Natural Progression of Childhood Asthma Symptoms and Strong Influence of Sex and Puberty

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Abstract

Rationale: Asthma prevalence, onset, remission and relapse, and healthcare use have been intensively studied. However, asthma symptom progression through childhood and adolescence has not been well studied, in part due to the challenges in obtaining consistent and robust long-term follow-up data on a large series of subjects with asthma.

Objectives: To use the asthma diary symptom data of the Childhood Asthma Management Program placebo group (5 yr, 418 subjects, and total 564,518 records) to establish sex-specific high-resolution time courses of the natural progression of asthma symptoms through childhood and adolescence.

Methods: We used the asthma diary symptom code as a measure of daily disease severity. Annual records of Tanner stage were used

to determine the influence of puberty on severity. A data alignment technique was used to derive 13-year time courses of mean symptoms and mean Tanner stage.

Measurements and Main Results: Data analyses showed three age- and sex-related phases of asthma symptom progression: Phase 1 (ages 5 and 6 yr)—greater severity in boys; Phase 2 (ages 7 to 9 yr)—no sex difference in severity; and Phase 3 (age 10–17 yr)—greater severity in girls. The continuous decline of symptoms in both sexes stops abruptly at the onset of puberty.

Conclusions: The severity of asthma symptoms varies through childhood and adolescence, and patterns differ by sex. Puberty has a strong influence on symptom progression in both sexes. Progression of symptoms is a distinct aspect of asthma epidemiology.

Keywords: epidemiology; sex difference; sex dominance

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The progression of asthma symptoms through childhood and adolescence is complex, variable, and poorly understood. Asthma is known to affect males more in childhood and females more in adulthood (1–3). Studies supporting this observation have focused on four epidemiologic aspects of the disease: (1) cross-sectional prevalence (4–17), (2) onset (18–20), (3) remission and relapse (21–31), and (4) healthcare use (32–40).

Study on each of the four aspects requires unique type of data and only provides a partial view of asthma epidemiology. Prevalence studies of asthma collect data from a general population and describe the percentage of participants with asthma. Studies of asthma onset follow a population without asthma and describe a one-way Boolean (yes or no) transition of developing asthma. Studies of asthma

remission and relapse follow a population with asthma and describe a two-way Boolean transition. Studies of asthma healthcare use describe a mixed effect of prevalence and symptom severity (both higher prevalence and more severe symptoms tend to contribute more).

There is another important aspect of asthma epidemiology, namely, the progression of asthma symptoms. Differing

from the above four aspects, studying asthma symptom progression generally has to follow a population with asthma and quantitatively describes the temporal change of symptom severity. The existing studies on prevalence, onset, remission and relapse, and healthcare use do not directly describe the longitudinal progression of asthma symptoms.

Presently, there is little knowledge on how symptoms vary with age and between two sexes. Herein, we attempt to fill this knowledge gap by analyzing the data of the Childhood Asthma Management Program (CAMP) (41). We expect that sex and age significantly affect the symptom progression, just like they affect the other four aspects of asthma epidemiology. However, we expect that the trend and properties of symptom progression will differ from those of the other four aspects. In addition, we investigate whether puberty influences the symptom progression.

Methods

The CAMP and its continuation study are the largest and longest clinical studies in children with mild to moderate asthma. The objective of CAMP is to study the long-term effect of regular use of asthma control medication on the growth of children with asthma. To study the progression of symptoms unaffected by any intervention, we analyzed the CAMP asthma symptom code variable (XSYMP) of diary data from the CAMP placebo group: 5 years of daily records of symptom data from 418 participants (184 girls, 234 boys), total 564,518 records. To define the influence of puberty on symptom progression in each sex, we also analyzed the Tanner stage data of the CAMP placebo group.

CAMP Diary Symptom Data

The symptom code, XSYMP, of the CAMP diary data of the placebo group was used to study the natural progression of asthma symptoms from childhood through adolescence. The XSYMP code is defined as follows:

An asthma episode is a single period of one or more asthma “stop signs,” such as wheezing, coughing, chest tightness, or shortness of breath;

- 0 = no asthma episodes;
- 1 = one to three asthma episodes, each lasting 2 hours or less, all mild;

- 2 = four or more mild asthma episodes, or one or more asthma episodes that temporarily interfered with activity, play, school, or sleep;
- 3 = one or more asthma episodes lasting longer than 2 hours, or resulting in shortening normal activity, or seeing a doctor for acute care, or going to a hospital for acute care.

The CAMP XSYMP data provide an objective, quantitative, and daily measure of the severity of asthma symptoms.

CAMP Tanner Stage Data

The pubic hair data of the placebo group were used to study the influence of puberty on asthma symptom progression.

All the CAMP data used in this study were obtained from BioLINCC (<https://biolincc.nhlbi.nih.gov/home>, Biologic Specimen and Data Repository Information Coordinating Center). Additional information about the CAMP diary symptom data code is available on the website of CAMP on www.ClinicalTrials.gov. The protocol of this study has been approved by the Institutional Review Board (Pro00002700).

Aligning Samples by Age

The CAMP participants can be divided into eight age groups according to their ages at enrollment (age 5, 6, 7, 8, 9, 10, 11, and 12 yr

at enrollment); the XSYMP and Tanner stage data of each age group span approximately 5 years. We used Aligning Samples by Age to generate sex-specific 13-year-long time courses of mean XSYMP and mean Tanner stage for the CAMP placebo group. The procedure of Aligning Samples by Age is as follows: (1) the date when each measurement was taken is converted to a subject's age (age X denotes the range $[X-0.5 \text{ yr}, X+0.5 \text{ yr}]$), (2) the measurements that fall into the same age are grouped. This method allows us to fully use the CAMP data to generate long-coverage time courses.

Modeling the Distribution of XSYMP

A truncated Poisson distribution,

$$T(X = k) = \frac{\lambda^k / k!}{\sum_{l=0}^3 \lambda^l / l!} \quad (k = 0, 1, 2, 3),$$

was used to model the distribution of XSYMP of each time point for each sex. k was truncated after 3 because the diary symptom code has only four values: 0, 1, 2, and 3. The actual histogram of XSYMP of each time point was compared with the fitted truncated Poisson distribution, and χ^2 was calculated to assess the goodness of fit.

We found that the distribution of XSYMP of each time point and for each sex can be accurately modeled by the truncated Poisson distribution (Figure 1; details in RESULTS). The average χ^2 (over all of the

Figure 1. Modeling of the diary symptom code data, XSYMP (Childhood Asthma Management Program [CAMP] placebo group), by truncated Poisson distribution. The truncated Poisson distribution (blue) was fitted to the actual histogram (red) of XSYMP at each time point for girls (A) and boys (B). As an evaluation of the goodness of fit, the average χ^2 (over all time points) is 0.01 for girls and 0.004 for boys. The results demonstrated that the XSYMP data of all time points in both sex-specific time courses can be accurately modeled by the truncated Poisson distribution. The four bins (from left to right) in each histogram correspond to the four values of XSYMP: 0, 1, 2, and 3; the details about XSYMP are in METHODS and the online supplement.

included time points) as a measure of fitting error was 0.01 for girls and 0.004 for boys. These results set the foundation of our data analysis, and specifically set the following important grounds (details in RESULTS):

1. Statistically, the XSYMP samples of each time point for each sex can be treated as independent samples drawn from the specific truncated Poisson distribution;
2. The distribution of XSYMP can be summarized by a single parameter;
3. For our specific truncated Poisson distribution (truncated after $k = 3$ and $\lambda \leq 0.75$), 30 samples are sufficient to ensure that the SE and bootstrapping SD equal the true SD of the mean.

According to ground 1, the XSYMP samples are independent from the subject who contributed the samples; therefore, the statistical significance is determined by the number of XSYMP samples rather than the number of subjects. The number of subjects would matter if XSYMP samples naturally cluster by subjects and follow a mixture of distributions (42). However, we have demonstrated that XSYMP samples fit accurately to a truncated Poisson distribution (a single distribution), proving that the XSYMP samples do not cluster by subjects.

Generally speaking, the mean of a variable with ordinal scale (XSYMP is a variable of ordinal scale) may not be meaningful. However, the fact that XSYMP accurately follows truncated Poisson distribution makes mean XSYMP meaningful, as explained below. Truncated Poisson distribution has only one parameter, λ , and λ is monotonically related to the mean (either one can be uniquely determined by the other, and they increase and decrease together). Therefore, mean XSYMP can be used to describe symptoms instead of λ because it completely determines the distribution of XSYMP. As mean XSYMP increases, the mass of XSYMP moves toward larger values (more severe symptoms) or vice versa; hence, mean XSYMP provides a concise and continuous measure for the symptoms.

In addition, ground 3 alone (without arguing the independence of the samples) ensures that SE (hence the 95% confidence interval [CI]) accurately assesses the variance of the mean XSYMP (there are thousands or even tens of thousands XSYMP samples for each time point; Table 1).

Table 1. The numbers of subjects and diary records for each time point in the asthma symptom time courses

Age, yr	Female		Male	
	Subjects	Diary Records	Subjects	Diary Records
5	8	477	16	1,470
6	29	6,429	52	10,407
7	51	11,342	83	22,187
8	76	19,765	114	30,713
9	101	27,956	148	41,690
10	130	32,022	169	45,028
11	141	37,164	166	43,762
12	142	36,303	153	38,181
13	116	28,371	135	36,406
14	86	18,839	102	26,006
15	60	12,067	73	16,561
16	31	4,987	46	9,983
17	11	1,593	28	4,809

Childhood Asthma Management Program placebo group. As established in METHODS, the statistical significance is determined by the number of diary records rather than the number of subjects.

Generating Asthma Symptoms and Tanner Stage Time Courses

We use Aligning Samples by Age to generate sex-specific mean XSYMP and mean Tanner stage time courses that cover from age 5 to 17 years. Note that although Tanner stage by definition is discrete (integers from 1–5), the pubertal development is naturally a continuous process. When this continuous process is described by discrete values, rounding errors (presumably follow a uniform distribution from -0.5 to 0.5) are produced. The rounding errors can be largely eliminated by averaging. Therefore, mean Tanner stage actually provides a more accurate description of the pubertal development. Tanner staging of the CAMP participants was performed once a year by the medical staff at the CAMP centers based on a well-defined somatic growth measures manual; hence, the data are more accurate than self-reported or parent-reported Tanner staging data.

Additional details about the data and method are in the online data supplement.

Results

Statistical Results of the Distribution Modeling of XSYMP

We found that the distribution of XSYMP at each time point and for each sex can be accurately modeled by the truncated Poisson distribution (Figure 1). The average χ^2 (over all time points) as a measure of

fitting error was 0.01 for girls and 0.004 for boys. Smaller χ^2 was achieved at the time points with larger sample sizes. For example, the fitting for the middle time points (where sample sizes are larger) was better than the end time points (Figure 1). Also, the fitting was generally better for boys than for girls, because the sample sizes are larger for boys for all time points (Table 1). These are strong indications that the truncated Poisson distribution is indeed the appropriate model for the distribution of XSYMP data. Model fitting of such high accuracy is rare in epidemiological studies of asthma, which is attributed to the high quality and high volume of the CAMP diary symptom data.

Using bootstrapping, we estimated the minimum number of samples required to achieve sound statistics in the distribution of XSYMP at each time point. By simulation, we have found that for $\lambda \leq 0.75$ (for the distribution of XSYMP), with a minimum of 30 samples, both the SE and bootstrap SD accurately match the true SD of the mean. As the sample size N further increases, all these three quantities remain essentially identical and scale as $1/\sqrt{N}$, precisely as predicted by the central limit theorem. The number of XSYMP samples for each sex at each time point is typically in thousands or even tens of thousands (Table 1). This exceptionally large volume of XSYMP data results in remarkably small statistical uncertainty, which is demonstrated by extremely small 95% CIs for all time

points in the time courses of mean XSYMP (Figure 2A). Similarly high statistical certainty has also been obtained in the time course of mean Tanner stage (Figure 2B).

Additional details about the statistical methods for data distribution modeling are in the online data supplement.

Influences of Sex, Puberty, and Age on Asthma Symptom Progression

Using the high-resolution time courses of symptoms and Tanner stage, we distinguish the influences of age and puberty (two concurrent influencing variables) and show that puberty has a strong influence on symptom progression in both sexes. Specifically, the onset of puberty in both sexes is the critical turning point of symptom progression: Symptoms in both sexes stop improving at the onset of puberty; girls' symptoms deteriorate during puberty and boys' symptoms do not improve until late puberty.

The symptom time courses (Figure 2A) show sex differences in progression of asthma symptoms through childhood and adolescence, ages 5 to 17 years, and there are essentially three distinct phases at these ages.

Phase 1 (ages 5 and 6 yr)—greater severity in boys. Boys had more severe symptoms than girls before age 7 years, and symptoms in both sexes improved. The mean XSYMP values (95% CI) of boys and girls were 0.72 (0.69–0.76) and 0.49 (0.44–0.54), respectively, at age 5 years, and declined to 0.44 (0.43–0.45) and 0.43 (0.43–0.44), respectively, at age 7 years. The sex difference in symptoms gradually and consistently diminished during this time.

Phase 2 (ages 7 to 9 yr)—no difference in severity by sex. The sex difference in symptoms was essentially indistinguishable at ages 7 to 9 years. Additionally, the continuous decline of symptoms stopped around age 9 for girls and age 10 for boys. Based on the Tanner stage time courses (Figure 2B) of the same subjects, ages 9 and 10 years mark the onset of puberty for female and male participants, respectively. Furthermore, the curve of mean XSMYP versus mean Tanner stage (Figure 2C) shows that the continuous decline in symptoms in both sexes stops abruptly when the mean Tanner stage begins to rise from 1 (onset of puberty).

Phase 3 (ages 10 to 17 yr)—greater severity in girls. Greater severity of symptoms among girls starts around age 10 years, after the halt of symptom improvement in both girls and boys, and

Figure 2. Sex-specific time courses of mean XSYMP and mean Tanner stage (Childhood Asthma Management Program [CAMP] placebo group). (A) We used Aligning Samples by Age to generate the sex-specific time courses of mean Tanner stage. Note that the Tanner stage is discrete number (1–5), but the mean Tanner stage is continuous. The error bars are 95% confidence intervals (CIs) (some are too small to be visible). These curves are highly consistent with the documented puberty development data, demonstrating the effectiveness of this method. (B) Using Aligning Samples by Age, we generated the sex-specific time courses of mean XSYMP. The time courses have high time resolution (with time interval of 1 year) and long coverage (covering 13 years, ages 5 to 17 years). Note that age X in the time course denotes the range $[X-0.5, X+0.5]$. The extremely small 95% CIs (error bars) indicate the high statistical power of CAMP diary symptom data. (C) The curve of mean XSYMP versus mean Tanner stage. This curve shows that the continuous decline of symptom severity in both sexes stops abruptly and the female sex dominance in severity starts precisely at the onset of puberty where the mean Tanner stage just departs from the value of 1. This indicates that puberty is a critical stage in symptom progression. With high temporal resolution and parallel Tanner stage data, we are able to clearly distinguish between the influences of two concurrent variables (i.e., age and puberty). The sudden interruptions of continuous symptom improvements at the onset of puberty in both sexes can only be attributed to puberty.

the severities in the two sexes become more far apart along puberty. Between ages 10 and 14 years, girls' symptoms start to worsen, and boys' symptoms remain stable. At late puberty, boys' symptoms resume improvement, and girls' symptoms continue to worsen. At age 17 years, the mean XSYMP value (95% CI) of girls reached 0.59 (0.56–0.62) (worse than their

symptoms at age 5 yr), but that of boys dropped to 0.28 (0.26–0.29).

The trend of symptom progression can also be observed, perhaps in more detail, by comparing the distributions of asthma symptom code, XSYMP, of all the time points (Figure 1). For girls (Figure 1A), from ages 5 to 9 years, the mass of the distribution moves from larger symptom

codes (e.g., non-zero codes) to smaller symptom codes (e.g., zero code). In other words, the participants gradually had fewer days with asthma episodes or with longer and more episodes from ages 5 to 9 years. After age 9 years, the opposite happened; the mass distribution moves back toward larger symptom codes for girls. For boys (Figure 1B), the mass of the distribution also moves toward smaller symptom codes from ages 5 to 10 years; during age 10 to 14 years, the distribution essentially remains unchanged, and after age 14 years the mass of the distribution again moves toward smaller symptom codes.

Discussion

Our study finds that the properties of asthma symptom progression distinctly differ from those of asthma prevalence. First, despite the large variations, previous studies generally indicate that a higher male prevalence continues at least to age 16 years (some studies even indicate that a higher male prevalence continues well into adulthood) (4, 8, 10, 12, 14, 17, 31). However, our results show that greater severity of symptoms among boys stops at age 7 years. Second, previous studies all show that the asthma sex dominance reversal is a simple crossover. Our results show a more nuanced pattern in symptom progression: symptoms of both sexes go through a short period of similarity, with sex differences disappearing at ages 7, 8, and 9 years before reversing and diverging. Third, puberty was shown to have minimal or no influence on prevalence (43–46). Our results show that puberty has a strong influence on altering the courses of asthma progression in both sexes and that it is associated with the reversal of sex dominance in symptom severity. All above evidences show that symptom progression is a distinct aspect of asthma epidemiology, and its properties cannot be deduced from those of other aspects.

Asthma exacerbations are usually episodic; therefore, asthma symptoms,

regardless of how defined and measured, have substantial fluctuations among individuals and within individual over time. To generate reliable symptom time courses, sufficient subjects and frequent measurements of symptoms for each subject at each time point are necessary to ensure satisfactory statistical certainty of symptom severity value at each time point. Besides, symptom data that cover many densely distributed time points are required for generating long-coverage and high-resolution time courses. Due to these challenges in obtaining such suitable symptom data, symptom progression has never been well defined. The CAMP diary symptom data (XSYMP) provide a rare opportunity in this regard. From the data distribution modeling and statistical analysis of XSYMP, we demonstrated the reliability of the symptom time courses generated in this study. In addition, diary symptom data have important advantages over questionnaire data that are often collected in many asthma cohort studies. First, daily recording of symptoms benefits from fresh memory. In contrast, a questionnaire typically asks the respondent to recall asthma-related incidences during a certain period in the past (e.g., past 6 months). If this period is too short, the answers may not accurately reflect symptoms of the respondent, given the episodic nature of asthma. If this period is too long, not only is the temporal resolution reduced but accuracy may be compromised. Second, diary data provide the possibility of building high-resolution symptom time courses.

Given the distribution of the participants in the CAMP placebo group over racial categories (around 70% white, 30% black, Hispanic, and others; details in the online supplement), the results and conclusions of this study can be applied to the general population of the United States.

The finding of this study regarding the influence of puberty on asthma symptoms suggests that sex hormones potentially play an important role in the pathogenesis of asthma. Indeed, a body of compelling

evidence supports the link between female sex hormones and the development of asthma and exacerbations of asthma during menstruation (47, 48) and potential protective effects of testosterone on asthma due to its immunosuppressing function (49). However, the exact mechanisms are unclear. In addition, our previous study found differential expressions of immune response genes of innate and adaptive immune systems in female and male mice during puberty, suggesting that the sexual dimorphism seen in postpubertal life start forming in puberty (50). Moreover, our study demonstrates that puberty is a critical stage in asthma symptom progression in both sexes. Future studies may focus on this specific period, and the ages immediately before and after, to identify the role of sex hormones on pulmonary physiology, immunology, and pathology of asthma.

In conclusion, we have established sex-specific high-resolution time courses for the natural progression of asthma symptoms through childhood and adolescence. Together with the parallel Tanner stage time courses, we untangle the effects of two concurrent variables, age and puberty. The sudden interruption of the trend that occurs at the onset of puberty for both sexes strongly suggests a much greater association between asthma symptoms and puberty rather than with age at that stage. The small 95% CIs of the mean symptom code at each time point in these time courses demonstrate statistical reliability of our results. We thus found that puberty had a strong influence on the progression of asthma symptoms in both sexes and was associated with sex reversal in symptom severity. Our results show that asthma symptom progression is a distinct aspect of asthma epidemiology and that its properties substantially differ from those of the other aspects, namely, prevalence, onset, remission and relapse, and healthcare use. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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