

Gender differences in asthma development and remission during transition through puberty: The TRacking Adolescents' Individual Lives Survey (TRAILS) study

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Background: During puberty, a gender shift in asthma prevalence occurs, with a preponderance of boys before puberty. The mechanisms underlying this gender shift are unclear.

Objectives: We assessed associations of pubertal stages and transition through puberty with (1) the prevalence, incidence, and remission of asthma in male and female subjects; (2) total IgE levels; and (3) peak expiratory flow (PEF) fall during a shuttle run test (SRT).

Methods: In the TRacking Adolescents' Individual Lives Survey study (n = 2,230; 51% female subjects), associations between pubertal stages and the prevalence, incidence, and remission of asthma were tested by using logistic regression and generalized estimating equations at a mean age of 11.1 (SD, 0.6), 13.6 (SD, 0.5), and 16.3 (SD, 0.7) years. Multiple linear regression analyses were used to study log-transformed total IgE levels and PEF fall during a SRT dependent on early versus late pubertal stages at a mean age of 16.3 years.

Results: The prevalence of asthma was similar in boys (7.7%) and girls (7.4%) at a mean age of 11.1 years. The prevalence of asthma was significantly higher in female (6.2%) than male (4.3%) subjects at 16.3 years of age. There were no significant associations between transition of pubertal stages and the presence of asthma, either cross-sectionally or longitudinally. Pubertal stages and log-transformed total IgE levels or PEF fall during a SRT at age 16.3 years were not correlated.

Conclusions: A shift in the prevalence of asthma occurs between 11.1 and 16.3 years, which is due to both an increased incidence and decreased remission of asthma in female compared with male subjects. Pubertal stages could not be proved to explain

the gender shift in asthma prevalence. (J Allergy Clin Immunol 2010;126:498-504.)

Key words: Longitudinal study, adolescents, asthma prevalence, total IgE, peak expiratory flow fall, pubertal stage

Asthma is a chronic inflammatory disease of the airways. Before puberty, the prevalence of asthma is higher in boys than in girls. By adulthood, a gender switch in the prevalence of asthma has occurred, with female subjects having a higher prevalence than male subjects.¹⁻⁵ The exact age at which this switch occurs has not been identified, and a number of age ranges have been described with respect to the changing ratio of asthma.⁶ Health care utilization related to asthma is significantly higher in male subjects aged 2 to 13 years, whereas it is greater in female subjects older than 23 years.⁶ Additionally, boys with asthma are significantly more often hospitalized than girls until the age of 14 years, whereas the opposite is true in adulthood.⁷ Because this change in male/female ratio occurs during puberty, hormonal changes throughout this period of life have been thought to be potential causative factors for the onset of asthma.

Female sex hormones have been linked to the development of asthma. In female subjects the risk of asthma is increased for those with early-onset menarche.^{5,8} This effect might be due to higher exposure to cumulative female sex hormone concentrations in early-onset compared with late-onset menarche.^{5,9,10} A longitudinal study showed that pregnancy, a state in which both progesterone and estrogen levels are increased, is also linked to the development of asthma.¹¹ However, cross-sectional studies did not show this association.¹⁰ A role for female sex hormones is also suggested by the fact that after menopause the incidence of asthma is decreased in female subjects when compared with that seen in premenopausal women or men.^{12,13}

Female sex hormones have also been linked to asthma morbidity. Approximately 30% to 40% of female asthmatic subjects experience perimenstrual asthma worsening,^{10,14} which associates with increased symptoms¹⁵ and a greater likelihood of hospitalization.¹⁴ The exact mechanism behind this perimenstrual worsening is not clear, but it might involve the increase in progesterone and estrogen levels during the luteal phase, leading to increased inflammation of the airway wall.^{10,16} Because oral contraceptives (OCs) suppress the increase in estrogen and progesterone levels during the luteal phase, the role of OCs on perimenstrual asthma has been studied. These studies suggest a small favorable effect of OCs on perimenstrual asthma and mild asthma^{8,14}; however, in women with more severe asthma, symptoms are increased.^{10,17} Studies assessing the role of pregnancy on asthma morbidity produced conflicting results.¹⁰ In an equal number of women with mild asthma, asthma symptoms improved,

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Abbreviations used

BMI:	Body mass index
GEE:	Generalized estimating equations
OC:	Oral contraceptive
PDS:	Pubertal Development Scale
PEF:	Peak expiratory flow
SRT:	Shuttle run test
TRAILS:	TRacking Adolescents' Individual Lives Survey

remained stable, or deteriorated, and only in the more severe cases of asthma did asthma symptoms increase.^{12,18}

Animal studies suggest that male hormones play a role in asthma development as well. Male androgens might protect against the development of asthma.¹⁹ Murine models of allergic airway disease show that male animals are less likely than female animals to have airway inflammation.²⁰ Castrated mice have low blood levels of testosterone and develop more severe airway inflammation than sham-operated mice, and their airway inflammation is comparable with that seen in female mice.²⁰ It is possible that higher testosterone levels in sham-operated mice lead to systematic inhibition of the T_H2 cell response and hence less severe airway inflammation.²⁰ Furthermore, administration of progesterone increases eosinophilic airway inflammation in male mice.²¹ These animal models suggest that changing levels of male and female sex hormones influence the level of inflammation in both male and female mice.

Contrary to the apparent role of hormones shown in animal studies, the effect of changing levels of sex hormones on asthma is less clear cut in human subjects.⁵ To our knowledge, only one study directly related the stage of puberty to the prognosis of asthma,³ but because this study was performed in adolescents with asthma, the association between pubertal stages and asthma incidence could not be studied.

As far as we know, no studies thus far have investigated the role of sex hormones on the development of asthma longitudinally. This is important because only with longitudinal methods can the association between hormonal changes during transition through puberty and the net change in the prevalence of asthma over time (net result of incidence and remission) be studied. We performed a prospective cohort study on the effect of changes in pubertal stages on asthma as a proxy for the hormonal changes that occurred during the ages of 11 to 16 years, the period in which transition through puberty takes place.

The aim of the current prospective study was to assess gender differences in the prevalence, incidence, and remission of asthma during transition through puberty. Additionally, we investigated gender differences in objective asthma-related phenotypes (total IgE levels and peak expiratory flow [PEF] fall after a shuttle run test [SRT]) in relation to the pubertal stage at a mean age of 16.3 years.

METHODS

Study population

The TRacking Adolescents' Individual Lives Survey (TRAILS) is a prospective cohort study among adolescents in the general Dutch population. Thus far, 3 surveys have been completed: survey 1 in 2001-2002 (mean age, 11.1 [SD, 0.6] years), survey 2 in 2003-2004 (mean age, 13.6 [SD, 0.5] years), and survey 3 in 2005-2007 (mean age, 16.3 [SD, 0.7] years). Adolescents will

be followed until at least the age of 24 years. Detailed information has been described elsewhere.^{22,23}

Questionnaire data

Data were collected on the presence of asthma, pubertal development (all 3 surveys), birth weight (first survey), cigarette smoking during pregnancy (third survey), and the use of OCs (third survey) (see Table E5 in this article's Online Repository at www.jacionline.org). Asthma was defined as a parentally reported physician's diagnosis of asthma and/or having symptoms of asthma and/or use of asthma treatment prescribed by a physician in the past 12 months. Incidence of asthma was defined as having asthma at a specific survey while not having asthma at the previous survey. Remission of asthma was defined as having asthma at a specific survey but not at the following survey.

Clinical characteristics

Height and weight were measured by using standardized protocols.²⁴ At each survey, body mass index (BMI) was calculated. Obesity is a risk factor for the development of asthma.²⁵ Therefore BMI was categorized as normal weight, overweight, and obesity based on age- and sex-specific cutoff points.²⁶

Total IgE

At the third survey (mean age, 16.3 years), 1,206 (66.4%) adolescents gave blood to determine serum total IgE levels.

Twenty-meter SRT

At the third survey, 629 (34.6%) adolescents completed a 20-m SRT, a reliable test to provoke exercise-induced asthma.²⁷ This test comprises running a 20-m track back and forth, starting at a speed of 8 km/h and increasing by 0.5 km/h every minute.^{28,29}

Heart rate monitoring was performed in a subsample of 241 (38.3%) adolescents who performed the SRT by using a Polar Team System type 1 as a control for maximal performance. The vast majority of the adolescents (>95%) performed a maximal test (≥ 185 beats/min).

PEF measurements were performed before and after the SRT by using a Mini-Wright PEF meter. The highest PEF of 3 measurements both before and after the SRT were used in the analyses. PEF fall was calculated as the difference between PEF after and before the SRT divided by PEF before the SRT.

Pubertal stages

Two measurements of pubertal development were used in this study: the Tanner stages of pubertal development,^{30,31} which were filled in by the parents at the first and second survey, and the Pubertal Development Scale (PDS) questionnaire,^{32,33} which was answered by the adolescents at the second and third surveys. The Tanner stages of pubertal development consist of schematic drawings of secondary sex characteristics (pubic hair and breast development for female subjects and pubic hair and genital development for male subjects).

A parent (usually the mother) selected the drawings that matched most closely to the actual pubertal development of the adolescent. Based on this rating, adolescents were classified into 5 Tanner stages of pubertal development, with stage 1 corresponding to the prepubertal stage and stage 5 corresponding to the postpubertal stage.²⁴ Adolescents answered in the PDS questions about their physical development, including changes in growth, body hair, and skin changes (acne). Also, female subjects were asked about breast development and menstruation, and male subjects were asked about voice changes and growth of facial hair.³⁴

The PDS questionnaire results were recoded into 5 stages of pubertal development by using the algorithm developed by Carskadon and Acebo.³⁵ By using this algorithm, female subjects without menarche and a total score of 5 or greater (body hair growth and breast development), male subjects with a total score of 4 to 5 and a 3-point response (body hair growth, voice changes,

TABLE I. Population characteristics of the study population (n = 2,230)

Variable	Female subjects, n = 1132 (51%)	Male subjects, n = 1098 (49%)
Age (y)	11.1 ± 0.5	11.1 ± 0.6
Tanner stage 1	327 (30.0)*	351 (34.3)
Tanner stage 2	496 (45.5)*	619 (60.5)
Tanner stage 3	203 (18.6)*	49 (4.8)
Tanner stage 4	59 (5.4)*	2 (0.2)
Tanner stage 5	6 (0.5)*	2 (0.2)
Tanner stage	2 (1-5)*	2 (1-5)
Asthma (%)	77 (7.4)	77 (7.7)
BMI (kg/m ²)	17.6 (12.7-33.9)*	17.1 (11.0-35.0)
Normal weight (%)	896 (81.5)*	920 (86.6)
Overweight (%)	166 (15.1)*	115 (10.8)
Obesity (%)	37 (3.4)*	27 (2.6)
Birth weight (100 g)	33.1 ± 6.1*	34.7 ± 6.1
Cigarette smoking during pregnancy (%)	267 (33.6)	212 (30.0)

Data are presented as numbers (percentages), where shown.

**P* < .05, significant difference between female and male subjects.

and facial hair growth), and male subjects with a total score of 6 to 8 and a 4-point response (body hair growth, voice changes, and facial hair growth) were not recoded into a stage of pubertal development. Therefore in line with other studies, in our study female subjects with no menarche and a total score of 5 or greater were classified as midpubertal,³² and male subjects with a total score of 4 to 5 and a 3 point-response and a total score of 6 to 8 and a 4-point response were classified as early and midpubertal, respectively. In the current study *early pubertal* was defined as stage 1, 2, or 3, whereas *late pubertal* was defined as stage 4 or 5.

Statistical analysis

Differences in continuous variables between groups were tested with the unpaired *t* test or the Mann-Whitney *U* test, as appropriate. Differences in cell counts were tested with the χ^2 or Fisher exact tests. Changes in proportions between 2 surveys within groups were tested by using the McNemar test. Distributions were checked for normality by means of visual inspection of the probability plots of the residuals. Based on the literature, the following variables were entered into all models: BMI (normal weight, overweight, and obesity),²⁵ birth weight,³⁶ and cigarette smoking during pregnancy.³⁷ Multiple logistic regression analysis was used to study the prevalence, incidence, and remission of asthma dependent on *early versus late pubertal stage*, as adjusted for potential confounders. Multiple linear regression analyses were used to study log-transformed total IgE levels and PEF fall during SRT dependent on *early versus late pubertal stage*, as adjusted for potential confounders. Both logistic and linear models were checked for multicollinearity. In none of the models was this a problem. Net changes in the prevalence of asthma over time (net result of incidence and remission) were estimated by using generalized estimating equations (GEE) models with age and age at first survey in the models. With GEE analyses, measurements of adolescents over time are analyzed, taking into account that these repeated measurements of 1 adolescent are not independent of each other. The relationship between pubertal stages and the development of asthma was analyzed separately for both the cross-sectional (between subjects at age 11.1 years) and longitudinal (within a subject) associations. The regression coefficient of the cross-sectional analyses reflected the effect of pubertal stages on the prevalence of asthma at age 11.1 years. The regression coefficient of the longitudinal analyses consisted of pooled analyses of both the cross-sectional and longitudinal effects of pubertal stages on asthma development. For all other variables, a pooled coefficient was given, consisting of both the cross-sectional and longitudinal (within-subject) components.³⁸ The association between Tanner stages (*early vs late pubertal*) and the prevalence of asthma was studied in the first and second survey. The association between PDS stages (*early vs late pubertal*) and the presence of asthma was studied at the second and third survey. Multiple logistic regression

analyses, multiple linear regression analyses, and GEE analyses were performed in the total dataset and stratified according to gender given the aims of our study: assessing gender differences in (risk factors for) incidence and remission of asthma during transition through puberty. Statistical analyses were performed with SPSS 16.0 software (SPSS, Inc, Chicago, Ill). *P* values of less than .05 (2-sided) were considered significant.

RESULTS

Study population

A total of 2,230 adolescents with a mean age of 11.1 (SD, 0.6) years was included (51% female subjects, Table I). At the second survey, 96% (n = 2149) were reassessed (mean age, 13.6 [SD, 0.5] years; 51% female subjects). Eighty-one percent of the original number (n = 1816) completed the third survey (mean age, 16.3 [SD, 0.7] years; 52% female subjects) (see Fig E1 in this article's Online Repository at www.jacionline.org). Adolescents who completed the third survey were significantly more often female and had a significantly lower BMI compared with the baseline population (see Table E1 in this article's Online Repository at www.jacionline.org).

Asthma prevalence

There was no significant difference in asthma prevalence between female and male subjects at 11.1, 13.6, or 16.3 years. In female subjects there was a significant difference in the prevalence of asthma between the ages of 11.1 and 13.6 years but not between the ages of 11.1 and 16.3 years and 13.6 and 16.3 years. In male subjects there was a significant difference in the prevalence of asthma between the ages of 11.1 and 16.3 years and between the ages of 13.6 and 16.3 years but not between the ages of 11.1 and 13.6 years (Fig 1). Twenty-one (43.8%) of 48 adolescents with asthma remission at 13.6 years were still in remission, 9 (18.8%) reported having asthma again at 16.3 years, and for 18 (37.5%), information about asthma status at age 16.3 years was missing.

Pubertal stages

At 11.1 years, 65 (5.9%) female and 4 (0.4%) male subjects were classified as *late pubertal* according to the Tanner stages. At the age of 13.6 years, 437 (51.4%) female and 91 (14.5%) male subjects were classified as *late pubertal* according to the Tanner stages, as well as 659 (65.4%) female and 121 (12.0%) male subjects according to the PDS questionnaire. At the age of 16.3 years, 851 (98.0%) female and 506 (65.5%) male subjects were classified as *late pubertal* according to the PDS questionnaire. At all ages, female subjects had significantly higher stages of pubertal development than male subjects. Information on both the Tanner stages and the PDS questionnaire was available for 1,403 adolescents at the age of 13.6 years.

Adolescents and parents agreed on classification as *early pubertal* 52% (726) of the time and agreed 27% (373) of the time about classification as *late pubertal*. Thus in 79% of the cases, there was agreement between adolescents and parents with respect to pubertal stages. The measurement of agreement (κ) was 0.54 (*P* < .001).

Asthma and pubertal stages

Complete data on gender, age, asthma, Tanner stage, BMI, birth weight, and cigarette smoking during pregnancy were

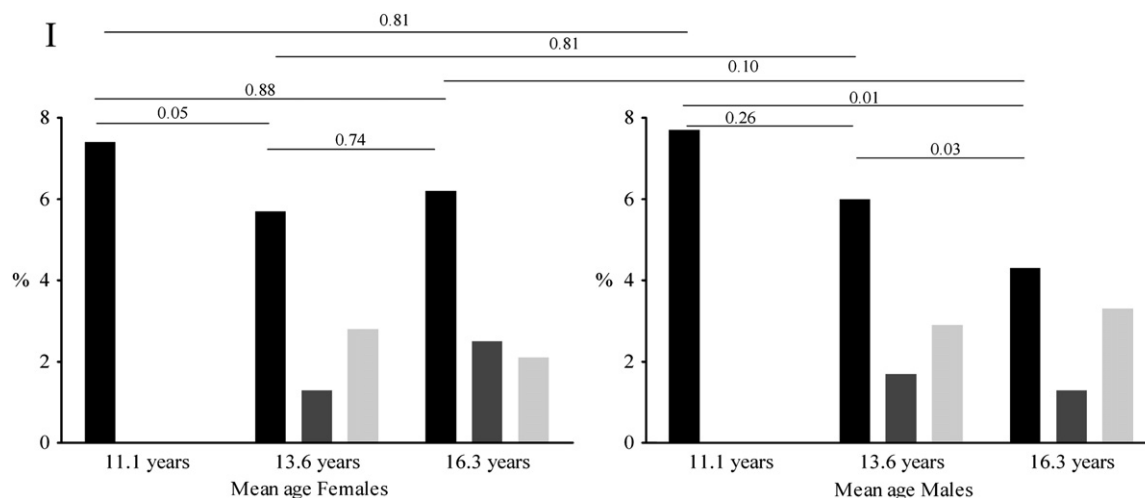


FIG 1. Prevalence, incidence, and remission of asthma. Dark column, prevalence; gray column, incidence; light column, remission.

TABLE II. Independent longitudinal effect estimates of risk factors on the presence of asthma

Variable	Pubertal stage							
	Age 11.1-13.6 y*				Age 13.6-16.3 y†			
	Female sex		Male sex		Female sex		Male sex	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age on inclusion (y)‡	1.38 (0.81-2.35)	.24	0.87 (0.48-1.57)	.64	1.14 (0.68-1.94)	.62	0.92 (0.51-1.67)	.79
Longitudinal effect of time	1.00 (0.88-1.13)	.95	0.98 (0.85-1.12)	.74	0.98 (0.85-1.13)	.75	0.81 (0.68-0.97)	.02
Pubertal stage§	0.75 (0.44-1.27)	.28	0.76 (0.21-2.78)	.68	1.00 (0.55-1.81)	.99	1.42 (0.80-2.52)	.23
Obesity	3.25 (1.10-9.58)	.03	0.56 (0.18-1.78)	.33	4.01 (1.30-12.35)	.02	1.12 (0.15-8.66)	.91
Overweight	2.01 (1.17-3.44)	.01	1.59 (0.83-3.04)	.17	2.44 (1.39-4.29)	<.01	2.21 (1.20-4.07)	.01
Birth weight (100 g)	1.00 (0.96-1.04)	.98	0.99 (0.94-1.04)	.68	1.00 (0.96-1.04)	.85	1.00 (0.94-1.06)	.90
Cigarette smoking during pregnancy	2.04 (1.15-3.60)	.01	1.30 (0.68-2.49)	.43	1.70 (0.97-2.69)	.06	1.18 (0.58-2.40)	.66

*Tanner stages.

†PDS stages.

‡Reflects difference between longitudinal and cross-sectional effect of pubertal stages.

§Defined as *early versus late pubertal*.

available for 719 (63.5%) female and 632 (57.6%) male subjects at the age of 11.1 years and for 637 (56.3%) female and 444 (40.4%) male subjects at the age of 13.6 years. Complete data on gender, age, asthma, pubertal development stage, BMI, birth weight, and cigarette smoking during pregnancy were available for 679 (60.0%) female and 636 (57.9%) male subjects at the age of 13.6 years and for 669 (59.1%) female and 586 (53.4%) male subjects at the age of 16.3 years. At the age of 11.1, 13.6, and 16.3 years, we observed no significant association between pubertal stages and asthma prevalence cross-sectionally in the total population or in female and male subjects separately. At the age of 13.6 and 16.3 years, we observed no significant association between pubertal stages and asthma incidence and remission cross-sectionally in the total population or in female and male subjects separately. A sensitivity analysis at the age of 13.6 years showed similar associations between parent-reported (Tanner) and adolescent-reported (PDS) pubertal stages and asthma. Restricting the analysis to the 1099 adolescents for whom both the parents and the adolescent agreed on pubertal stages did not affect the effect estimates. In longitudinal analyses we found no significant association between the pubertal stage and asthma

prevalence in female or male subjects (Table II). A sensitivity analysis in which male subjects with a total score of 4 to 5 and a 3-point response and male subjects with a total score of 6 to 8 and a 4-point response were recoded into midpubertal and late pubertal classifications, respectively, did not affect the effect estimates. Excluding age from the model did not affect the effect estimates. Excluding adolescents for whom BMI data were not available at all 3 surveys did not affect the effect estimates.

Thirty-one percent ($n = 248$) of the female subjects used OCs at the age of 16.3 years. There was no significant difference in BMI categories (normal weight, overweight, and obesity) between female subjects using OCs and those who did not use OCs. Controlling for OC use did not change the association between pubertal stages and asthma.

Total IgE

The total median IgE level was 73.0 kU/L (25th-75th percentile, 24.6-224.0 kU/L). In the total population there was a near-significant difference in total IgE levels between female and male subjects ($P = .052$). Adolescents with asthma had significantly

higher total IgE levels than adolescents without asthma. We did not find a significant association between pubertal stage and log-transformed total IgE levels in female or male subjects (see Table E2 in this article's Online Repository at www.jacionline.org). A sensitivity analysis in which male subjects with a total score of 4 to 5 and a 3-point response and male subjects with a total score of 6 to 8 and a 4-point response were recoded into mid-pubertal and late pubertal classifications, respectively, did not affect the effect estimates. Excluding age from the model did not affect the effect estimates.

PEF fall during SRT

The median PEF before the SRT was 540 L/min (range, 280-750 L/min) in male subjects and 440 L/min (range, 170-610 L/min) in female subjects. The median PEF after the SRT was 550 L/min (range, 300-750 L/min) in male subjects and 450 L/min (range, 190-630 L/min) in female subjects. Male subjects had significantly higher PEF values before and after the SRT (see Table E3 in this article's Online Repository at www.jacionline.org). Twenty-five percent of the population (total, 155; 88 female and 67 male subjects) had a fall in median PEF during the SRT of 20.0 L/min (range, 10-140 L/min). PEF fall during the SRT was 20 L/min (range, 10-140 L/min) in male subjects and 20 L/min (range, 10-130 L/min) in female subjects. There was no significant difference in PEF fall during the SRT between female and male subjects (see Table E3). Of the 155 adolescents with a PEF fall during the SRT, 11 (7%) adolescents had asthma, 132 (85%) did not have asthma, and 12 (8%) lacked information about asthma status at a mean age of 16.3 years. There was no significant difference in PEF fall during the SRT between adolescents with and without asthma. We found no significant association between PEF fall during the SRT with pubertal maturity in female or male subjects (see Table E4 in this article's Online Repository at www.jacionline.org). A sensitivity analysis in which male subjects with a total score of 4 to 5 and a 3-point response and male subjects with a total score of 6 to 8 and a 4-point response were recoded into midpubertal and late pubertal classifications, respectively, did not affect the effect estimates. Excluding age from the model did not affect the effect estimates.

DISCUSSION

Our longitudinal study in a large group of boys and girls followed through puberty did not show differences in asthma prevalence between boys and girls at the age of 11.1 and 13.6 years, whereas at 16.3 years of age, more female than male subjects had asthma. This higher prevalence of asthma at the age of 16.3 years was related to a higher incidence of asthma and lower remission of asthma in female compared with male subjects during this follow-up. This study did not show an association between pubertal stages and asthma prevalence.

Additionally, we found no significant association between pubertal stages and asthma-related phenotypes (log-transformed total IgE levels and PEF fall during SRTs).

The strength of the current study is the longitudinal study design, which allowed us to study the association between pubertal stages and changes in asthma prevalence during transition through puberty. Adolescents were followed up from the age of 11.1 years until 16.3 years. This is important because the mean age at which girls enter puberty is 10.5 years, completing sexual

development after 4.2 years on average, whereas boys enter puberty at 11.5 years and achieve complete sexual development after 3.5 years on average.³

Our results are largely in agreement with findings from a previous study showing that in early childhood the prevalence of asthma is higher in boys than in girls.¹⁰ Between the ages of 9 and 11 years, the difference in the prevalence of asthma between boys and girls disappeared.³⁹ In agreement with these results, we found no difference in the prevalence of asthma between boys and girls at a mean age of 11.1 years. Nicolai et al³ followed up adolescents with asthma from the age of 10 years until 14 years. At 20 years of age, these adolescents were re-examined, together with a sample of nonasthmatic adolescents from the original cross-sectional study. At this time point, there were still more male subjects with asthma than female subjects in the initially studied group. However, in the group without asthma at the age of 10 years, twice as many female subjects had asthma at age 20 years,⁴ indicating a higher incidence of asthma in female compared with male subjects between the ages of 10 and 20 years. This is in agreement with our data, in which the incidence of asthma was higher and remission was lower in female compared with male subjects between the ages of 13.6 and 16.3 years.

We are the first to study the association between pubertal stages and the net change in the prevalence of asthma over time (net result of incidence and remission) using longitudinal methods. Despite the fact that we identified the hypothesized gender switch in the prevalence of asthma, we observed no association between pubertal stages in and asthma prevalence. In addition, we found no significant associations between pubertal stages and asthma-related phenotypes, such as log-transformed total IgE levels or PEF fall during SRTs at the age of 16.3 years. As far as we know, only 1 previous study has directly related pubertal stages to asthma, but this study of Nicolai et al³ included asthmatic subjects only and their prognosis. In this study menarche, voice changes, and serum androstenediol glucuronide levels (an endocrine marker that reflects peripheral testosterone metabolism) were used as a surrogate for late puberty. In accordance with the results of our study, Nicolai et al³ found no statistically significant relationship between the reported signs of late puberty and remission of asthma in adolescents who had had active asthma at age 10 years. Likewise, no association was found between androstenediol glucuronide levels and asthma.³

There is a randomized, double-blind, multicenter clinical trial that investigated the relationship between airway responsiveness and pubertal stages.⁴⁰ This study consisted of a treatment phase (budesonide, 400 µg daily, or nedocromil sodium, 16 mg daily) and an observation phase (with asthma care based on national guidelines). Children aged 5 to 12 years with mild-to-moderate asthma were followed up 8.6 ± 1.8 years, and methacholine provocation tests were performed before randomization, 8 months after randomization, and then yearly. They found that between the ages of 5 and 11 years, PC₂₀ values increased in both girls and boys. However, after the age of 11 years, PC₂₀ values continued to increase in boys compared with the minimal increase seen in girls. This increase in PC₂₀ values in boys relative to girls started at Tanner stage 2. The mean age at which children enter Tanner stage 2 is 11 years. The results of this study are not consistent with our results, namely no association between pubertal stages and asthma. Possible explanations for this inconsistent finding could be the fact that our study was a population-based study, and in the study of Tantisira

et al,⁴⁰ children with mild-to-moderate asthma were included. Second, Tantisira et al studied airway responsiveness, whereas we studied exercise-induced asthma. Third, in the study of Tantisira et al, assessment of pubertal stages was done by a physician. We used both parent-reported and adolescent-reported pubertal development.

The suggestion that hormonal changes, as occur during puberty, play a role in asthma development and remission^{5,8-10,14,15,19,20} was not confirmed by our study. We used questionnaires as proxy measures of what is really happening during puberty (ie, changes in sex hormones). However, questionnaires might be too insensitive to reflect hormonal changes.

If the gender switch in the prevalence of asthma is not due to changing levels of sex hormones, the question arises of which other mechanisms could potentially explain this development. One potential mechanism is the difference in physical growth of the lungs from birth into adulthood between boys and girls. At birth, boys have narrower airways in proportion to total lung volume than girls. The development of the lungs continues until adolescence,⁴¹ when a difference in maturation of the airways in comparison with lung parenchyma and airspace exists between female and male subjects.¹⁰ This leads to a smaller airway diameter in relation to lung volume in female compared with male subjects at the age of 16 years.^{10,16} This gender difference in lung growth could explain why male subjects are at risk for asthma early in life but female subjects are at risk especially after puberty. However, there is also evidence that a smaller airway size does not simply lead to a higher risk of asthma because, especially in children, there is not much difference in the absolute size of the airways between boys and girls.¹⁰

A second potential mechanism to explain the gender switch in the prevalence of asthma occurring during puberty is obesity, a recognized risk factor for the development of asthma.²⁵ Obesity is accompanied by an increased production of estrogens and is therefore related to the development of puberty in a gender-specific way. Obesity is associated with early menarche in girls and a delayed puberty in boys.⁴² Obese girls with early menarche (before the age of 11 years) have a higher risk of asthma than those with late-onset menarche.^{42,43} Both in cross-sectional and longitudinal analyses, we identified obesity as a risk factor for asthma in female subjects. For male subjects, we found no association between obesity and asthma both in cross-sectional and longitudinal analyses. These findings could indicate a positive role for BMI in the development of asthma in female subjects. However, the difference in BMI development during transition through puberty could not explain the observed sex-related switch in asthma prevalence because of the fact that boys and girls had the same increase in BMI during transition through puberty.

Our study has some limitations. In the current study puberty was assessed by using 2 different questionnaires, one filled in by the parents at the first (mean age, 11.1 years) and second (mean age, 13.6 years) surveys (Tanner), and the other (PDS) filled in by the adolescents at the second (mean age, 13.6 years) and third (mean age, 16.3 years) surveys. The fact that we analyzed the data for the Tanner stages and PDS questionnaire separately decreased the power to detect a significant association between pubertal stages and asthma prevalence and resulted in large CIs for the estimated odds ratios.

The second limitation was that asthma was defined as having a parentally reported physician's diagnosis of asthma and/or having symptoms of asthma and/or use of asthma treatment prescribed

by a physician in the past 12 months. Based on our data, we cannot determine whether children had just exercise-induced asthma in isolation or transient wheeze related to a respiratory tract infection or more established asthma. We know from (unpublished) data of the Dutch part of the European Community Respiratory Health Survey that in the general population 98% of the subjects who report asthma indeed have a physician's diagnosis of asthma. Therefore we believe that using questionnaire data to define asthma status is a reliable way to determine the presence of asthma in a Dutch general population-based cohort like TRAILS.

One advantage of the longitudinal study design used in this study is the fact that both the cross-sectional and longitudinal effects of pubertal stages on the development of asthma could be analyzed. However, at the age of 11.1 years, 99.6% (1,019) of the boys were classified as *early pubertal*, and therefore analyzing both the longitudinal and cross-sectional effects of the Tanner stages on the development of asthma was not possible. At the age of 13.6 years, 12.0% (121) of the male subjects were classified as *late pubertal*. At this age, we could study both the cross-sectional and longitudinal effects of the PDS stages on the development of asthma between the ages of 13.6 and 16.3 years. We found no significant association between the cross-sectionally and longitudinally analyzed PDS stages and asthma development (data not shown).

In summary, our longitudinal study shows that a shift in asthma prevalence has already started at the age of 11.1 years and goes on until 16.3 years. This shift is due to both a higher incidence of asthma and a lower remission of asthma in female compared with male subjects during this pubertal period. This shift cannot simply be explained by changes in pubertal stages. At the age of 16.3 years, no association was found between pubertal stages and asthma-related phenotypes (log-transformed total IgE levels and PEF fall during SRTs). We found no association between the sex switch in asthma and pubertal stage, and therefore questionnaires (Tanner and PDS) to assess pubertal stage might be too insensitive to estimate hormonal changes. More studies, using even smaller time intervals and measuring actual levels of sex hormones, are needed to disentangle the role of sex hormones in the development and remission of asthma during puberty.

Key messages

- This longitudinal study shows that the shift in the prevalence of asthma already starts at the age of 11.1 years and remains until the age of 16.3 years.
- This shift is due to both a higher incidence and lower rate of remission of asthma in female compared with male subjects during this pubertal period.
- This shift cannot be simply explained by changes in pubertal stages.

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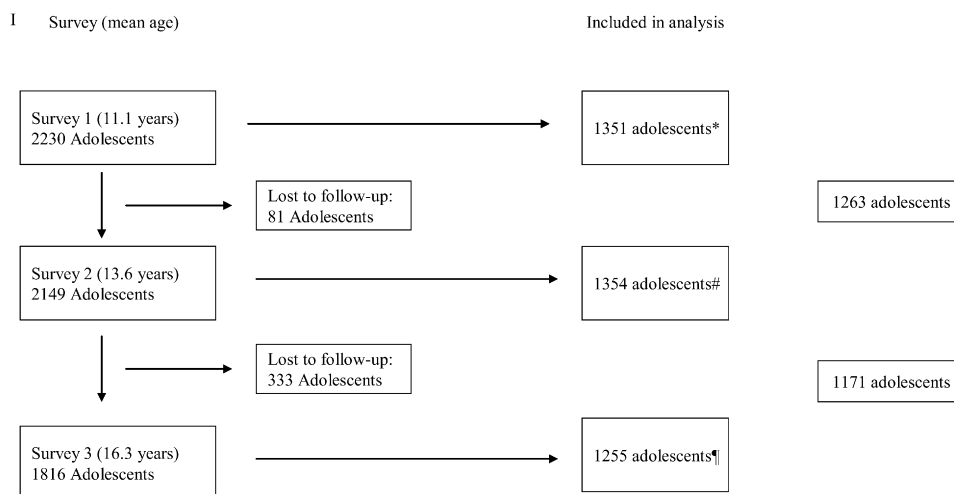


FIG E1. Overview of adolescents included in the study. *Tanner questionnaire. #Tanner or pubertal development questionnaire. ¶Pubertal development questionnaire.

TABLE E1. Comparison of baseline characteristics between adolescents who completed the third survey and those who were lost to follow-up

Baseline variable	Follow-up, n = 1816	Lost to follow-up, n = 414
Female sex	950 (52.3)*	182 (44.0)
Male sex	866 (47.7)*	232 (56.0)
Age (y)†	11.1 ± 0.6	11.1 ± 0.5
Pubertal stages‡	2 (1-5)	2 (1-5)
Asthma	124 (7.3)	30 (8.6)
BMI‡§	17.3 (11.0-35.0)*	17.7 (12.8-31.6)
Birth weight (100 g)†	33.9 ± 6.1	33.8 ± 6.3
Cigarette smoking during pregnancy	479 (31.9)	NA

Data are presented as numbers with percentages.

NA, Not assessed.

* $P < .05$, significant difference between follow-up and lost to follow-up.

†Mean ± SD.

‡Median (range).

§Defined as *early versus late pubertal*.

TABLE E2. Independent cross-sectional associations of risk factors for serum log transformation of total IgE levels in female and male subjects at the age of 16.3 years

Variable	Female subjects		Male subjects	
	b (95% CI)	P value	b (95% CI)	P value
Age (y)	−0.04 (−0.13 to 0.06)	.43	0.01 (−0.09 to 0.11)	.86
Pubertal stage*	−0.20 (−0.59 to 0.20)	.33	0.05 (−0.08 to 0.18)	.44
Obesity	0.29 (−0.09 to 0.67)	.14	0.28 (−0.09 to 0.65)	.13
Overweight	0.06 (−0.13 to 0.24)	.52	−0.01 (−0.22 to 0.20)	.94
Birth weight (100 g)	0.01 (−0.00 to 0.02)	.09	0.00 (−0.01 to 0.01)	.63
Cigarette smoking during pregnancy	0.04 (−0.09 to 0.17)	.54	−0.18 (−0.32 to −0.05)	.01

b, Regression coefficient.

*Defined as *early versus late pubertal*.

TABLE E3. SRT

Variable	Female subjects	Male subjects	P value
PEF before SRT (L/min)	440 (170-610)*	540 (280-750)	<.001
PEF after SRT (L/min)	450 (190-630)*	550 (300-750)	<.001
PEF fall during SRT (%)	20 (10-130)	20 (10-140)	.99

*Values are expressed as medians, with ranges in parentheses.

TABLE E4. Independent cross-sectional associations of risk factors for percentage fall in PEF after SRT in female and male subjects at the age of 16.3 years

Variable	Female subjects		Male subjects	
	b (95% CI)	P value	b (95% CI)	P value
Age (y)	−0.48 (−2.53 to 1.57)	.65	0.61 (−1.25 to 2.46)	.52
Pubertal stage*	1.86 (−4.04 to 7.76)	.54	1.70 (−0.34 to 3.73)	.10
Obesity	2.36 (−6.40 to 11.11)	.60	−7.88 (−15.22 to −0.53)	.04
Overweight	0.43 (−3.47 to 4.33)	.83	−3.42 (−6.85 to 0.01)	.05
Birth weight (100 g)	−0.23 (−0.41 to −0.06)	.01	−0.19 (−0.35 to −0.03)	.02
Cigarette smoking during pregnancy	0.44 (−1.91 to 2.78)	.71	0.54 (−1.66 to 2.74)	.63

b, Regression coefficient.

*Defined as *early versus late pubertal*.

TABLE E5. Questions on questionnaires

Questionnaire	
filled in by:	Question
Parent	Did your child have asthma symptoms during the last 12 months?
Parent	Did your child use asthma medication during the last 12 months?
Parent	Was your child treated for asthma by a physician during the last 12 months?
Parent	Did a physician give your child a diagnosis of asthma?
Parent*	Did the mother smoke any cigarettes during the first trimester of pregnancy?
Parent*	Did the mother smoke any cigarettes during the second trimester of pregnancy?
Parent*	Did the mother smoke any cigarettes during the third trimester of pregnancy?
Parent	What was your child's birth weight?

*Smoking during pregnancy.