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Association of Age at Menarche and Menstrual Characteristics with Adult Onset Asthma among Reproductive Age Women

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Abstract

Background—Observations of increasing asthma incidence, decreasing age at menarche, and common risk factors have led investigators to hypothesize potential associations of age at menarche or menstrual characteristics with incidence of adult onset asthma. We evaluated these associations among reproductive age women.

Methods—Study participants were selected from among women enrolled in a pregnancy cohort study. Information on age at menarche, menstrual characteristics, and history of asthma was collected using interviewer-administered questionnaires. Adult onset asthma was defined as asthma first diagnosed after onset of menarche. Women who had no information on asthma and menstrual history and those who were diagnosed with asthma before menarche were excluded. A total of 3,461 women comprised the analytic population. Logistic regression was used to estimate adjusted relative risk (aRR) and 95% confidence intervals (95% CI) relating age at menarche and menstrual characteristics with adult onset asthma.

Results—Mean age at menarche was 12.8 years (standard deviation=1.46). Among study participants, 7.5% were diagnosed with asthma after the onset of menarche. After controlling for potential confounders (age, race, body mass index, and socio-economic status), women who had early menarche (<12 years old) had 60% higher risk of being diagnosed with adult onset asthma as compared with women who did not have early menarche (≥ 12 years old) (aRR= 1.59, 95% CI 1.19 – 2.13). Menstrual irregularities or abnormal (short or long) cycle length were not associated with risk of adult onset asthma. In addition, no significant interaction was observed between age at menarche or menstrual characteristics with body mass index or physical activity (in adolescence) in relation to adult onset asthma.

Conclusion—Early menarche is associated with a higher risk of developing adult onset asthma among reproductive age women. Mechanisms for this association are potential areas of future research.

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Background and significance

Asthma, a complex disease with adverse outcomes, presents an ongoing public health challenge in the United States [1–2]. Etiologic factors of asthma and associated mechanisms have not been fully described. Observations of increasing asthma incidence, decreasing age at menarche, common risk factors led investigators to hypothesize potential associations of age at menarche or menstrual characteristics with incidence of adult onset asthma [3].

Investigators have hypothesized the role of several pathophysiologic pathways (including those that involve hormonal changes) in the development of asthma [4]. Higher levels of leptin and increased insulin resistance in women with early menarche may influence inflammation and innate immunity, potentially contributing to higher risk of asthma [5–8]. Early menarche, menstrual irregularity, and longer cycle length have been shown to be risk factors for asthma symptoms, adult onset asthma, and bronchial hyperreactivity in some [3, 6, 9–12] but not all [5, 13] studies. Potential reasons for observed inconsistencies could be differences in study population characteristics (e.g. obesity), including those that may modify observed associations [14–15]. To date, few US studies have examined associations of age at menarche, menstrual regularity or cycle length with adult onset asthma; and, even fewer evaluated role of potential effect modifiers (such as overweight/obesity status or physical activity).

The objectives of this study were to examine associations of age at menarche and menstrual characteristics with adult onset asthma among reproductive age women and to evaluate the extent to which potential effect modifiers influence these associations. Findings of this study may enhance understanding of risk factors of incident adult onset asthma and identification of high risk populations for targeted preventive interventions.

Methods

Overview and study setting

The current study was conducted in the setting of the Omega study. The Omega study (1996–2008), a prospective cohort study, was designed to investigate risk factors and outcomes of pregnancy complications among women attending prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Seattle, Washington and Tacoma, Washington, respectively. The Omega study was conducted at the Center for Perinatal Studies, Swedish Medical Center in Seattle, Washington.

Study participants (Figure 1)

Participants for the current study were selected from among Omega study participants. Omega study participants were pregnant women who initiated prenatal care before 20 weeks of gestation. Eligible participants were > 18 years old, were able to speak and read English, plan to carry the pregnancy to term, and planned to deliver at either of the two research hospitals. A total of 5,063 eligible women were approached during the study period and 4,000 (79%) were enrolled in the study. For the current study, all Omega study participants with information on asthma and age at menarche were included (N=3,683) (Figure 1). Women who had diagnosed asthma before their age at menarche were excluded (N=222). A

total of 3,461 women comprised the final analytic study population. The study protocol was approved by the Institutional Review Boards of the Swedish Medical Center and Tacoma General Hospital. All participants provided informed consent.

Data collection

Data were collected using in-person interviews, shortly after enrollment. Information was collected on age, race/ethnicity, educational attainment, height, weight at age 18 years, occupation, smoking, leisure time physical activity during ages 13 – 17 years, and, detailed reproductive, medical, and family histories (including history of chronic hypertension and diabetes mellitus). Age at menarche was based on subjects' self-reported age at menarche in response to the question "At what age did you have your first menstrual period?" Cycle length was based on the response to the question "On average, how often did you have your menstrual period? That is, how many days were there between the first day of one menstrual period and the first day of the next?" Information on menstrual regularity was based on the response to the question "During the first year after starting your menstrual periods, did your periods become regular? That is, could you predict within one week when your next menstrual period would begin?" and "Have your period ever been regular without using birth control pills, injection, or implants?"

History of asthma diagnosis was determined by self-report using the response to the question "Has a doctor ever told you that you have asthma?" Adult onset asthma was defined as asthma diagnosed one or more years after self-reported age at menarche. Body mass index (BMI) was computed by dividing weight (in kg) by height (in meters). Leisure time physical activity for teen (13–17) years was determined by using the response to the question "on average, how many hours each week did you participate in moderate / strenuous physical activity?" Moderate physical activity was defined as exercise which moderately increases heart rate, but enables talking while engaged in the activity. Strenuous physical activity was defined as physical activity which considerably increases heart rate, sweating, and makes it difficult to talk while engaged in the activity.

Statistical analysis

Descriptive analysis—The study population was characterized using number (%) and mean (standard deviations, SD) for categorical and continuous variables, respectively. Early menarche was defined as menarche occurring before age 12 years, which is one standard deviation less than the mean age at menarche among study participants. This distribution is comparable to previous reports [3]. Menstrual cycle regularity was categorized as a yes/no dichotomous variable. Participants were categorized into four menstrual cycle length categories consisting of ≤24, 25–30, 31–35, and ≥36 days. BMI at age 18 years was categorized into lean (BMI < 18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2) categories. Leisure time physical activity between ages 13 –17 years was categorized into a yes/no dichotomous variable. For categorical variables, chi-square tests were used to detect statistically significant differences in participant characterstics among strata defined by age at menarche or menstrual characteristics. Similarly, analyses of variance (one – way ANOVA) were used to examine

statistically significant differences in distribution of continuous variables among strata defined by age at menarche or menstrual characteristics.

Association analyses

We used logistic regression to estimate unadjusted and adjusted relative risks (RRs and aRRs, respectively) and 95% confidence intervals (95% CIs) for associations of age at menarche, menstrual regularity, or menstrual cycle length with adult onset asthma. *A priori* identified confounders (e.g. age, race/ethnicity, BMI at age 18 years, educational status, smoking, leisure time physical activity during ages 13–17 years, parity, history of diabetes, and history of hypertension) as well as covariates that alter relative risks by 10% or more were considered as potential confounders and included in final adjusted models. The reference groups in models evaluating age at menarche, menstrual regularity, or cycle length as risk factors were participants whose age at menarche was ≥12 years, had regular menstrual cycles, and had cycle length between 25–30 days, respectively. In logistic regression models, we tested for linear trend of associations by including continuous variables representing ordered categories of the exposure variable (of interest) and examining p-values for the beta coefficients (p-value for trend).

Effect modification analyses

Effect modifications of associations of age at menarche, menstrual regularity, or menstrual cycle length with adult onset asthma by potential modifiers (BMI at age 18 years and leisure time physical activity between ages 13 and 17 years) were assessed by fitting stratified models (stratified by potential modifier). In addition, joint models were fit that included terms representing the exposure, the potential modifier, and an interaction term. In these analyses, the interaction term p-value was used to test for statistical significance of interactions.

A two sided p-value < 0.05 was used to determine statistical significance. All analyses were conducted using STATA 10.1 software (Stata Corp, College Station, TX).

Results

General characteristics of study participants, according to age at menarche, menstrual regularity, and menstrual cycle length, are presented in Table 1. The average age at menarche was 12.8 years (SD=1.5). Among study participants, 14.2% (N=506) had early menarche (menarche before age 12 years) (Table 1). In addition, 7.5% (N=261) of participants were diagnosed with asthma after the onset of menarche. The prevalence of adult onset asthma among women who had early menarche was significantly higher (10.9%) compared with (7%) among women who did not have early menarche (p-value <0.005). The prevalence of adult onset asthma among participants who had irregular menstrual cycles (N=504, 14.6%) was comparable to the prevalence among participants who had regular menstrual cycles (7.1% vs. 7.4%, respectively). Similarly, the prevalence of asthma was comparable (range from 7.2% to 8.5%) among participants in the different strata defined by menstrual cycle length.

Among 25–34 year old participants, those who had early menarche had higher prevalence of adult onset asthma compared with participants who did not have early menarche (24.1% vs. 13.8%) (p-value < 0.05) (Figure 2). Among participants who were either <25 years old or ≥35 years old, the difference in prevalence of adult onset asthma among participants with or without early menarche was not significantly different (25.0 % vs. 29.4% and 15.8% vs. 13.1%, respectively) (p-values >0.05 in both comparisons).

In the study population, women with early menarche had a 60% higher risk of adult onset asthma as compared with women who did not have early menarche: RR= 1.56 [95% CI 1.17, 2.07] (Table 2). The association of early menarche with adult onset of asthma remained significant after adjustment for potential confounders (including age, race, educational status, BMI at age 18 years, history of diabetes, physical activity and marital status: aRR = 1.59 [95% CI 1.19, 2.13]. Neither menstrual irregularities nor menstrual cycle length was associated with risk of adult onset asthma.

In effect modification analyses (Tables 3 and 4), we found no significant interactions of age at menarche or menstrual characteristics with either BMI at age 18 or physical activity during ages 13–17 on risk of adult onset asthma.

Discussion

In this cohort study, early menarche was associated with a higher risk of developing adult onset asthma. Women with early menarche (<12 years) had a 60% higher risk of adult onset asthma as compared with women who did not have early menarche (≥12 years old). We did not observe associations of menstrual regularity and menstrual cycle length with adult onset asthma. In addition, BMI at age 18 years and leisure time physical activity during ages 13–17 years did not modify observed associations.

Few previous studies have evaluated associations of early menarche and risk of adult onset asthma [3, 6, 12]. Some of the findings of these earlier studies are similar to ours [3, 6, 12]. Al-Sahab et al examined association of early menarche with incidence of adult onset asthma in a prospective cohort of Canadian women. In that study, the authors reported that participants with early menarche (menarche before 11.56 years) had more than twice the risk of developing asthma during adulthood compared with participants who did not have an early menarche (adjusted odds ratio, aOR, 2.34, 95% CI; 1.19–4.59) [3]. Similarly, Salam et al, in their prospective cohort study among the California Children's Study participants, observed that women who had their menarche before 12 years of age were 2 times more likely (aOR=2.08, 95% CI; 1.05–4.12) to develop asthma later in adulthood compared with women who had menarche at or after age 12 years [12]. In the European Community Respiratory Health Survey, women with early menarche (≤ 10 years) had more frequent asthma (aOR=1.80, 95% CI; 1.09–2.97) and asthma with bronchial hyper reactivity (aOR=2.79, 95% CI; 1.06–7.34) symptoms compared with women who had menarche when they were 13 years old [6].

However, our findings of increased risk of adult onset asthma among women with early menarche are not in accordance with other previous reports [5, 13]. Burgess et al reported

that age at menarche was not associated with asthma that developed between 7 and 21 years of age (aOR=0.99, 95% CI; 0.73–1.33; p-value=0.93) or after 21 years of age (aOR=0.96, 95% CI; 0.70–1.30; p-value=0.78) [13]. Jartii et al also reported that age at menarche was not associated with prevalent asthma among participants who were 24–39 years old [5].

We did not observe significant associations of irregular menses or long cycles with risk of asthma reported by investigators of previous studies. Svanes et al, in a study conducted among 8,588 women enrolled in the European Community Respiratory Health Survey, found significant associations of irregular menses with asthma (aOR=1.54, 95% CI; 1.11–2.13) [16]. In the same study population, among 28 – 44 year old participants long menstrual cycles were significantly associated with frequent asthma symptoms (aOR=1.76, 95% CI; 1.29–2.40) and allergic asthma (aOR=2.46, 95% CI; 1.43–4.23) [17].

Various mechanisms have been proposed for observed potential association between early menarche and adult onset asthma. Sex hormones like estrogen, through their function as immune modulators and potential interplay with metabolic factors, may result in airflow obstruction and increased bronchial hyper-responsiveness [18]. Female sex steroids, estrogen and progesterone, are known pro-inflammatory hormones involved in increased susceptibility to asthma and other inflammation related complications (such as diabetes mellitus and cardiovascular diseases) [18–20]. Women who have early menarche would have been exposed to these pro-inflammatory hormones very early [12] which increases their risk of developing asthma [5–8]. Other hormones that constitute the hypothalamic-pitutary-gonadal axis can also potentially contribute to associations of early menarche and onset of asthma [21]. For instance, leptin, which has been associated with early menarche [21] increases proliferative responses of CD4+ T cells, activation of mast cells, transcription factors (AP-1 and NFκB), or interferon gamma responses, all of which result in reduced lung function (forced expiratory volume in one second, FEV1 and forced expiratory vital capacity, FVC) and asthma symptoms [21–22]. In addition, insulin resistance, which may occur with irregular menses or early menarche, has been associated with lower lung function and asthma symptoms [5, 2, 7, 8]. Therefore, risk factors (e.g. obesity) and pathologic mechanisms (e.g. elevated leptin levels) related to insulin resistance may result in associations of lower age at menarche with increased risk of asthma.

Our study has multiple strengths. It adds to the few studies in the US examining associations of age at menarche or menstrual characteristics with adult onset asthma. The cohort design, the well characterized study population, and the large sample size allow for adequate characterization of the relationships. In addition, we were able to control for multiple potential confounders and evaluate potential effect modifiers of examined associations.

Our study has some limitations. First, we defined participants' asthma status from participant's self-report of "physician-diagnosed asthma". This may lead to possible misclassification and under-diagnosis of asthma. However, the use of self-report of physician diagnosed asthma to ascertain asthma status has been widely used in many epidemiological studies; and, good agreement with kappa values ranging from 0.7 to 0.9 had been reported between self-reported data on asthma diagnosis and data pooled from medical records [12, 23]. Second, we have used self-report of age at menarche, menstrual

characteristics, and related covariates which can also lead to potential misclassification due to recall bias. However, previous studies (including validation studies) have shown that these events are significant events in a woman's life and overall a women's recall regarding these events is accurate with minimal recall bias [24]. The measurement of leisure time physical activity during ages 13 – 17 using questionnaires is susceptible to misclassification due to recall error. However, this likely is non-differential and could have resulted in underestimation of the role of physical activity in the associations. Third, confounding by unmeasured characteristics such as exposure to non-steroidal anti-inflammatory drugs or use of hormonal contraceptives, as well as residual confounding are possible. Finally, our study participants comprised of mostly Non-Hispanic White and well-educated women which would limit generalizability of our findings. The concurrence of our findings with findings from earlier studies of different geographically, racially and ethnically diverse populations lessens this concern.

In summary, we found increased risk of adult onset asthma among reproductive age women who had early menarche compared with their counterparts who did not have early menarche. We did not find associations of menstrual irregularity or long cycle length with risk of adult onset asthma. Mechanistic studies and large, well- designed prospective cohort studies among different socio-culturally diverse study populations will enable clearer understanding of relationships between age at menarche, menstrual characteristics, and risk of adult onset asthma. This will eventually facilitate institution of preventive efforts to improve lung health among reproductive age women.

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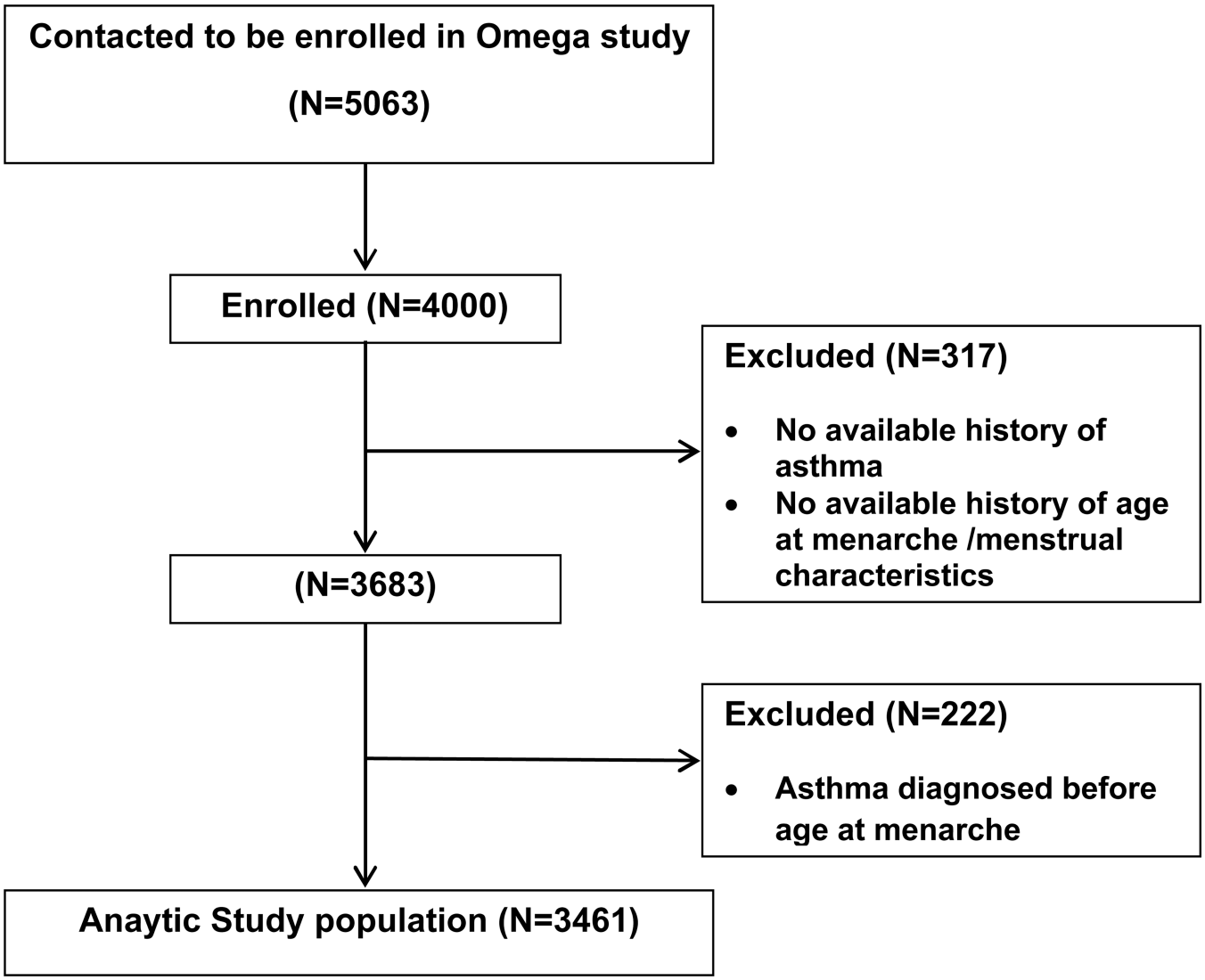

Figure 1.
Flow Chart of Study Participants

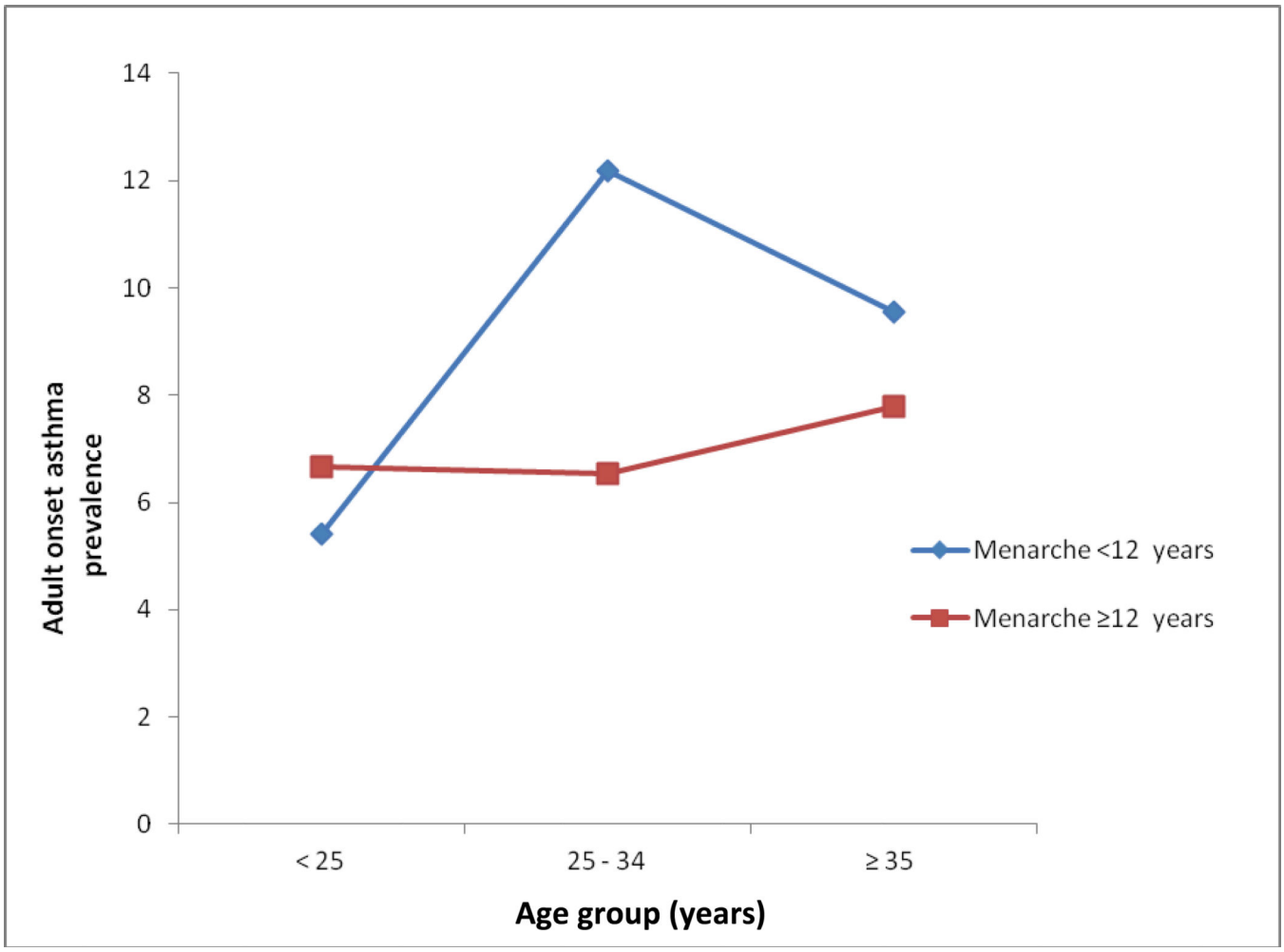

Figure 2.
Age at Menarche and Adult Onset Asthma by Age Group

Table 1

Selected characteristics of the study population by age at menarche and menstrual characteristics

		Cohort	Early menarche*		Regular menses		Cycle length (days)			
			Yes	No	Yes	No	<24	25 – 30	31 – 35	≥36
Maternal characteristics	**N= (3461)**		**N= (506)**	**N= (2955)**	**N= (2951)**	**N= (504)**	**N= (166)**	**N= (2534)**	**N= (479)**	**N= (282)**
Age (years)*		32.7 ±4.5	32.0 ±4.9	32.8 ±4.4	32.7 ±4.5	32.8 ±4.5	31.8 ±4.6	33.0 ±4.6	32.7 ±4.1	31.8 ±3.9
	<25	127 (3.7)	37 (7.3)	90 (3.0)	13 (2.6)	114 (3.9)	8 (4.8)	101 (4.0)	8 (1.7)	10 (3.5)
	25 – 34	2151 (62.1)	312 (61.7)	1839 (62.2)	312 (62.9)	1834 (62.1)	107 (64.5)	1515 (59.8)	329 (68.7)	200 (70.9)
	≥35	1183 (34.2)	157 (31.0)	1026 (34.7)	179 (35.5)	1003 (34.0)	51 (30.7)	918 (36.2)	142 (29.6)	72 (25.5)
NH White[a]		3000 (86.9)	395 (78.4)	26.0 (88.2)¥	2564 (86.9)	431 (85.5)	148 (89.2)	2195 (86.7)	416 (86.5)	241 (85.8)¥
High school completed		3327 (96.1)	474 (93.7)	2853 (96.5)¥	2837 (96.1)	484 (96.0)	156 (93.9)	2426 (95.7)	475 (99.2)	270 (95.7)¥
Married		3162 (91.4)	448 (88.5)	2714 (91.8)¥	2694 (91.3)	462 (91.7)	151 (90.9)	2292 (90.4)	461 (96.2)	258 (91.5)¥
Nulliparous		2175 (62.8)	314 (62.1)	1861 (62.9)	1858 (62.9)	315 (62.5)	103 (62.0)	1593 (62.9)	297 (62.0)	182 (64.5)
BMI at age 18, kg/m²** ‡		20.7 ±2.9	21.77 ±3.6	20.5 ±2.79¥	20.7 ±2.9	20.7 ±2.7	20.5 ±2.8	20.7 ±2.9	20.4 ±2.6	20.9 ±3.6
	<18.5	2569 (75.4)	374 (75.4)	2195 (75.4)	2184 (75.1)	381 (76.7)	121 (74.7)	1884 (75.5)	360 (76.3)	204 (73.1)
	18.5–24.9	616 (18.1)	56 (11.3)	560 (19.2)	527 (18.1)	87 (17.5)	34 (20.1)	436 (17.7)	89 (18.9)	57 (20.4)
	25–29.9	170 (4.9)	45 (9.1)	125 (4.3)	146 (5.0)	24 (4.8)	5 (3.1)	136 (5.4)	20 (4.2)	9 (3.2)
	≥30	53 (1.6)	21 (4.2)	32 (1.1)	48 (1.6)	5 (1.0)	2 (1.2)	39 (1.6)	3 (0.6)	9 (3.2)
Physically active**		3248 (93.8)	473 (93.5)	2775 (93.9)	2768 (93.8)	474 (94.0)	156 (93.9)	2369 (93.4)	456 (95.2)	267 (94.7)
History of hypertension		170 (4.9)	29 (5.7)	141 (4.7)	149 (5.0)	20 (4.0)	9 (5.4)	121 (4.8)	27 (5.6)	13 (4.6)
History of diabetes mellitus		44 (1.3)	13 (2.6)	31 (1.0)¥	39 (1.3)	4 (0.8)	1 (0.6)	34 (1.3)	4 (0.8)	5 (1.8)
Never smoker		2494 (72.3)	355 (70.4)	2139 (72.7)	2123 (72.2)	367 (73.0)	116 (69.9)	1796 (71.2)	364 (76.3)	218 (77.6)
Adult onset asthma		261 (7.5)	55 (10.9)	206 (6.9)¥	219 (7.4)	36 (7.1)	10 (6.0)	193 (7.6)	34 (7.1)	24 (8.5)

*Early menarche age <12years

**Mean (SD) otherwise n (%).

‡Body mass index (kg/m^2)*

***Between age 13 –17 years

¥p-value <0.05

[a]NH – Non-Hispanic

Table 2

Associations of age at menarche, menstrual characteristics, and adult onset asthma

	Adult onset asthma		Unadjusted	Adjusted*
Characteristics	**Yes (N=261)**	**No (N=3200)**	**RR 95% (CI)**	**RR 95% (CI)**
Early Menarche*				
No	206 (78.93)	2749 (85.91)	Referent	Referent
Yes	55 (21.07)	451 (14.09)	1.56 (1.17,2.07)	1.59 (1.19,2.13)
P- value			0.002	0.002
Regular Menses				
Yes	219 (85.88)	2732 (85.38)	Referent	Referent
No	36 (14.12)	468 (14.63)	0.96 (0.68,1.35)	0.95 (0.67,1.34)
P- value			0.825	0.774
Menstrual Cycle Length (days)				
<24	10 (3.83)	156 (4.88)	0.79 (0.43,1.46)	0.81 (0.44,1.51)
25 – 30	193 (73.95)	2341 (73.16)	Referent	Referent
31 – 35	34 (13.03)	445 (13.91)	0.93 (0.65,1.32)	0.88 (0.61,1.27)
≥36	24 (9.20)	258 (8.06)	1.11 (0.74,1.67)	1.08 (0.71,1.63)
	Trend P- value			0.238

*Adjusted for age, race/ethnicity, BMI at age 18 years, educational status, smoking, physical activity between ages 13 – 17 years, parity, history of diabetes and history of hypertension

Table 3

Interaction of Age at Menarche and Menstrual Characteristics with Body Mass Index on Adult Onset Asthma

	Adult onset asthma		Stratified model		Joint model	
Characteristics	**Yes (N=257)**	**No (N=3151)**	**Adj. RR**	**95% (CI)**	**Adj. RR**	**95% (CI)**
BMI at age 18 and age at menarche						
<25kg/m^2,> 11 years	191 (81.28)	2564 (86.92)	Referent	Referent	Referent	Referent
<25kg/m^2,≤ 11 years	44 (18.72)	386 (13.08)	1.52	(1.10,2.08)	1.5	(1.11,2.05)
≥25kg/m^2,> 11 years	12 (54.55)	145 (72.14)	Referent	Referent	1.1	(0.62,1.94)
≥25kg/m^2,≤ 11 years	10 (45.45)	56 (27.86)	1.99	(0.87,4.55)	2.18	(1.19,3.98)
P-value for interaction						0.523
BMI at age 18 and menstrual regularity						
<25kg/m^2, regular menses	198 (86.46)	2513 (85.19)	Referent	Referent	Referent	Referent
<25kg/m^2, irregular menses	31 (13.54)	437 (14.81)	0.91	(0.63,1.31)	0.91	(0.63,1.31)
≥25kg/m^2, regular menses	18 (81.82)	176 (87.56)	Referent	Referent	1.25	(0.78,2.00)
≥25kg/m^2,irregular menses	4 (18.18)	25 (12.44)	1.59	(0.57,4.44)	1.84	(0.73,4.63)
P-value for interaction						0.384
BMI at age 18 and usual cycle length						
<25kg/m^2, < 36 days	208 (90.83)	2715 (92.50)	Referent	Referent	Referent	Referent
<25kg/m^2, ≥36 days	21 (9.17)	220 (7.50)	1.23	(0.80,1.89)	1.23	(0.80,1.89)
≥25kg/m^2, <36 days	20 (90.91)	182 (91.46)	Referent	Referent	1.36	(0.87,2.13)
≥25kg/m^2, ≥36 days	2 (9.09)	17 (8.54)	1.07	(0.26,4.31)	1.51	(0.41,5.66)
P-value for interaction						0.886

Adjusted for – age, race/ethnicity, educational status, smoking, physical activity between ages 13 – 17yrs, parity, history of diabetes and history of hypertension

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Table 4

Interaction of Age at Menarche and Menstrual Characteristics with Physical Activity on Adult Onset Asthma

	Adult onset asthma		Stratified model		Joint model	
Characteristics	**Yes (N=257)**	**No (N=3151)**	**Adj. RR**	**95% (CI)**	**Adj. RR**	**95% (CI)**
Physically active and age at menarche						
Yes, >11 years	199 (78.97)	2576 (85.98)	Referent	Referent	Referent	Referent
Yes, ≤11 years	53 (21.03)	420 (14.02)	1.6	(1.19,2.15)	1.58	(1.18,2.13)
No, >11 years	7 (77.78)	173 (84.80)	Referent	Referent	0.56	(0.26,1.18)
No, ≤11 years	2 (22.22)	31 (15.20)	2.21	(0.51,9.59)	0.95	(0.24,3.65)
P-value for interaction						0.943
Physically active and menstrual regularity						
Yes, regular menses	212 (86.18)	2556 (85.31)	Referent	Referent	Referent	Referent
Yes, irregular menses	34 (13.82)	440 (14.69)	Referent	(0.65, 1.32)	0.93	(0.65, 1.32)
No, regular menses	2 (22.22)	28 (13.73)	Referent	Referent	0.52	(0.25,1.10)
No, irregular menses	7 (77.78)	176 (86.27)	1.11	(0.22,5.67)	0.89	(0.23,3.41)
P-value for interaction						0.668
Physically active and usual cycle length						
Yes,<36 days	7 (77.78)	186 (91.63)	Referent	Referent	Referent	Referent
Yes,≥36days	2 (22.2)	17 (8.37)	2.51	(0.58, 10.77)	2.83	(0.63,12.68)
No, <36days	224 (91.06)	2758 (92.55)	Referent	Referent	2.80	(0.95, 4.18)
No, ≥36 days	22 (8.94)	222 (7.45)	1.16	(0.76,1.78)	2.33	(1.01,5.36)
P-value for interaction						0.262

Adjusted for age, race/ethnicity, BMI at age 18, educational status, smoking, parity, history of diabetes and history of hypertension, * physical activity for teen years (13– 17) years