Age at Menarche and Asthma Onset Among US Girls and Women: Findings from NHANES, 2001-2018

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Research

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Abstract

Background: Findings on the association between early menarche and asthma onset remain inconsistent and the evidence in the US is lacking. Furthermore, there was no clear separation of childhood- and adult-onset asthma in previous studies. Therefore, we aim at quantitatively estimating the association of age at menarche with risk of childhood- and adult-onset asthma separately in US girls and women.

Methods: We conducted a retrospective cohort study of 24,282 US girls and women aged less than 80 years by using continuous NHANES data in 2001-2018. Weighted Cox proportional-hazards regression models with censoring ages of 19 and 79 were used to separately estimate hazard ratios of childhood- and adult-onset asthma associated with age at menarche.

Results: Each one-year increase of age at menarche was significantly associated with a 17% (HR [95%CI]: 0.83 [0.77, 0.90]) decrease in the risk of childhood-onset asthma. Compared with age at menarche of 12-14, we observed a 60% (HR [95%CI]: 1.60 [1.22, 2.09]) increased risk of childhood-onset asthma for early menarche (age at menarche <12 years) and 41% (HR [95%CI]: 0.59 [0.32, 1.08]) decreased risk for late menarche (age at menarche ≥15 years). Race, family income, education and family history of asthma did not modify these associations. No significant association between age at menarche and adult-onset asthma.

Conclusions: In this US nationally representative study, we found that early menarche was associated with increased risk of childhood-onset asthma, but not adult-onset asthma. These findings help demonstrate early menarche may be a risk factor for childhood-onset asthma in US, indicating timely and effective management of special individuals with early menarche for preventing asthma.

Background

Asthma is a major public health concern in the US, costing about $80 billion for asthma-related mortality and medical usage in 2013. [1] Although numbers of risk factors such as genetic susceptibility [2, 3], environment tobacco smoke, [4, 5] air pollution, [6] diet and obesity [7, 8] have been explored and asthma control strategies have been applied, the prevalence of asthma has been increased in the US between 2001-2010. [9]

Sex differences in asthma prevalence that switch from male to female predominance during adolescence and adulthood[10] suggest effect of puberty on asthma incidence. Compared with men, women are more likely to suffer from asthma after puberty. Age at menarche is regarded as a convenient marker for the timing of puberty in girls. Given that the increasing prevalence of asthma[11] is coincided with declining trends in age at menarche,[12–14] several studies have investigated the effect of age at menarche on asthma. However, the results remain inconsistent. For example, the positive association between early menarche and risk of asthma was observed in women from UK, Poland, and Canada,[15–19] but not for those from Swiss and Germany.[18, 20, 21] To date, there was no evidence for the effect of early menarche

on asthma among US general population yet, except for one study conducted in non-Hispanic and well-educated pregnant women.[22] Furthermore, although all previous studies focused on asthma onset, few clearly separated patients into childhood- and adult-onset asthma.[22] Due to the differences in the prevalence, physiopathological mechanisms and clinical characteristics between childhood- and adult-onset asthma,[23, 24] it is necessary to clearly separate the two types of asthma when identifying the effects of potential risk factors for asthma onset.

Here, we used data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the US population, to quantitatively estimate the associations of age at menarche with risk of childhood- and adult-onset asthma separately. Effect modifications of race, income and family history of asthma on the associations was further examined.

Methods

Data sources and study population

The continuous NHANES is a cross-sectional survey designed to assess the health and nutritional status of children and adults in the US. It included a series of nationally representative interviews and health examinations through cycles of 2-year intervals since 1999. In each cycle, a sample representative of the civilian noninstitutionalized resident population of the US was selected using a complex, stratified, multistage probability cluster sampling design. Due to lacking information on age at asthma among participants aged ≥20 in cycle 1999-2000, we included nine cycles between 2001-2018 in this analysis.

Exposure and outcome

In this study, we defined age at menarche as the exposure, and defined asthma onset as the outcome. Information on menarche and asthma was obtained based on self-reported responses to specific questions. Participants were asked for age at menarche by the question "*How old were you when you had your first menstrual period?*". Information on asthma onset was collected by the question "*Has a doctor or other health professional ever told you that you have asthma?"*. Participants with positive answers were further asked "*How old were you when you were first told you had asthma?"* to obtain age at asthma onset. Childhood- and adult-onset asthma were defined as age at asthma onset <20, and ≥20 respectively.

Covariates

Information on demographic variables such as age group (<20, 20-39, 40-59, and ≥60), race (Mexican American and other Hispanic, Non-Hispanic white, Non-Hispanic black, and other), and ratio of family income to poverty (<1 and ≥1) were collected according to self-reported responses to questionnaires. Family history of asthma were defined as close relative had asthma by the question "*Including living and deceased, were any of close biological that is, blood relatives including father, mother, sisters or brothers, ever told by a health professional that they had asthma?*". Body mass index (BMI) was calculated

according to height and weight, which were measured in a mobile examination center using standardized techniques and equipment. All missing responses in covariates were classified into “Unknown” group in the analysis.

Statistical analysis

Accounting for differential probabilities of selection and the complex sample design, we used the survey design variables including masked variance pseudo-PSU and pseudo-stratum to adjust the standard errors. We constructed sample weights by combining nine-year cycles of the continuous NHANES from 2001-2002 to 2017-2018 to account for unequal probabilities of selection and nonresponse. Participants were divided into three groups including early menarche, normal and late menarche by age at menarche of <12, 12-14 and ≥15 years. Nelson-Aalen analysis were used to estimate the cumulative-hazard rates of the three groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional-hazards regression models to estimate the associations between age at menarche and risk of asthma. Two models were performed to test the reliability and stability of the results. The first model included age at menarche alone and used age as the timescale without adjustment (Model 1), while the second was adjusted for race, income, height, and family history of asthma (Model 2). Meanwhile, we fitted models with different censoring age to identify the associations of age at menarche with childhood- and adult-onset asthma separately. To estimate the risk of childhood-onset asthma, we used models with censoring age at 19 years, and participants first had asthma at age of 20 or more were treated as non-asthmatics, for adult-onset asthma, we excluded those who suffered from asthma before 20 years old (N=560), and then fitted models with censoring age at 79 years. We estimated the HRs associated with each one-year increase in age at menarche by including age at menarche as a continuous variable in the models. To examine the shape of the exposure-response association, we further conducted categorical analyses by dividing age at menarche into three categories including early (age at menarche <12 years), normal (age at menarche during 12-14 years), and late menarche (age at menarche ≥15 years), and used normal age at menarche as the reference category.

Stratified analyses were conducted to investigate whether any of covariates can modify the associations in separate Cox proportional-hazards regression models, with exclusion of the stratification variable. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R (version 3.6.0).

Results

The analysis of the 2001-2018 data was from 42,540 girls and women who aged less than 80 years and completed both the interview and examination. The unweighted sample sizes for the selection process of the participants in this study were summarized in Figure 1. After excluded 18,258 participants lacking information on menarche or asthma, aged at menarche of 20 or more, or aged at menarche after asthma onset, there were 24,282 examined samples extracted from the nine-cycle NHANES.

The sample size for different age at menarche by age group, race, ratio of family income to poverty, and family history of asthma are shown in Table 1. The included participants were aged between 12 to 79

years, and 24.5% were reported as early menarche. There were 9.0% participants (unweighted) suffering from asthma after menarche, including 560 childhood-onset asthma (2.3%) and 1623 adult-onset asthma (6.7%). Asthma prevalence by category of age at menarche was 10.7%, 8.5%, and 8.1% for early, normal and late menarche, respectively, while the mean (SD) of age at asthma onset was 30.5 (16.5), 34.7 (16.2), and 39.0 (16.3) years for early, normal, and late menarche, respectively. Early menarche has the highest cumulative-hazard rates than normal or late menarche (p <0.001) (Shown in Figure 2).

Table 2 presents the HRs for risk of both childhood- and adult-onset asthma associated with age at menarche. Analyses adjusting for race, income, height, and family history of asthma revealed that early menarche was significantly associated with increased risk of childhood-onset asthma. Each one-year increase in age at menarche was significantly associated with a 17% (HR [95%CI]: 0.83 [0.77, 0.90]) reduction in risk of childhood-onset asthma. The categorical analyses showed a 60% (HR [95%CI]: 1.60 [1.22, 2.09]) increased risk of childhood asthma for early menarche and 41% (HR [95%CI]: 0.59 [0.32, 1.08]) decreased risk for late menarche, when compared to those who had menarche in normal age (Model 2). However, the inverse associations were not detected for adult-onset asthma (HR [95%CI]: 0.97 [0.94, 1.01]). Similar results were found in unadjusted models (Model 1).

Table 3 shows results of the stratified analyses. When compared with normal menarche, we found significant associations of early menarche with increased risk of childhood-onset asthma in all subgroups except for other race (all p values < 0.05). Remarkable decreased risks were observed in other race and participants with family history of asthma (HRs [95%CIs]: 0.04 [0.01, 0.30] and 0.41 [0.20, 0.84] respectively). There was no significant association of early or late menarche with risk of adult-onset asthma (all p values > 0.05). None of the race, ratio of family income to poverty, or family history of asthma modified the association between age at menarche and risk of childhood- or adult-onset asthma (all p values for effect modification > 0.05).

Discussion

In this large sample of the US population, we quantitatively assessed the exposure-response association of age at menarche with risk of childhood- and adult-onset asthma separately. A novel effect of early menarche was only observed on childhood-onset asthma. Each one-year increase in age at menarche was associated with 17% decrease in risk of childhood asthma. There was about 60% increased risk of childhood-onset asthma for early menarche and 41% decreased risk for late menarche when compared to those with normal menarche. None of race, family income, or family history of asthma could modify the associations.

The link between age at menarche and asthma onset appears to be equivocal. Studies from Germany and Swiss did not observe any effect of menarche on asthma among young populations [21, 25]. In contrast, a 60%, 108% and 134% increase in risk of asthma onset were reported in British, US and Canadian girls who had early menarche, respectively.[16, 18, 19] Notably, the study from British reported that the girls with early menarche had more asthma at all ages, but the association reached statistical

significance only among girls age 11 years at the time of follow-up.[18] Similar results were also observed in a Sweden study of 2492 adults aged 18-60 years,[20] but inconsistent with the findings from a recently published study which included 0.24 million women aged 40-69 years based on UK biobank data and reported 8% increase in the risk of asthma for early menarche and 8% decrease for late menarche by using mendelian randomization.[15] One possible reason for the inconsistent results in these studies might be the different ages at menarche used as the reference category (including age of 12-13,[18, 26] 12-14,[15] >12,[16] ≥12,[20, 22] and 12.66[19] years). A meta-analysis helped solve the problem by combining the findings from of seven cohort studies with consistent definition of early menarche as age at menarche>12 years. Results of the meta-analysis study showed a 37% increase in risk of asthma for early menarche when comparing groups with late menarche in women aged from 7 to 57 years.[27] Our findings confirmed and extended the adverse effect of early menarche on asthma onset in US general population. By further distinguishing the childhood- and adult-onset asthma in our study, we found the novel effect of early menarche only on childhood asthma rather than adult-onset asthma. Although there was no guideline for clear distinction between childhood and adult-onset asthma, several obvious differences such as symptoms and sensitivity to allergens were observed.[28] The results from our study indicate potential differences in risk factors and pathogenesis of the two types of asthma.

The underlying mechanisms for the early menarche related asthma is still unclear. Menarche is an indicator of pubertal onset for women and early menarche is generally considered to be a sign of precocious puberty, companying with changes of sex hormone levels. A recent nationwide study of US adults reported the association between sex hormone levels and the risk of asthma,[29] providing a possible reason for increased risk of asthma onset among participants with early menarche. Besides, other risk factors associated with precocious puberty such as obesity, depression, anxiety, and psychosomatic symptoms[30, 31] have been demonstrated to participate in activating inflammatory mediators,[32] which have been regarded as important role on asthma development.[27, 33, 34]

Our results have important public health implication. Asthma is one of the leading chronic diseases, affecting 339.4 million people and contributing to 420,000 deaths globally in 2016.[35, 36] It was estimated that there were about 6.2 million children under the age of 18 with asthma.[37] The present study confirms and extends previous research by quantifying the effect of age at menarche on the risks of childhood asthma, suggesting early menarche may be a risk factor for childhood-onset asthma in US. Timely and effective management of individuals with early menarche should be a part of the prevention for asthma.

There are several strengths in this study. To our knowledge, this is the first representative study to quantitatively estimate the association of age at menarche with asthma onset in a general population of US girls and women, covering all races in the US and those aged from 12 to 79 years. Furthermore, we identified childhood- and adult-onset asthma according to age at asthma onset, accounting for the effect of asthma phenotypes on the association.[38] In addition, most previous studies used logistic regression models to assess the associations,[18-20, 22, 39, 40] ignoring the effect of the event time. Due to the potential

impact of age at menarche upon the time asthma takes to happen, it seems to be more appropriate to account for time scales in the analyses. Therefore, we performed Cox proportional-hazards regression models with age as the timescale to study the age at menarche that are significantly associated with the timing of the asthma onset.

Limitations

The main limitation of this study is that the definitions of age at menarche and asthma were based on self-report rather than medical records, which might cause recall bias. Continuous available examination data or prospective study design should be considered to help increase the reliability in the further studies.

Conclusions

In summary, this study provides a comprehensive picture of association of age at menarche with childhood- and adult-onset asthma among the US girls and women. The observed linear association between age at menarche and risk of childhood-onset asthma provided evidence for the detrimental effect of precocious puberty on respiratory health during childhood and adolescence. These findings emphasize the needs and importance of precocious interventions for prevention of asthma, especially during childhood and adolescence.

Abbreviations

NHANES: National Health and Nutrition Examination Survey

NCHS: National Center for Health Statistics

BMI: Body mass index

HRs: Hazard ratios

CIs: confidence intervals

Declarations

Ethics approval and consent to participate

NHANES was approved by the National Center for Health Statistics (NCHS) research ethics review board (Protocol #98-12, #2005-06, #2011-17, and #2018-01), and all the adult participants enrolled had written consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available at NHANES official website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.Z. and Y.L. supervised the entire study, including procedures, conception, design, and completion. L.C. were major contributors in data analysis and writing the manuscript. L.C., L.Q., Y.W., L.W., X.W., and R.X. participated in the interpretation of the data and in revisions to the article. All authors read and approved the final manuscript.

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Tables

Table 1. Unweight Sample Sizes for US population from the NHANES, 2001-2018 (N=24,282).

Variable	No. (%) of participants			
	Overall	Age at menarche, year		
		Early menarche (<12 years)	Normal menarche (12-14 years)	Late menarche (≥15 years)
No. of participants	24,282	5937	15,378	2967
Age group, year				
<20	5240 (21.6)	1809 (30.5)	3264 (21.2)	167 (5.6)
20-39	6732 (27.7)	1636 (27.6)	4304 (28.0)	792 (26.7)
40-59	6654 (27.4)	1425 (24.0)	4205 (27.3)	1024 (34.5)
≥60	5656 (23.3)	1067 (18.0)	3605 (23.4)	984 (33.2)
Race				
Mexican American and other Hispanic	7080 (29.2)	1964 (33.1)	4305 (28.0)	811 (27.3)
Non-Hispanic white	9400 (38.7)	2000 (33.7)	6347 (41.3)	1053 (35.5)
Non-Hispanic black	5517 (22.7)	1535 (25.9)	3286 (21.4)	696 (23.5)
Other	2285 (9.4)	438 (7.4)	1440 (9.4)	407 (13.7)
Ratio of family income to poverty				
<1	5388 (22.2)	1421 (23.9)	3287 (21.4)	680 (22.9)
≥1	17045 (70.2)	4067 (68.5)	10925 (71.0)	2053 (69.2)
Unknown	1849 (7.6)	449 (7.6)	1166 (7.6)	234 (7.9)
Family history of asthma				
Yes	5043 (20.8)	1378 (23.2)	3078 (20.0)	587 (19.8)
No	16,307 (67.2)	3605 (60.7)	10,460 (68.0)	2242 (75.6)
Unknown	2932 (12.1)	954 (16.1)	1840 (12.0)	138 (4.7)
Asthma				
Childhood-onset asthma*	560 (2.3)	234 (3.9)	301 (2.0)	25 (0.8)
Adult-onset asthma†	1623 (6.7)	401 (6.8)	1008 (6.6)	214 (7.2)
No asthma	22,099 (91.0)	5302 (89.3)	14,069 (91.5)	2728 (91.9)

*Childhood-onset asthma was using models with censoring age at 19 years, and participants first had asthma at age of 20 or more were treated as non-asthmatics

†Adult-onset asthma was using models with censoring age at 79 years, after excluding those suffered from asthma before 20.

Table 2. Hazard Ratios for Childhood- and Adult-onset Asthma Associated with Age at Menarche in US girls and Women.

Type of asthma	Model	Hazard ratios (95%CI)				*p* value for trend†
		Each one-year old increase *	Age at menarche, years			
			Early menarche (<12 years)	Normal menarche (12-14 years)	Late menarche (≥15 years)	
Childhood-onset asthma‡ (N=24,282)						
	Model 1‖	0.81 (0.75, 0.89)	1.67 (1.28, 2.19)	1 (ref)	0.57 (0.31, 1.05)	<0.0001
	Model 2**	0.83 (0.77, 0.90)	1.60 (1.22, 2.09)	1 (ref)	0.59 (0.32, 1.08)	<0.0001
Adult-onset asthma§ (N=23,722)						
	Model 1‖	0.97 (0.94, 1.00)	1.07 (0.92, 1.24)	1 (ref)	0.87 (0.71, 1.06)	0.06
	Model 2 **	0.97 (0.94, 1.01)	1.04 (0.90, 1.21)	1 (ref)	0.86 (0.70, 1.04)	0.10

*Estimated changes for the relationship of age at menarche with risk of adult asthma was conducted by continuous analyses.

† *p* values for trend of the coefficients in categorical analyses are the *p* values for the estimated changes by the age at menarche as continuous variable.

‡Childhood-onset asthma was using models with censoring age at 19 years, and participants first had asthma at age of 20 or more were treated as non-asthmatics

§Adult-onset asthma was using models with censoring age at 79 years, after excluding those suffered from asthma before 20.

‖Model 1 included only age at menarche.

**Model 2 were further adjusted for race, income, height, and family history of asthma.

Table 3. Hazard Ratios for Childhood- and Adult-onset Asthma Associated with Age at Menarche by Stratified Analysis.

Type of asthma	Variates	Age at menarche, year*			*p* value for effect modification
		Early menarche (<12 years)	Normal menarche (12-14 years)	Late menarche (≥15 years)	
Childhood-onset asthma† (N=24,282)					
	Race				0.71
	Mexican American and other Hispanic	2.05 (1.17, 3.61)	1 (ref)	0.93 (0.39, 2.21)	
	Non-Hispanic white	1.59 (1.13, 2.24)	1 (ref)	0.65 (0.31, 1.37)	
	Non-Hispanic black	1.47 (1.07, 2.03)	1 (ref)	0.48 (0.18, 1.25)	
	Other	1.27 (0.54, 2.95)	1 (ref)	0.04 (0.01, 0.30)	
	Ratio of family income to poverty				0.99
	<1	1.71 (1.10, 2.65)	1 (ref)	0.47 (0.20, 1.10)	
	≥1	1.60 (1.17, 2.19)	1 (ref)	0.66 (0.31, 1.41)	
	Family history of asthma				0.54
	Yes	1.64 (1.08, 2.49)	1 (ref)	0.41 (0.20, 0.84)	
	No	1.52 (1.04, 2.22)	1 (ref)	0.80 (0.36, 1.80)	
Adult-onset asthma‡ (N=23,722)					
	Race				0.47
	Mexican American and other Hispanic	0.84 (0.63,	1 (ref)	0.81 (0.56,	

		1.11)		1.17)	
	Non-Hispanic white	1.03 (0.86, 1.24)	1 (ref)	0.86 (0.67, 1.12)	
	Non-Hispanic black	1.28 (0.98, 1.66)	1 (ref)	1.13 (0.82, 1.57)	
	Other	1.15 (0.70, 1.86)	1 (ref)	0.63 (0.35, 1.15)	
	Ratio of family income to poverty				0.90
	<1	1.14 (0.81, 1.62)	1 (ref)	1.32 (0.97, 1.80)	
	≥1	1.03 (0.86, 1.23)	1 (ref)	0.81 (0.64, 1.03)	
	Family history of asthma				0.67
	Yes	1.10 (0.88, 1.38)	1 (ref)	0.81 (0.56, 1.16)	
	No	1.01 (0.82, 1.25)	1 (ref)	0.88 (0.69, 1.13)	

*All models were adjusted for race, income, height, and family history of asthma, with excluding the stratification variable. Interaction testing was performed by including an interaction term of each covariate and age at menarche.

†Childhood onset asthma was using models with censoring age at 19 years, and participants first had asthma at age of 20 or more were treated as non-asthmatics.

‡Adult-onset asthma was using models with censoring age at 79 years, after excluding those suffered from asthma before 20.

Figures

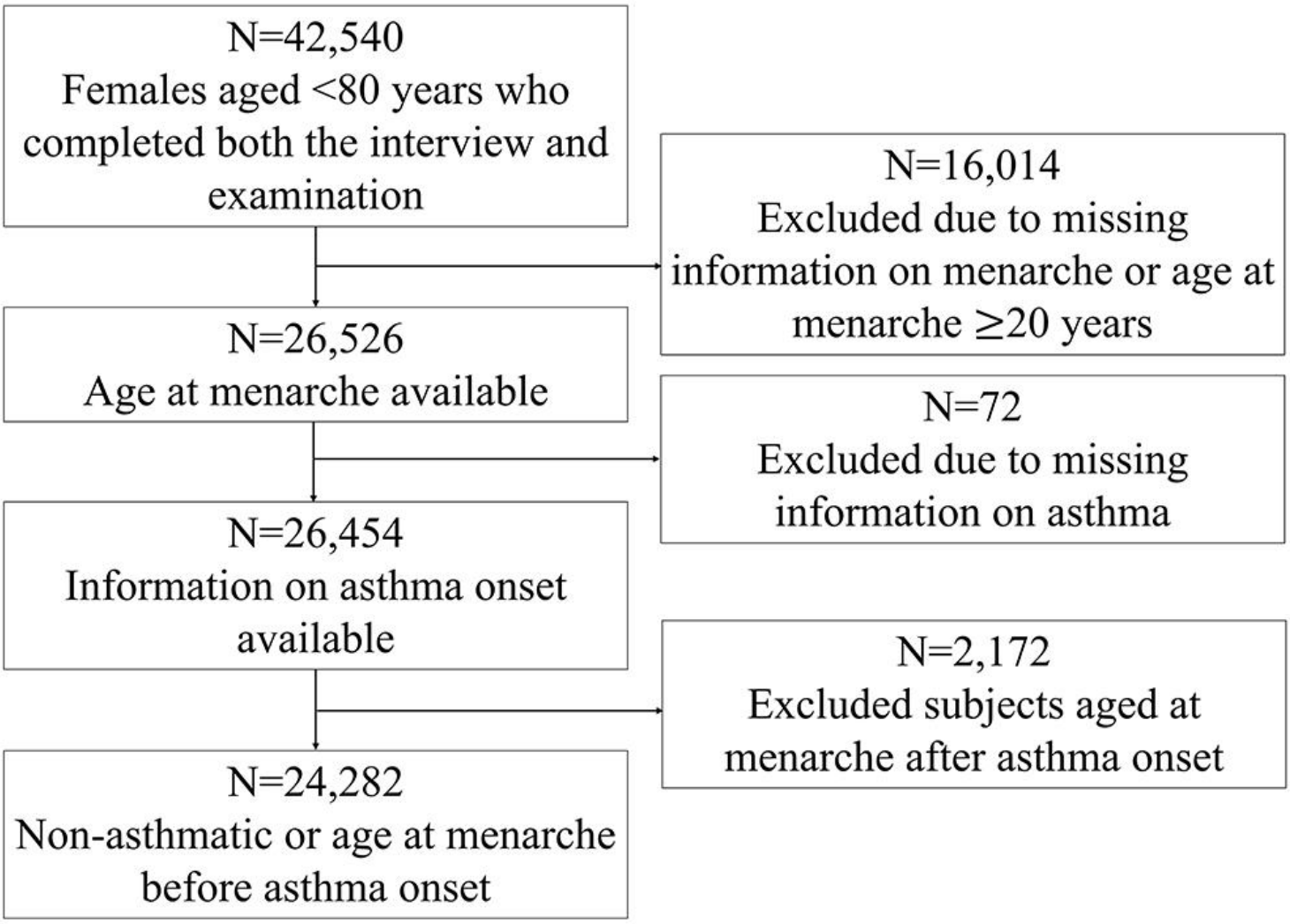

Figure 1

Unweighted sample sizes for the selected process of the study participants in NHANES, 2001-2018.

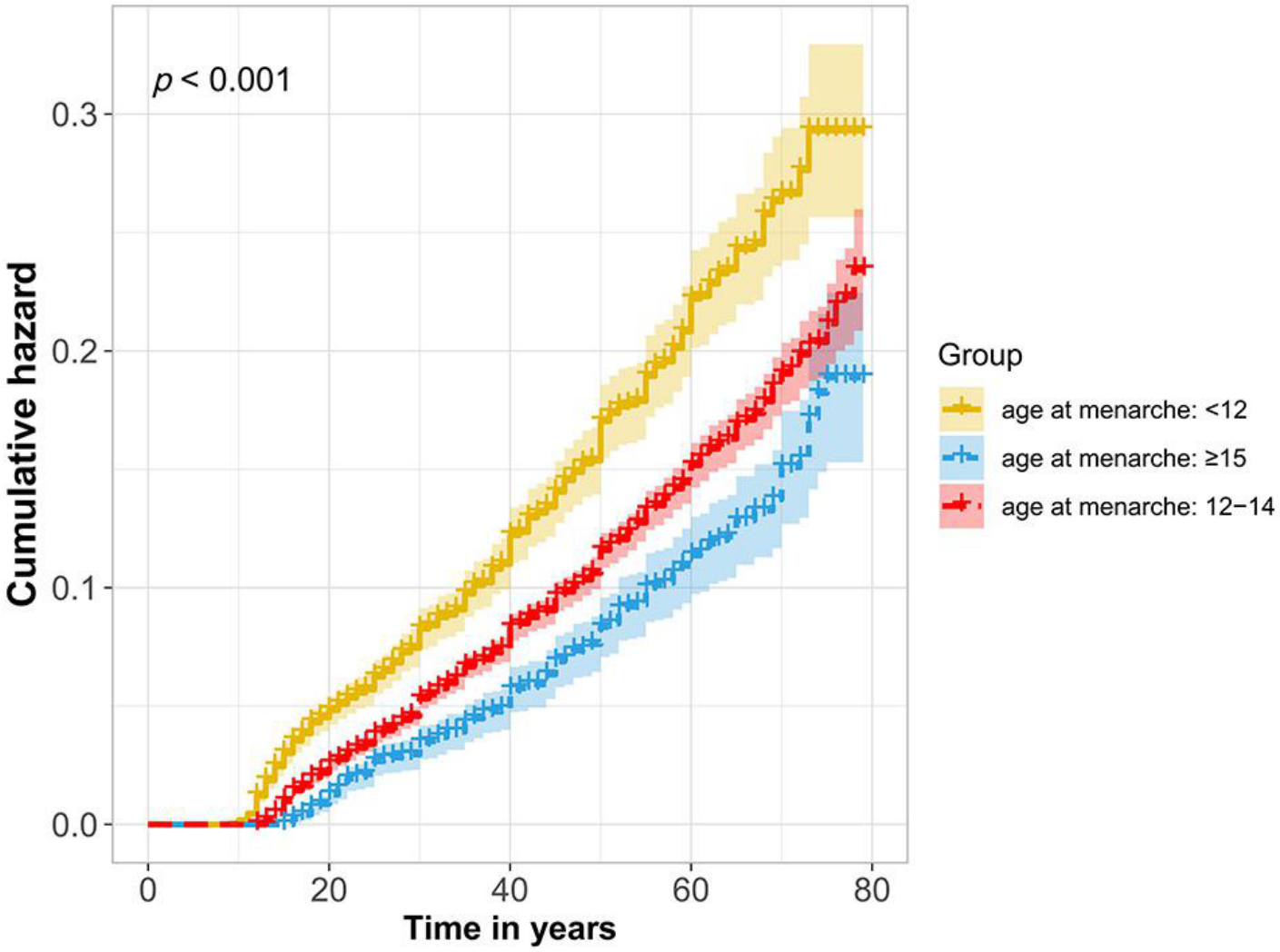

Figure 2

Cumulative-hazard rates in participants with early menarche (yellow broken line), normal menarche (red broken line) and late menarche (blue broken line) from the National Health and Nutrition Examination Survey, 2001-2018 (N=24,282).