between 1st January 2003 and 30th April 2007, and with growth data from birth to at least 24 months of age
N = 14,764 (7,584 boys and 7,180 girls)
Birth register data
Exclusion 1:
Gestational age < 37 wks, and/or
Congenital syndrome, and/or
Lack of perinatal data
1,381 children (9.4%)
N = 13,383
Medical records
Exclusion 2:
Growth disorder and/or
Regular medication potentially affecting growth (not inhaled corticosteroids or other drugs for wheezing/asthma)
901 children (6.1%)
N = 12,482
Drug purchase register
Final study population, N = 12,482 (6,391 boys and 6,091 girls):
11,496 healthy children (without exposure to inhaled corticosteroids, per oral corticosteroids, montelucast and/or inhaled β-sympathomimetic drugs)
562 children with exposure to inhaled corticosteroids
244 children with exposure to budesonide only
283 children with exposure to fluticasone only
35 children with exposure to both budesonide and fluticasone
424 children with exposure to other medications for wheezing/asthma (per oral corticosteroids, montelucast and/or inhaled β-sympathomimetic drugs)

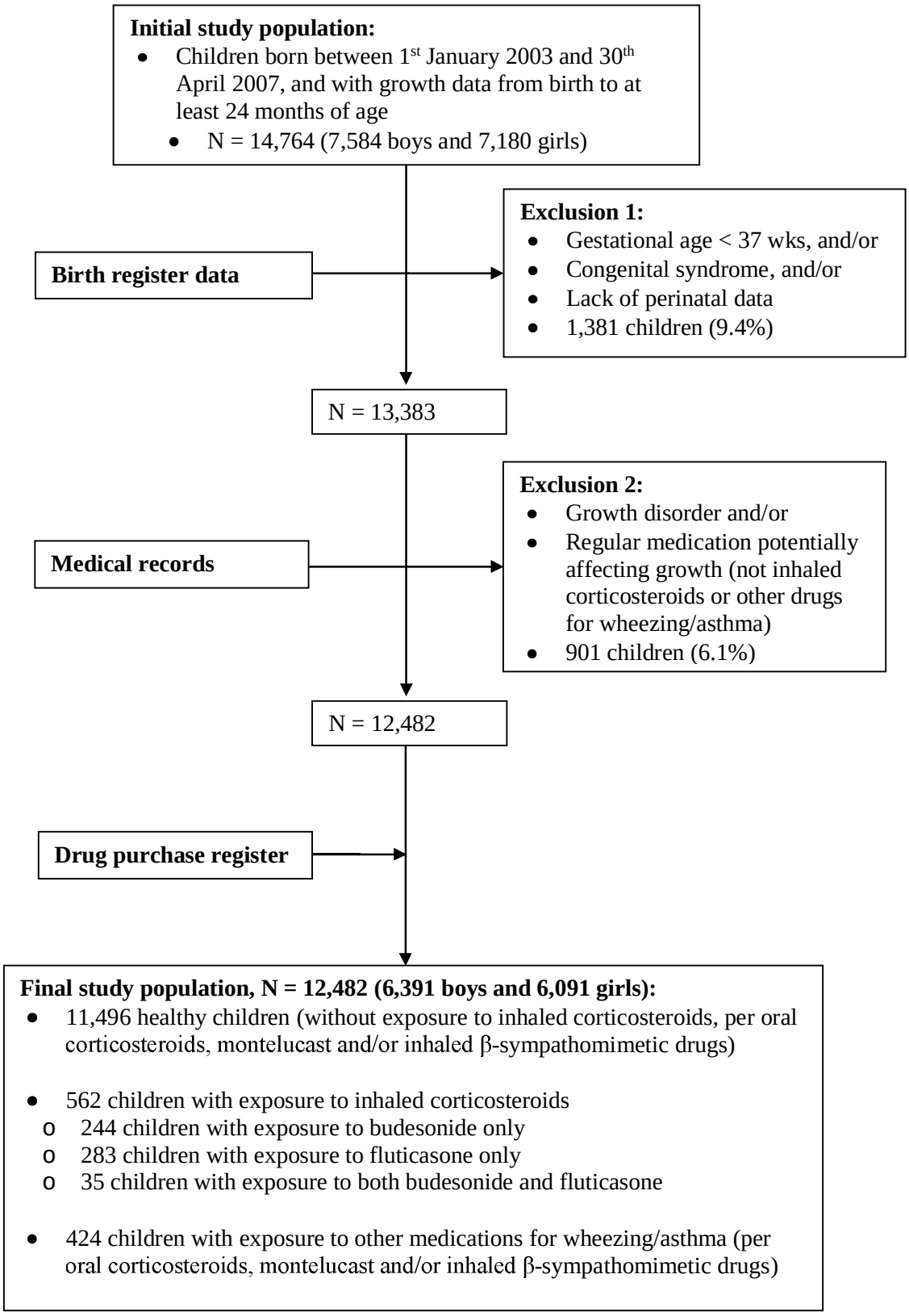

Table E1 Use of inhaled corticosteroids (ICS) and other asthma medications before the age of 24 months in the study population of 12,482 children.

	Total n = 12,482 (100%)	**Male n = 6,391 (100%)**	**Female n = 6,091 (100%)**	***p*-value[a]**
EXPOSURE TO ICS	562 (4.5)	375 (5.9)	187 (3.1)	<0.001
Average daily dose[b] and duration of the treatment				
Minimal dose				
<3 months	204 (1.6)	135 (2.1)	69 (1.1)	
3 - 6months	19 (0.2)	13 (0.2)	6 (0.1)	
>6 months	27 (0.2)	21 (0.3)	6 (0.1)	
Low dose				
<3 months	109 (0.9)	65 (1.0)	44 (0.7)	
3 - 6 months	59 (0.5)	38 (0.6)	21 (0.3)	
>6 months	62 (0.5)	49 (0.8)	13 (0.2)	
Medium/high dose				
<3 months	28 (0.2)	19 (0.3)	9 (0.1)	
3 - 6months	22 (0.2)	13 (0.2)	9 (0.1)	
>6 months	32 (0.2)	22 (0.3)	10 (0.2)	
EXPOSURE TO OTHER ASTHMA MEDICATIONS THAN ICS[c]	424 (3.4)	273 (4.3)	151 (2.5)	<0.001
NO EXPOSURE TO ANTI-ASTHMATIC MEDICATION	11,496 (92.1)	5,743 (89.9)	5,753 (94.5)	<0.001

[a]Comparison between males and females

[b]The average daily dose of ICS was defined as medium/high (equal or more than daily BUD 400 µg or FP 200 µg via spacer, and BUD 1000 µg via nebulizer), as low (half of the medium dose), or as minimal (equal or less than one quarter of the medium dose), according to the Global Initiative for Asthma report. [E10]

[c]Orally administered corticosteroids, montelukast, and/or inhaled β-sympathomimetic drugs

Table E2 Background factors potentially associated with linear growth or with exposure to inhaled corticosteroids in infancy in the study population of 12,482 children

	Height-for-age percentile[a]			Exposure to inhaled corticosteroids		
Column, count (%)	**<50th**	**≥50th**	***p*-value**	**No**	**Yes**	***p*-value**
Total count	6,382	6,100		11,920	562	
Gender			0.90			<0.001
Male	3,264 (51.1)	3,127 (51.3)		6,016 (50.5)	375 (66.7)	
Female	3,118 (48.9)	2,973 (48.7)		5,904 (49.5)	187 (33.3)	
Exposure to oral corticosteroids			0.42			<0.001
No	6,338 (99.3)	6,065 (99.4)		11,880 (99.7)	523 (93.1)	
Yes	44 (0.7)	35 (0.6)		40 (0.3)	39 (6.9)	
Exposure to antibiotics			0.04			<0.001
No	1,506 (23.6)	1,347 (22.1)		2,838 (23.8)	15 (2.7)	
Yes	4,876 (76.4)	4,753 (77.9)		9,082 (76.2)	547 (97.3)	
Obesity or overweight[a]			<0.001			0.003
No	5,416 (84.9)	4,872 (79.9)		9,851 (82.6)	437 (77.8)	
Yes	966 (15.1)	1,228 (20.1)		2,069 (17.4)	125 (22.2)	
Maternal age			0.60			0.67
<30 years	2,607 (40.8)	2,520 (41.3)		4,901 (41.1)	226 (40.4)	
≥30 years	3,775 (59.2)	3,580 (58.7)		7,019 (58.9)	336 (59.8)	
Maternal smoking			0.12			0.50
No	5,760 (90.3)	5,555 (91.1)		10,801 (90.6)	514 (91.5)	
Yes	622 (9.7)	545 (8.9)		1,119 (9.4)	48 (8.5)	
Maternal relationship			0.88			0.02
Partner	5,977 (93.7)	5,717 (93.7)		11,154 (93.6)	540 (96.1)	
Single	405 (6.3)	383 (6.3)		766 (6.4)	22 (3.9)	
Gestational age at birth			<0.001			0.31
<40 weeks	3,124 (49.0)	2,680 (43.9)		5,531 (46.4)	273 (48.6)	
≥40 weeks	3,258 (51.0)	3,420 (56.1)		6,389 (53.6)	289 (51.4)	
Season at birth			0.79			0.92
Spring or summer	2,697 (42.3)	2,592 (42.5)		5,052 (42.4)	237 (42.2)	
Autumn or winter	3,685 (57.7)	3,508 (57.5)		6,868 (57.6)	325 (57.8)	
Mode of delivery			0.23			0.35
Vaginal	5,313 (83.2)	5,127 (84.0)		9,978 (83.7)	462 (82.2)	
Caesarean section	1,069 (16.8)	973 (16.9)		1,942 (16.3)	100 (17.8)	
Plurality			0.11			0.80
Singleton	6,247 (97.9)	5,995 (98.3)		11,690 (98.1)	552 (98.2)	
Twin	135 (2.1)	105 (1.7)		230 (1.9)	10 (1.8)	

[a]Finnish growth reference[E3]
[b]Finnish birth size reference[E5]

Continued Table E2 Background factors potentially associated with linear growth or with exposure to inhaled corticosteroids in infancy in the study population of 12,482 childen.

	Height-for-age percentile[a]			**Exposure to inhaled corticosteroids**		
Column, count (%)	**<50th**	**≥50th**	***p*-value**	**No**	**Yes**	***p*-value**
Parity			<0.001			<0.001
0 sibling	2,882 (45.2)	3,040 (49.8)		5,711 (47.9)	211 (37.4)	
≥1 siblings	3,500 (54.8)	3,060 (50.2)		6,209 (52.1)	351 (62.6)	
Birth length[b]			<0.001			0.003
AGA	6,109 (95.7)	5,768 (94.6)		11,354 (95.3)	523 (93.0)	
SGA	214 (3.4)	30 (0.5)		222 (1.9)	22 (3.9)	
LGA	59 (0.9)	302 (5.0)		344 (2.9)	17 (3.0)	
Birth weight[b]			<0.001			0.01
AGA	6,098 (95.5)	5,837 (95.7)		11,409 (95.7)	526 (93.6)	
SGA	216 (3.4)	45 (0.7)		239 (2.0)	22 (3.9)	
LGA	68 (1.1)	218 (3.6)		272 (2.9)	14 (2.5)	

[a]Finnish growth reference[E3]

[b]Finnish birth size reference[E5]

Abbrevations: AGA: Appropriate for gestational age; LGA: Large for gestational age; SGA: Small for gestational age

Table E3 Comparison of the birth size and growth at the initiation of ICS medication[a] between the children exposed to inhaled corticosteroids (ICS) and the unexposed reference population (N =11,496).

	Mean z-score difference from the unexposed children (95% CI)					
	Any ICS (N = 562)	***p*-value**	**Budesonide only (N = 244)**	***p*-value**	**Fluticasone propionate only (N = 283)**	***p*-value**
Birth length z-score[b]	0.02 (-0.06 – 0.11)	0.61	0.05 (-0.07 – 0.18)	0.41	-0.02 (-0.14 – 0.09)	0.69
Birth weight z-score[b]	0.00 (-0.08 – 0.09)	0.93	0.07 (-0.05 – 0.20)	0.25	-0.06 (-0.18 – 0.06)	0.33
Height-for-age z-score[c]	-0.07 (-0.16 – 0.02)	0.12	0.03 (-0.10 – 0.16)	0.62	-0.17 (-0.29 – -0.05)	0.01
Height-for-age z-score deviation from target height	-0.10 (-0.18 – -0.01)	0.04	-0.03 (-0.16 – 0.10)	0.66	-0.16 (-0.29 – -0.04)	0.01
Weight-for-height z-score[c]	0.14 (0.05 – 0.22)	0.001	0.14 (0.02 – 0.27)	0.02	0.14 (0.02 – 0.27)	0.02

[a]Median age (interquartile range) at initiation of ICS use was 12 (10 – 18) months. In unexposed infants, baseline growth data was analysed at the closest visit to 12 months of age (median age 12 [12 – 12])
[b]Finnish growth reference for birth size[E3]
[c]Finnish growth reference[E5]

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Yes	44 (0.7)	35 (0.6)		40 (0.3)	39 (6.9)	
Exposure to antibiotics			0.04			<0.001
No	1,506 (23.6)	1,347 (22.1)		2,838 (23.8)	15 (2.7)	
Yes	4,876 (76.4)	4,753 (77.9)		9,082 (76.2)	547 (97.3)	
Obesity or overweight[a]			<0.001			0.003
No	5,416 (84.9)	4,872 (79.9)		9,851 (82.6)	437 (77.8)	
Yes	966 (15.1)	1,228 (20.1)		2,069 (17.4)	125 (22.2)	
Maternal age			0.60			0.67
<30 years	2,607 (40.8)	2,520 (41.3)		4,901 (41.1)	226 (40.4)	
≥30 years	3,775 (59.2)	3,580 (58.7)		7,019 (58.9)	336 (59.8)	
Maternal smoking			0.12			0.50
No	5,760 (90.3)	5,555 (91.1)		10,801 (90.6)	514 (91.5)	
Yes	622 (9.7)	545 (8.9)		1,119 (9.4)	48 (8.5)	
Maternal relationship			0.88			0.02
Partner	5,977 (93.7)	5,717 (93.7)		11,154 (93.6)	540 (96.1)	
Single	405 (6.3)	383 (6.3)		766 (6.4)	22 (3.9)	
Gestational age at birth			<0.001			0.31
<40 weeks	3,124 (49.0)	2,680 (43.9)		5,531 (46.4)	273 (48.6)	
≥40 weeks	3,258 (51.0)	3,420 (56.1)		6,389 (53.6)	289 (51.4)	
Season at birth			0.79			0.92
Spring or summer	2,697 (42.3)	2,592 (42.5)		5,052 (42.4)	237 (42.2)	
Autumn or winter	3,685 (57.7)	3,508 (57.5)		6,868 (57.6)	325 (57.8)	
Mode of delivery			0.23			0.35
Vaginal	5,313 (83.2)	5,127 (84.0)		9,978 (83.7)	462 (82.2)	
Caesarean section	1,069 (16.8)	973 (16.9)		1,942 (16.3)	100 (17.8)	
Plurality			0.11			0.80
Singleton	6,247 (97.9)	5,995 (98.3)		11,690 (98.1)	552 (98.2)	
Twin	135 (2.1)	105 (1.7)		230 (1.9)	10 (1.8)	

[a]Finnish growth reference[E3]
[b]Finnish birth size reference[E5]

Continued Table E2 Background factors potentially associated with linear growth or with exposure to inhaled corticosteroids in infancy in the study population of 12,482 childen.

	Height-for-age percentile[a]			**Exposure to inhaled corticosteroids**		
Column, count (%)	**<50th**	**≥50th**	***p*-value**	**No**	**Yes**	***p*-value**
Parity			<0.001			<0.001
0 sibling	2,882 (45.2)	3,040 (49.8)		5,711 (47.9)	211 (37.4)	
≥1 siblings	3,500 (54.8)	3,060 (50.2)		6,209 (52.1)	351 (62.6)	
Birth length[b]			<0.001			0.003
AGA	6,109 (95.7)	5,768 (94.6)		11,354 (95.3)	523 (93.0)	
SGA	214 (3.4)	30 (0.5)		222 (1.9)	22 (3.9)	
LGA	59 (0.9)	302 (5.0)		344 (2.9)	17 (3.0)	
Birth weight[b]			<0.001			0.01
AGA	6,098 (95.5)	5,837 (95.7)		11,409 (95.7)	526 (93.6)	
SGA	216 (3.4)	45 (0.7)		239 (2.0)	22 (3.9)	
LGA	68 (1.1)	218 (3.6)		272 (2.9)	14 (2.5)	

[a]Finnish growth reference[E3]

[b]Finnish birth size reference[E5]

Abbrevations: AGA: Appropriate for gestational age; LGA: Large for gestational age; SGA: Small for gestational age

Table E3 Comparison of the birth size and growth at the initiation of ICS medication[a] between the children exposed to inhaled corticosteroids (ICS) and the unexposed reference population (N =11,496) .

	Mean z-score difference from the unexposed children (95% CI)					
	Any ICS (N = 562)	***p*-value**	**Budesonide only (N = 244)**	***p*-value**	**Fluticasone propionate only (N = 283)**	***p*-value**
Birth length z-score[b]	0.02 (-0.06 – 0.11)	0.61	0.05 (-0.07 – 0.18)	0.41	-0.02 (-0.14 – 0.09)	0.69
Birth weight z-score[b]	0.00 (-0.08 – 0.09)	0.93	0.07 (-0.05 – 0.20)	0.25	-0.06 (-0.18 – 0.06)	0.33
Height-for-age z-score[c]	-0.07 (-0.16 – 0.02)	0.12	0.03 (-0.10 – 0.16)	0.62	-0.17 (-0.29 – -0.05)	0.01
Height-for-age z-score deviation from target height	-0.10 (-0.18 – -0.01)	0.04	-0.03 (-0.16 – 0.10)	0.66	-0.16 (-0.29 – -0.04)	0.01
Weight-for-height z-score[c]	0.14 (0.05 – 0.22)	0.001	0.14 (0.02 – 0.27)	0.02	0.14 (0.02 – 0.27)	0.02

[a]Median age (interquartile range) at initiation of ICS use was 12 (10 – 18) months. In unexposed infants, baseline growth data was analysed at the closest visit to 12 months of age (median age 12 [12 – 12])

[b]Finnish growth reference for birth size[E3]

[c]Finnish growth reference[E5]