International Journal of Public Health (2020) 65:957–967
https://doi.org/10.1007/s00038-020-01435-x

ORIGINAL ARTICLE

Understanding the dynamics of asthma symptoms between childhood and adolescence using latent transition analysis

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Received: 2 February 2020 / Revised: 8 July 2020 / Accepted: 12 July 2020 / Published online: 31 July 2020

Abstract

Objectives Asthma patterns in childhood are important predictors of unwanted outcomes in adolescence. We aimed to define asthma phenotypes in childhood and adolescence and evaluate the transitions between these phenotypes and factors potentially associated with the transitions.

Methods Baseline (1445 children), first round (1363 children/early adolescents) and second round (1206 adolescents) data from the SCAALA Project in Salvador, Brazil, were used. Phenotypes were defined by latent class analysis at three time points. Transitions between phenotypes were described and the effects of factors associated with transition probabilities estimated using latent transition analysis.

Results The "asymptomatic" and "symptomatic" phenotypes were identified. Approximately 5–6% of asymptomatic children in childhood/later childhood and early adolescence became symptomatic later in time. Maternal common mental disorders were identified as important risk factor for unhealthy states.

Conclusions Asthma manifestations are characterized by frequent movements, especially between childhood and adolescence. Our study, by simultaneously defining disease subtypes, and examining the transitions and their potential predictors, highlights the importance of longitudinal studies to advance the understanding of the effects of social, environmental and biological mechanisms underlying asthma trajectories over time.

Keywords Latent transition analysis · Longitudinal studies · Childhood and adolescence · Asthma symptoms

Introduction

Asthma is a chronic respiratory disease that most affects children and adolescents, being considered a major public health problem worldwide with a huge impact on the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00038-020-01435-x) contains supplementary material, which is available to authorized users.

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quality of life of patients and their families and significant economic costs (Reddel et al. 2015; GINA 2016). Individuals with asthma suffer not only from symptoms caused by the disease, but also from restrictions in daily life and poor quality of life, which may pose a risk for problems in future ages (Chatkin and Menezes 2005). Despite decades of research, understanding the natural history of asthma is still an area of dispute. This is mainly due to the fact that asthma can be considered an umbrella term under which there are various diseases presenting with similar symptoms, such as wheezing and cough, but differing in their etiology, pathogenesis and responses to treatment (Wenzel 2006; Haldar et al. 2008).

Asthma manifestations vary with age, may appear and disappear at any stage of life and are subject to the interaction of numerous factors, including environmental, socioeconomic, genetic, gestational, nutritional and psychosocial conditions (Pinto et al. 2008; Gupta et al. 2009; Asher et al. 2010; Alcantara-Neves et al. 2012; Strina et al. 2014; Lind et al. 2015). Most studies, however, fail to clarify the asthma course in important stages of life, such as the transition from childhood to adolescence. This article aims to define asthma profiles in childhood and adolescence using the concept of latent variable, and to evaluate the transitions between these profiles and the potential factors associated with the transition process.

The latent variables modeling encompasses a broad and expanding research area for modeling unobserved variables (Kline 2005; Chavance et al. 2010). Specifically, latent class analysis (LCA) is a method for dealing with categorical observed and latent variables, representing subpopulations in situations where population classification is not previously known. It is an unsupervised, data-driven statistical approach, used to incorporate constructs in health-disease process studies and to define disease phenotypes (Depner et al. 2014; Hose et al. 2017; Mäkikyrö et al. 2017). The latent transition analysis (LTA) is an extension of the LCA, when repeated measures for the same indicators are available. LTA allows to assess longitudinal patterns of various manifestations of a disease in a single model to simultaneously define phenotypes/profiles, examine their transitions over time and predict effect of covariates on the transitions (Collins and Lanza 2010).

LTA, commonly used in social and behavioral sciences (Chung et al. 2005; Guo et al. 2009; Lanza et al. 2010; Sagoe et al. 2017), has been recently incorporated to address health questions, especially those related to chronic diseases (Landau et al. 2015), such as identification of patterns in the natural history of asthma over time (Soto-Ramírez et al. 2013; Panico et al. 2014; Garden et al. 2016). LTA can provide empirical evidence to support the claim that asthma is a heterogeneous entity, so that some children with wheezing and other early respiratory symptoms progress to asthma between childhood and adolescence, while others do not and become asymptomatic. In addition, LTA has been important in assisting to establish childhood and adolescence asthma/wheezing patterns, as well as to identify and define unrecognized asthma phenotypes. Soto-Ramírez et al. (2013) used LTA to identify constructs related to the occurrence of asthma and wheezing and to evaluate their transition probabilities at different ages (1 or 2, 4, 10 and 18 years). Garden et al. (2016) fitted latent transition models to define childhood respiratory symptom phenotypes in childhood (1.5–5 years) and mid-childhood (8–11.5 years) and evaluated the transitions between phenotypes at each stage of life. Early identification of factors associated with different respiratory outcomes may contribute to promote interventions that may alter the course of the disease and the dynamics of its symptoms. In our study, we define asthma profiles in childhood/later childhood, early adolescence and adolescence and assess the effect of risk factors on the profiles and their transitions using longitudinal data from the SCAALA (Social Changes, Asthma and Allergy in Latin America) project, conducted between 2005 and 2013 in the city of Salvador, Brazil (Barreto et al. 2006).

Methods

Population

This study draws on the data from a larger research program (SCAALA) aimed to investigate the effect of environmental, immunological and psychosocial factors on asthma and other allergic diseases (Barreto et al. 2006). The SCAALA participants comprise a group of 1445 children (aged 4–11 years) living in 24 areas from poor neighborhoods throughout the city of Salvador, Brazil (2005, baseline survey). On its turn, this population had been part of a previous study to evaluate the impact of sanitation program, implemented in Salvador, on the occurrence of childhood diarrhea (Barreto et al. 2007). Our study used data from the three SCAALA surveys conducted in 2005, 2007 and 2013. Data on asthma and allergic diseases, family socioeconomic conditions and family history of asthma, among others, were collected; blood samples were taken and parasitological tests undertaken in 2005 (Barreto et al. 2006). The second survey, conducted in 2006–2007 on 1363 participants out of the original ones, aged 5–13 years, gathered information about home exposure to formaldehyde, besides data on asthma symptoms and psychosocial factors. In 2013, the third survey was conducted on 1206 adolescents, aged 12–19 years, out of the original 1445 participants, and gathered information about asthma, allergic diseases,

socioeconomic conditions, family history of asthma and psychosocial assessments.

Measures

Five binary indicators related to asthma symptoms in the last 12 months prior to the interview were used to define asthma phenotypes: having wheezing/wheezing attacks; having woken up at night because of wheezing; having had difficulty of speaking because of wheezing; wheezing while breathing or exercising and having a dry cough at night. The indicators were based on questions taken from the International Study of Asthma and Allergies in Childhood (ISAAC) standardized questionnaire, validated and translated into Portuguese (Cunha et al. 2010), and answered by the participant's parent/guardian. Each of the five asthma symptoms was measured in 2005 (Time 1), 2007 (Time 2) and 2013 (Time 3). Baseline covariates, as taken in Time 1, include gender (female, male), age (years), atopy (yes/no, according to specific IgE-allergen dosage for *Periplaneta americana*, *Dermatophagoides pteronyssinus*, *Blomia tropicalis* and *Blattella germanica* categorized into not detectable if concentration was less than 0.70 kU/L and detectable otherwise) (Alcantara-Neves et al. 2012), maternal asthma (yes/no) and suspected maternal common mental disorder (CMD) (as 8 or more positive responses to the SRQ-20 questionnaire) (do Carmo et al. 2009). The body mass index (BMI) was calculated using weight and height measurements from 2005, while BMI Z-score was obtained using reference curves from WHO Multicentre Growth Reference Study Group (2006), by age and gender. For our models, we considered data on 1043 participants with complete data for the set of covariates described here. To facilitate the presentation and interpretation of the results over time, we named the time points by age groups: childhood/later childhood (time 1: 4–10 years), later childhood/early adolescence (time 2: 5–12 years) and adolescence (time 3: 12–18 years).

Data analysis

LTA is a dynamic model of sequential phases of latent variables (latent states), which allows to capture the movement of individuals in longitudinal data analysis (Collins and Wugalter, 1992) (Details at Online Resource 1). LTA is used here to evaluate the transition between asthma phenotypes (Fig. 1a) and the effect of covariates on the probabilities of latent state membership and on their transition probabilities (Fig. 1b). LCA was used to define the latent classes in each time point, previously to LTA. The designation of the latent classes/status was based on the interpretation of the estimated conditional probabilities. Both LCA and LTA are able to handle missing data in its indicators, assuming a missing at random mechanism and using the full information maximum likelihood (FIML) estimation method unless missing data occur in the covariates (Collins and Lanza 2010). The measurement invariance over time is assumed, meaning that the latent variable is the same at all time points, i.e., all item response probabilities are equal across time (Collins and Lanza 2010). This assumption facilitates the use and interpretation of LTA. Another assumption is conditional independence, that is, the indicator variables are mutually independent conditional on the latent class. This assumption is evaluated using the model residuals (values less than 2 are expected). No assumptions are made about the distribution of variables. The number of latent states was first selected using AIC and BIC, by fitting a set of models (with classes numbers varying between 2 and 4) using LCA. Other criteria for model selection include model entropy and the Vuong–Lo–Mendell–Rubin likelihood ratio test (Nylund et al. 2007).

Figure 1a and b represent, respectively, LTA path diagrams with and without covariates considering 5 asthma symptom indicators ($X1$–$X5$) assessed at 3 time points. The squares represent the observed variables, and the circles represent the latent variables. The horizontal arrows represent the transitions occurring between the latent states at the three time points. In Fig. 1b, in the left bottom square are the set of covariates associated with the latent state in childhood and the transitions between latent states.

The introduction of covariates into an LTA model allows to identify characteristics that predict belonging to a given latent status and/or the transitions between latent states (Collins and Lanza 2010). The covariates are commonly incorporated into the LTA model using the logit link function and are specified as predictors of the probability of transition between consecutive times. The results are expressed as odds ratios (OR) and 95% confidence intervals. The assumption of measurement invariance is retested after the inclusion of covariates using the likelihood ratio test. Statistical software Mplus version 7 was used for data analysis. Data were anonymized and irreversibly de-identified to protect participants.

Results

Sample characteristics

The mean age of the participants at baseline was 6.8 years (SD = 1.7 years), 53.7% were male, 61.9% were non-atopic, 91.1% had mothers without history of asthma, and 63.5% had mothers with a common mental disorder. In the 2005 survey, 16.0% of the children were less than 5 years of age and only 11.6% were older than 8 years, while

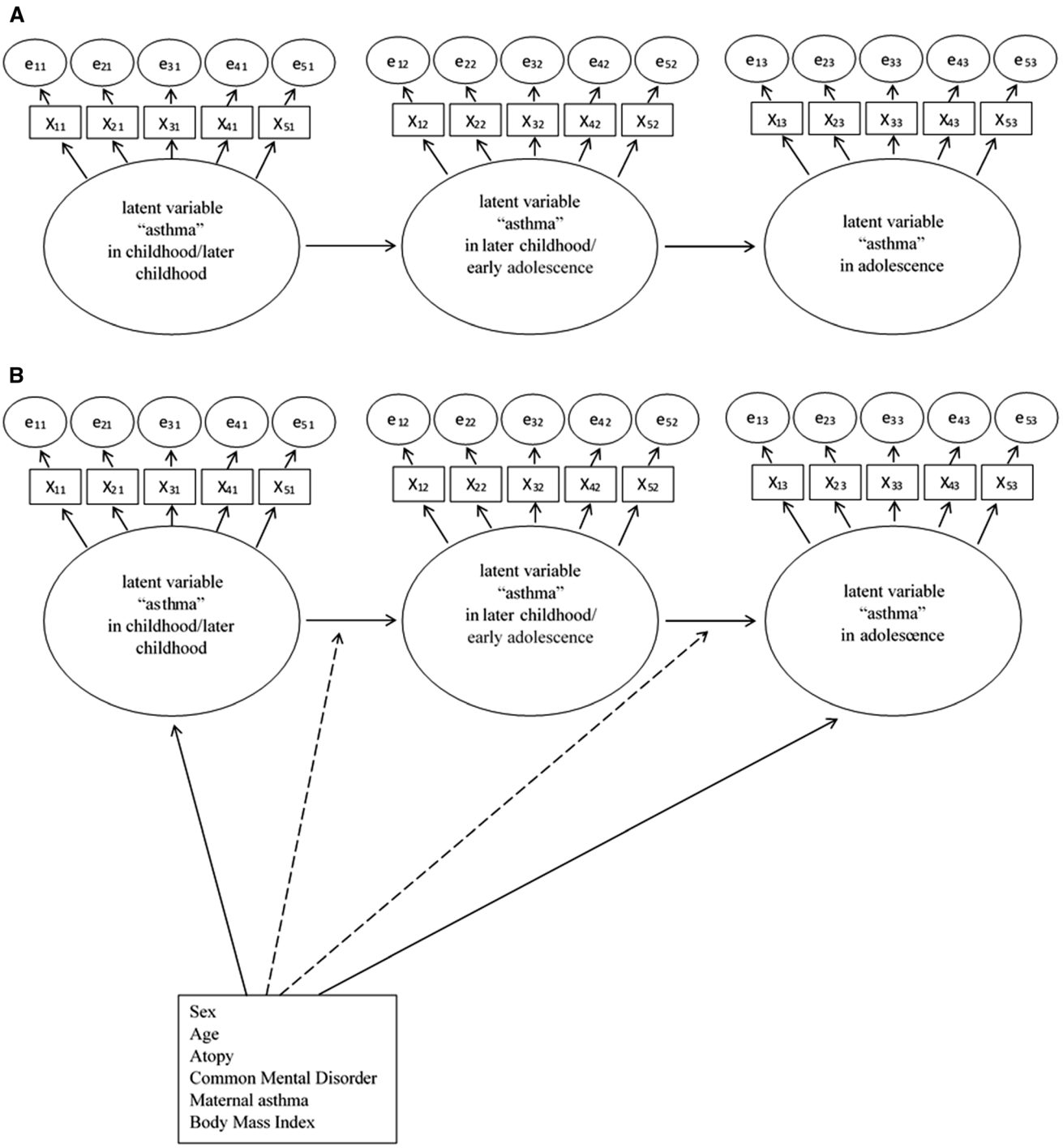

Fig. 1 Graphical representation of the latent transition model for asthma data, considering the five asthma symptom indicators ($x1$–$x5$) and three time points: **a** without covariates and **b** with covariates. $X1j$ = wheezing attacks; $X2j$ = wake up at night because of wheezing; $X3j$ = difficulty speaking because of wheezing; $X4j$ = wheezing while breathing/exercising; $X5j$ = dry cough at night, j = 1, 2, 3 denotes the corresponding time points of the study; e = error terms associated to each indicator

55.6% of the participants were 8 years and above (mean age 8.6, SD = 1.7) in 2007. In 2013, on its turn, 72.7% of them were between 13 and 16 years (mean age 14.6, SD = 1.4). Table 1 presents the frequency distribution of the five indicators from the ISAAC questionnaire used to define the latent variable "asthma phenotype." The most reported symptom was "having had a dry cough at night in the last 12 months." In addition, there was a tendency for the frequency of all symptoms to decrease over time.

Table 1 Frequency of asthma symptom indicators at each time point. Salvador-Bahia, Brazil, 2005, 2007 and 2013

Indicators of asthma phenotypes	Frequency (%) at time 1 (n = 1445) (2005)	Frequency (%) at time 2 (n = 1363) (2007)	Frequency (%) at time 3 (n = 1206) (2013)
Wheezing attacks	26.8	15.9	9.8
Wake up at night because of wheezing	20.8	10.9	6.2
Difficulty speaking because of wheezing	6.1	3.2	1.9
Wheezing while breathing/exercising	9.3	5.0	5.3
Dry cough at night	35.0	31.4	25.2

Symptom profiles and dynamics

The chosen number of latent classes obtained through LCA separately performed at each time point (2005, 2007 and 2013) was two (Online Resource 2, Table 2a). The null hypothesis of measurement invariance over time (p = 0.02) was rejected, but BIC indicated that the best model assumes invariance (Online Resource 2, Table 2b). Additionally, the conditional probabilities at each time point were quite similar. Residual analysis did not indicate violation of the assumption of local independence. Further information can be found at Online Resource 3.

Asymptomatic individuals were less likely to report the occurrence of any of the symptoms in the last 12 months, while the opposite was noticed among symptomatic individuals. In particular, 95.8% of the symptomatic individuals reported wheezing attacks and 76.4% woke up at night because of wheezing, while these percentages are 1.9% and 0.0% among asymptomatics (Table 2). Figure 2 shows the prevalence of each latent state at the three time points, the probabilities of remaining in the same latent state (thicker arrows), and the probabilities of moving from one state to another one at the subsequent time (dotted and dashed arrows). Most individuals (68.9% in childhood/later childhood, 84.0% in later childhood/early adolescence and 90.7% in adolescence) were asymptomatic throughout the study. We observed that 38.7% and 94.2% of symptomatic and asymptomatic children, respectively, remained in the same state between childhood/later childhood and later childhood/early adolescence. Symptomatic individuals in childhood/later childhood are likely to transit to asymptomatic state in later childhood/early adolescence (61.3%); and this probability increases (68.1%) between later childhood/early adolescence and adolescence. These results are consistent with the reduction of symptoms with increasing age.

Variables associated with status membership and dynamics

Table 3 presents odds ratios (ORs) and respective 95% confidence intervals for the effect of each covariate on latent state at time 1 (childhood/later childhood) using multivariate LTA. Except for gender, all covariates were significantly associated with the latent states in childhood/later childhood. The atopic participants and those whose mothers had CMD are twice as likely to belong to the symptomatic latent state, adjusted for all other covariates (OR 2.07, 95% CI 1.54–2.74; OR 2.03, 95% CI 1.51–2.71, respectively). Individuals whose mothers have a history of asthma are approximately three times more likely to belong to the symptomatic latent state (OR 2.63, 95% CI

Table 2 Probabilities of positive answers[a] to each indicator using latent transition analysis with two latent status assuming measurement invariance. Salvador-Bahia, Brazil, 2005, 2007 and 2013

Indicators of asthma phenotypes	Latent states (n = 1043)	
	Symptomatic	Asymptomatic
Wheezing attacks	0.958	0.019
Wake up at night because of wheezing	0.764	0.000
Difficulty speaking because of wheezing	0.231	0.000
Wheezing while breathing/exercising	0.331	0.015
Dry cough at night	0.671	0.234

[a]In the last 12 months

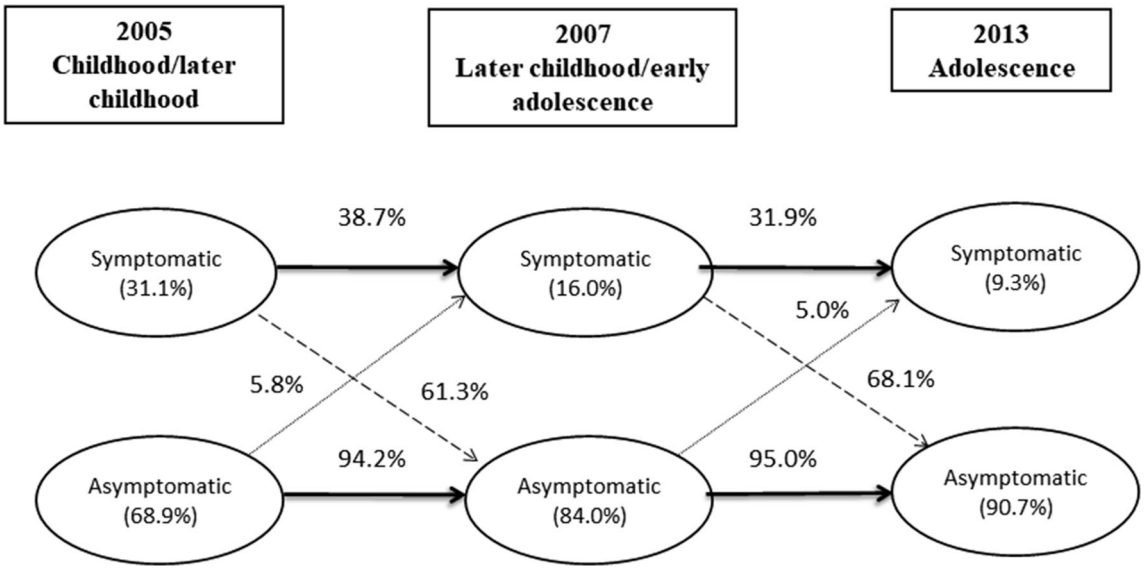

Fig. 2 Prevalence of latent states (in brackets) and transition probabilities of latent states at subsequent times. Salvador-BA, Brazil, 2005, 2007 and 2013. Ticker arrows represent the probabilities of remaining in the same state; dotted and dashed arrows represent the probabilities of moving from one state to another

Table 3 Effect of covariates on latent state membership at time 1 (childhood/later childhood). Salvador-Bahia, Brazil, 2005, 2007 and 2013

Covariate[a]	Latent status in time 1: symptomatic[b] Odds ratio (OR)	95% Confidence interval (95% CI)
Gender (boy)	1.06	0.79; 1.43
Age (in years)	**0.75**	0.68; 0.82
Atopy (yes)	**2.07**	1.54; 2.74
Maternal CMD (yes)	**2.03**	1.51; 2.71
Maternal asthma (yes)	**2.63**	1.61; 4.30
BMI Z-score	1.03	0.91; 1.17

Bold values represent $p < 0.05$

CMD common mental disorder, *BMI* body mass index

[a]Risk level or units in parentheses

[b]Reference for latent states is asymptomatic

1.61–4.30), and the chance of being symptomatic in childhood/later childhood reduces by 25% for every 1-year increase in age (OR 0.75, 95% CI 0.68–0.82).

To better understand the dynamics of asthma symptoms from childhood to adolescence, covariates were incorporated in LTA to estimate their effects on the transition probabilities (Table 4). Adjusting for all covariates, boys who were asymptomatic in childhood/later childhood are 42% more likely than girls to become symptomatic in later childhood/early adolescence (OR 1.44, 95% CI 0.33–2.54), but the opposite is observed in adolescence (OR 0.43, 95% CI 0.07–0.79). Atopic individuals who were symptomatic in childhood/later childhood were 34% less likely than non-atopic individuals (95% CI 0.33–0.99) to become asymptomatic in later childhood/early adolescence and 52% more likely (95% CI 0.75–2.28) to remain symptomatic. Among individuals who were asymptomatic in childhood/later childhood, there was a reduction of 54% (95% CI 0.12–0.69) and 46% (95% CI 0.15–0.893) of the chance to remain asymptomatic in later childhood/early adolescence and adolescence, respectively, if their mothers have suspected CMD. No significant effect of BMI was observed for any transitions.

Discussion

It is known that asthma starting in childhood or adolescence is transient in the largest part of the population and persistent in a small group (To et al. 2007; Sears 2015). This dynamism of symptoms makes difficult the diagnosis of the disease and its study in populations. Developing

Table 4 Estimation of the effect of covariates (ORs and 95% CI) on the transition from childhood to adolescence[a]. Salvador-Bahia, Brazil, 2005, 2007 and 2013

Covariate[b]	Transition from time 1 To time 2		Transition from time 2 To time 3	
	Latent status		Latent status	
	Asymptomatic OR (CI 95%)	Symptomatic OR (CI 95%)	Asymptomatic OR (CI 95%)	Symptomatic OR (CI 95%)
Gender (boy)				
Asymptomatic	0.70 (0.16; 1.23)	1.44 (0.33; 2.54)	2.31 (0.39;4.22)	**0.43 (0.07;0.79)**
Symptomatic	0.99 (0.49; 1.48)	1.05 (0.51; 1.52)	1.04 (0.20;1.88)	0.96 (0.18;1.74)
Age (in years)				
Asymptomatic	1.34 (0.98; 1.71)	**0.74 (0.54; 0.95)**	0.92 (0.70; 1.14)	1.09 (0.83; 1.35)
Symptomatic	1.00 (0.85; 1.15)	1.00 (0.85; 1.15)	1.22 (0.90; 1.53)	0.82 (0.61; 1.03)
Atopy (yes)				
Asymptomatic	**0.50 (0.13; 0.87)**	1.99 (0.52; 3.45)	0.62 (0.13; 1.12)	1.60 (0.34; 2.87)
Symptomatic	**0.66 (0.33; 0.99)**	1.52 (0.75; 2.28)	0.77 (0.13; 1.42)	1.29 (0.21; 2.37)
Maternal CMD (yes)				
Asymptomatic	**0.46 (0.12; 0.69)**	2.46 (0.75; 4.17)	**0.54 (0.15; 0.93)**	1.85 (0.50; 3.20)
Symptomatic	0.93 (0.47; 1.39)	1.08 (0.54; 1.61)	1.20 (0.24; 2.16)	0.83(0.17; 1.50)
BMI-Z score				
Asymptomatic	0.94 (0.66; 1.22)	1.06 (0.75; 1.38)	1.21 (0.83; 1.59)	0.82 (0.57; 1.08)
Symptomatic	0.96 (0.76; 1.16)	1.05 (0.83; 1.26)	0.71 (0.50; 0.93)	1.40 (0.97; 1.83)

Bold values represent $p < 0.05$

OR odds ratio, *CI* confidence intervals, *CMD* common mental disorder, *BMI* body mass index

[a]Estimation of maternal asthma effect in the transition model does not achieve convergence

[b]Risk level or units in parentheses

models that can cope with this dynamism is a challenge for the analysis of longitudinal data related to asthma epidemiology in childhood and adolescence. Moreover, the heterogeneity of manifestations of asthma during these life stages has major implications for the investigation of its etiology, mechanisms, management and dynamics over time at the population level. We aimed to explore patterns in the occurrence of asthma symptoms, with two objectives: (1) to analyze asthma symptoms, assessed at three different times between childhood and adolescence, and to classify individuals accordingly and (2) to extend these cross-sectional analyses to a longitudinal analysis, examining the transitions between individuals with and without symptomatology over time and assessing the role of covariates in these transitions.

The variations found in the phenotypes identified so far can be attributed mainly to differences in populations and asthma symptoms included in the statistical analysis. Characterization of asthma phenotypes in children may help to clarify the underlying mechanisms through which the disease occurs and may increase the strength to detect causal factors (Granell et al. 2016).

Mixture models, such as LCA and LTA (Henderson et al. 2008; Savenije et al. 2011; Weinmayr et al. 2013), have been increasingly adopted as an efficient complement to approaches based on the application of a priori definitions (Brand et al. 2008) to assist in the identification of new or previously unrecognized phenotypes (Garden et al. 2016). Studies have shown that the use of LCA can produce clinically meaningful and interpretable phenotypic classifications, relevant to disease prognosis (Depner et al. 2014). Recently, the use of statistical approaches for data-driven longitudinal data, such as LTA, has aided in the recognition of asthma phenotypes, as well as the transitions between such phenotypes and possible predictors of these transitions. Earlier attempts to incorporate the longitudinal pattern of various asthma manifestations into a statistical model to simultaneously define phenotypes and examine transitions over time have been limited to assessing asthma/asthma symptoms at different stages of life. This study advances by including covariates that may potentially explain the transitions between asthma phenotypes, which had not yet been identified in the asthma literature, using LTA with covariates. LTA has proved to be a refined approach that can parsimoniously produce a summary of the heterogeneity of asthma symptoms from childhood to adolescence. Conducting an LTA requires the following basic steps: (1) performing a good descriptive analysis of indicators and possible predictors; (2) adjusting LCA models for each time point; (3) assessing the assumption of

measurement invariance over time; (4) exploring transitions without including covariates and 5) including covariates to predict belonging to a given latent state at time 1 and transitions between latent states.

In our research, we observed a reduction of asthma symptoms frequency with increasing age (Table 1). Few (around 6%) individuals belonging to asymptomatic phenotypes in childhood/later childhood became symptomatic in later childhood/early adolescence, and the similar result was observed from later childhood/early adolescence to adolescence (5%). On the other hand, 38.7% and 31.9% of individuals classified as symptomatic in childhood/later childhood or in later childhood/early adolescence remained symptomatic in later childhood/early adolescence and adolescence, respectively (Fig. 2). The inclusion of covariates in the LTA model allowed us to evaluate the association of predictors with the latent states (symptomatic and asymptomatic) in childhood/later childhood, as well as with the transitions between latent states over time. Except for gender and BMI, all factors were statistically associated with the symptomatic latent state in childhood/later childhood (Table 3). On the other hand, atopy and maternal CMD were important factors for predicting transitions to symptomatic phenotype, with CMD representing a risk factor both in childhood and in adolescence (Table 4). Research has already shown the negative impact of poor maternal mental health on children's respiratory health (Kozyrskyj et al. 2008), but the effect of this factor was not yet investigated over time, particularly in the transition from childhood to adolescence. Garden et al. (2016) separately assessed childhood and mid-childhood asthma phenotypes and transitions between phenotypes in each phase. They found four distinct phenotypes in early and in mid-childhood using occurrence of atopy, symptoms of asthma and rhinitis, hyperresponsiveness and airway inflammation. They found that the transition between phenotypes occurs most commonly in early childhood. Soto-Ramirez et al. (2013) investigated the occurrence of asthma and wheezing using data from early childhood, childhood, middle-childhood and adolescence (at 1 or 2, 4, 10 and 18 years of age, respectively) and assessed their transition probabilities stratified by sex. Bourdier et al. (2013) identified seven adult asthma phenotypes and also examined their transitions. However, none of those studies has examined the role of predictors in the transition between phenotypes considering a population of children and adolescents, nor has it described what the disease dynamics is between these two phases.

The classification of individuals according to the asthma symptoms described in this study cannot be fully compared with that of other studies because of the differences in age, number of latent states and number and types of indicators capturing the heterogeneity of asthma phenotypes. Our study identified two phenotypes. The Tucson Respiratory Study, using cross-sectional wheezing data over the last 12 months in preschool children (aged 3–6 years), described three wheezing phenotypes, and classified children into transient early wheezing, late onset wheezing and persistent wheezing (Martinez et al. 1995). However, this classification was not based on an agnostic, purely statistical methodology, but on a priori definitions of the researcher. An Australian cohort study (Childhood Asthma Prevention Study, CAPS) used data from 370 participants to define phenotypes in childhood (1.5–5 years) and mid-childhood (8–11.5 years) (Garden et al. 2016). Their phenotypes, however, were not the same for the two time points evaluated (childhood and mid-childhood), making it unfeasible, differently from our study, to evaluate the transitions between the different phenotypes over time. Soto-Ramirez et al. (2013) used data from a cohort on Isle of Wright (UK) to describe childhood transitions into gender-specific phenotypes that were defined based on two indicators: physician-diagnosed asthma and wheezing. Asthma subtypes are a complex field of study, and usually what has been done was an attempt to identify such subtypes by combining etiological factors and asthma outcomes, which makes difficult to compare results from different studies.

With respect to the methodological approach adopted by our study, LTA is an innovative method for addressing the issue of how childhood asthma symptoms change over time, by reducing repeated observations into meaningful interpretable patterns. In addition, it differs from other longitudinal analyses in that it models transitions rather than trajectories, thus avoiding the assumption that all members of a given latent state have the same dynamics over time (Garden et al. 2016). Thus, LTA represents a parsimonious but refined approach to define the heterogeneous behavior of wheezing in important stages of life, such as childhood and adolescence. Classical measures, such as incidence or remission, commonly used to characterize the epidemiology of chronic diseases such as asthma, are not informative enough and are not the most appropriate way to draw conclusions about specific changes over time regarding the disease state. In revealing changes in prevalence, transition probabilities are a useful tool to describe disease dynamics. In addition, the transition probabilities obtained through LTA do not require a stable cohort, making it possible to study a dynamic cohort, which means that participants can drop out for whatever (random) reason from the study, but later reintegrate, thus providing a better and more complete understanding of disease dynamics.

LCA and LTA, however, have some limitations that should be taken into account. For example, the method's ability to detect a latent structure is limited when inappropriate indicators are chosen for the analysis. In our

study, the identification of the phenotypes was based on five questions about wheezing in the last 12 months included in the ISAAC questionnaire. This choice was due to the necessity of having the same indicators measured at all time points. Availability of additional indicators would help to expand the identification of meaningful phenotypes. Although the sample size for this analysis was relatively large, the time elapsed between the evaluations (2 years between the first measurement and the second, and 6 years between the second and the third one) was not short, which can influence the interpretation of the transitions between states. For further technical details see Online Resource 3.

To our knowledge, no studies were so far published, especially in Latin America, that incorporated the longitudinal dynamics of asthma symptoms into a statistical model, able to simultaneously define disease subtypes, examine the transitions between them and consider potential predictors of these transitions. However, there is a need for research to refine the phenotypes identification with the inclusion of asthma-related traits of different nature, such as other predictors of both risk (immunological, genetic or nutritional elements) or protection (e.g., resilience), which may contribute to a more satisfactory explanation of the behavior of asthma dynamics between childhood and adolescence, assisting in improving prognostic and therapeutic strategies.

There is limited literature to provide substantive explanation about the biological, environmental and social impact of many factors on the respiratory symptoms over time. An important factor usually associated with asthma and other respiratory symptoms is atopy, likely related to the deterioration of lung function and increased bronchial hyper-reactivity observed in asthma, especially in cases with persistent symptoms, even though full consensus about that is still lacking (Silva et al. 2005; Cooper et al. 2009). If true, this might explain why symptomatic individuals tend to remain symptomatic later in life (Table 4). Furthermore, the asthma proportion attributed to atopy may vary, suggesting different causal pathways, such as environmental exposures, urbanization, migration and lifestyle changes (Cooper et al. 2009; Cunha et al. 2010). Another issue is the difficulty to distinguish asthma in early life from other transient wheezing disorders due to viral infections, which are usually related to exposures to other children at home, or at day-care centers or schools (Benício et al. 2004). Besides that, both allergic sensitization and asthma seem to be affected by genetic factors (Silva et al. 2005; Di Cicco et al. 2020). Mechanisms proposed to link maternal mental disorder and asthma in their children include the fact that maternal mental health disorders may lead to poor management of the child's asthma (do Carmo et al. 2009; da Costa et al. 2020). Furthermore, behavioral and emotional maternal changes activated by stressful events may trigger immunological modifications involved in allergic inflammation in children (do Carmo et al. 2009; Yamamoto and Nagano 2015). Further research is recommended to better understand the relationship between maternal mental status and the persistence of asthma symptoms in their children.

In conclusion, asthma is a heterogeneous entity, encompassing different diseases with different pathophysiological mechanisms, whose manifestations vary with age, and therefore can hardly be characterized by a single quantitative measure (Bush 2019). Our paper shows how LTA can be an interesting and useful tool to model longitudinal changes and to assess how latent state membership changes over time due to exposure to some important predictors. In this paper, it was possible to capture the dynamics of asthma symptoms during childhood, later childhood/early adolescence and adolescence, represented by two distinct latent status. We confirmed that wheezing is not a stable phenomenon and its movements from childhood to adolescence are frequent. The importance of maternal mental health as a risk factor for a poor respiratory health in childhood, as well as its maintenance in adolescence, was also evidenced. To our knowledge, no studies were so far published incorporating the longitudinal dynamics of asthma symptoms, by simultaneously defining disease subtypes and examining the transitions and their potential predictors. Our study highlights the relevance of longitudinal studies to advance the understanding of the effects of social, environmental and biological mechanisms underlying asthma trajectories over time.

Acknowledgements Our grateful thanks go to all participants. Ana Clara P. Campos was funded by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico)/Brazil scholarship during her doctorate. Leila D.A.F. Amorim was partially funded by FAPESB (Fundação de Amparo à Pesquisa do Estado da Bahia)/Brazil (Grant No. RED005/2014).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval of studies using pre-existing data Data were anonymized and irreversibly de-identified to protect participants.

Informed consent Informed consent was obtained from all individual participants included in the study.

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