

Early menarche and new onset of asthma: Results from the SAPALDIA cohort study



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ABSTRACT

Rationale: The association between early menarche and new onset of asthma warrants further investigation in those aged > 30 years.

Objectives: Using data from the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), we investigated whether early menarche was associated with new onset of asthma in women aged 18–60 years at baseline.

Methods: Our analysis included 2492 women with information on age at menarche and doctor-diagnosed asthma, who had been asthma free at the time of menarche and had complete covariate information. New onset of asthma was defined as newly reported doctor-diagnosed asthma which occurred at least one year after menarche. Asthma incidence and its association with early menarche was analysed using logistic regression, adjusting for age, atopy, smoking, BMI, parental asthma, urbanity, education and study area, and additionally stratifying by atopy and BMI.

Results: After adjustment of relevant confounders, women with early menarche did not have a significantly higher risk of onset of asthma than women without early menarche (OR 1.23, 95% CI 0.85–1.80). Young atopic women with early menarche appeared to have an increased risk of asthma compared with non-atopic women (OR 2.21, 95% CI 0.90–5.43); however, our results did not reach statistical significance.

Conclusion: We could not substantiate an association of early menarche with new onset of asthma in this Swiss population-based cohort aged 18–60 years at baseline. Future studies may need to prospectively assess age of menarche to investigate the association with new onset of asthma in those aged > 30 years.

1. Introduction

The gender-related life-course pattern of asthma is characterised by higher incident rates in boys than girls, followed by a female preponderance in early and middle-adulthood [1,2]. Because this switch takes place around puberty, hormonal factors have been suggested as one possible explanatory pathway. Observations of increasing asthma incidence and decreasing age at menarche, have led investigators to hypothesize potential associations of age at menarche with incident

asthma.

Studies have consistently found an association between early menarche and new-onset of asthma [3], at least in young adulthood. The cause for the observed association between early menarche and asthma is poorly understood. Some suggest that it could reflect genetic and early life environment as the timing of both events are affected by early life factors, or that menarche itself might induce immunological and hormonal changes as well as changes in airway function [4]. Higher levels of leptin and increased insulin resistance in women with

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early menarche may influence inflammation and innate immunity, potentially contributing to higher risk of asthma [5,6]. Animal studies have provided evidence that estrogen and progesterone have effects on humoral and cellular immunity and smooth muscle function [7]. Therefore, hormonal factors might be expected to be associated with the clinical occurrence of asthma in humans.

What remains unclear is whether the observed association between early menarche and asthma, also holds for older adulthood. With the exception of five studies [4,6,8–10], the association between early menarche and asthma incidence has not been investigated in adults > 30 years. Lieberoth et al. (2015) [4] found a significant association in women aged 12–41 years, Macsali et al. (2011) [8] in women aged 27–57 years, and Fida et al. (2012) [9] in women aged 18–35 years. However, in the study by Gnatiuc et al. (2013) [10] they did not find a significant association between early menarche and asthma at age 33 and neither did Jartti et al. (2009) [6] in women at ages 24–39 years. The association between early menarche and new-onset of asthma warrants further investigation in those aged > 30 years.

Making use of the on-going Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA), [11,12], we investigated whether early menarche was associated with new-onset of asthma in women aged 18–60 at baseline.

2. Methods

2.1. Study design & population

The “Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults” (SAPALDIA) (see Appendix A) was initiated in 1991 (SAPALDIA 1 [S1]) in eight geographically diverse areas in Switzerland, recruiting 9651 participants (51% female) aged 18–60 at baseline through random population sampling. Re-assessments took place in 2002/2003 (SAPALDIA2 [S2], $n = 8047$) and in 2010/2011 (SAPALDIA3 [S3], $n = 6088$). The protocol and participation rates have been described elsewhere [11,12]. Starting in SAPALDIA 2, the Women's Health Questionnaire of the European Community Respiratory Health Study was introduced [13] which included detailed questions on women's reproductive histories. This analysis includes 2,492 women who provided retrospective information on age at menarche in either S2 or S3, provided information on doctor-diagnosed asthma in at least S1, S2 or S3, reported asthma-onset after menarche, and had complete covariate information (Fig. 1). Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional committees, and written informed consent was obtained from all participants.

2.2. Definition of asthma and asthma incidence

New-onset of adult asthma was defined as newly reported doctor-diagnosed asthma at baseline or follow-up which occurred at least one year after reported age at menarche. Doctor diagnosed asthma was defined as a positive answer to both questions ‘have you ever had asthma?’ and ‘was this confirmed by a doctor?’ For the purpose of sensitivity analyses, two additional definitions of asthma were created: (a) self-report only and (b) doctor-diagnosed asthma with current medication.

2.3. Definition early menarche

The primary definition of early menarche used for our analysis, as also defined in other studies [4,10,14], was menarche < 12 years. If age of menarche was reported < 12 years in S2 or S3, then the individual was considered as having early menarche. For the purpose of sensitivity analyses, three further definitions were created based on other literature findings (Table 1): age at menarche 1 standard deviation (SD) less than the mean [7,9,15], age at menarche 2 SD less than the mean [16,17], and finally age at menarche 1 SD less than the language region

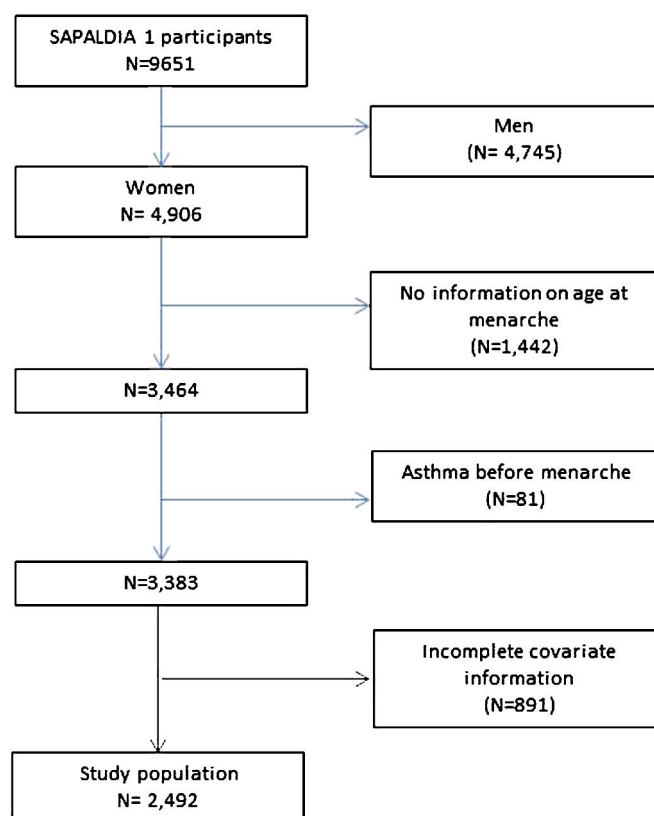


Fig. 1. Study population.

specific mean (German, French and Italian), based on findings by Dratva et al. (2007) that age at menarche differs in these three Swiss language regions [18]. Additionally, we grouped early menarche into a categorical variable of whole years and compared the risk of new-onset of asthma in women with menarche at 10 years to women with menarche at the mean age of menarche, as done by Macsali et al. (2011) [8].

2.4. Atopy & BMI

Atopy was defined as a positive response to the skin prick test or Phadiatop test (Phadia, Uppsala, Sweden) at baseline. Allergically sensitised subjects with doctor-diagnosed asthma were considered as having allergic asthma. Body mass index (BMI) at baseline was calculated as weight in kilograms, divided by the square of height in meters. For the descriptive tables and stratification by BMI, 3 categories were created according to the WHO cut off points (47) for underweight (BMI < 18.50), normal weight (BMI 18.50–24.99), and overweight/obese (BMI ≥ 25.00).

2.5. Further covariates

Smoking status at baseline, S2 and S3 were categorized as never-smoker, former-smoker and current-smoker. Smoking status at S3 was defined in a cumulative way, never-smokers being consistent never smokers across all three surveys, current smokers being smokers at S3, and ex-smokers being people who were smokers at S1 and/or S2, but not at S3. Education was categorized into primary education (low), secondary or middle school education (intermediate), and having a technical or university degree (high). For the descriptive tables and models, cumulative education, (the highest educational level reported at S1/S2), was used. Parental asthma was defined as a positive answer to the question ‘did one or both of your parents ever have asthma?’ Urbanity was defined as residing in the following study areas: Basel,

Table 1
Definitions of early menarche.

Short name	Definition	Literature with same definition
Early menarche	< 12 years	Lieberoth et al. (2014) [4] Gnatiuc et al., 2013 [10] Salam et al. (2006) [14] Wei et al. (2015) [7]
Early menarche 1SD	1 SD < mean	Fida et al. (2012) [9] Al-Sahab (2011) [15]
Early menarche 2SD	2 SD < mean	Varraso et al. (2005) [17] Burgess et al. (2007) [16]
Early menarche 1SD area	1 SD < language region specific mean (German, French, Italian)	Dratva et al. (2007) [18]

Lucano, Aarau or Geneva. All of these covariates were selected based on literature findings.

2.6. Statistical analysis

Asthma incidence and its association with early menarche was analysed using logistic regression adjusting for age (S1), atopy (S1), cumulative smoking (S1–S3), BMI (S1), parental asthma (S1), urbanity (S1), cumulative education (S1–S3) and study area (S1) as described above. Based on a priori reasons [1,10,19–22] we additionally stratified our analysis by atopy and BMI to see whether the patterns of determinants differed.

We conducted several sensitivity analyses. Firstly, to make our results comparable to other studies, we ran our analysis using three different early menarche definitions (Table 1) and in addition, grouped early menarche into a categorical variable of whole years as done by Macsali et al. (2011) [8].

Secondly, to assess whether early menarche might be associated with an increased asthma risk only for some limited years following menarche, we split occurrence of asthma into 3 groups: asthma occurring (a) 1–3 years after menarche, (b) 4–10 years after menarche and (c) more than 10 years after menarche.

Thirdly, to address the validity of recalled age of menarche, we restricted our analysis to those aged ≤ 30 years at baseline and also ran our analysis using information on age at menarche from S2 only—the earliest time point at which participants gave information on age at menarche. Furthermore, we analysed whether report of age at menarche differed with increasing time since menarche, calculating the Kappa statistic for agreement between reported age at menarche in S2 and S3 overall, as well as between the three created age groups at baseline (≤ 30 , 31–45, 46–60).

Fourthly, to address potential inconsistent reporting in age at menarche between the two surveys, we ran our analysis excluding women reporting early menarche only in one follow-up, as well as running our analysis excluding women who reported a difference in age of menarche in the two follow-ups of ≥ 1 year and ≥ 2 years.

Finally, to account for potential bias due to loss to follow up, models were furthermore run with inverse probability weighting and in addition, excluding covariates with the largest amount of missing information.

All analyses were conducted using Stata V.12 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Study population

Our study population consisted of 2492 women who provided information on age at menarche and doctor-diagnosed asthma, reported onset of asthma after menarche, and had complete covariate information (Fig. 1). The characteristics of the study population as well as of women excluded from the analyses are given by age at menarche in

Table 2. In our study population women with early menarche tended to be younger, atopic, and live in an urban environment. Women with early menarche who were excluded from our study, tended to be living in an urban environment, but did not significantly differ on other covariates.

3.2. Age at menarche & new-onset of asthma

The mean age at menarche was 13.5 years overall, varying from 13.1 years in the Italian language region, to 13.3 years in the French and 13.7 years in the German language region. 300 (12.0%) women reported age at menarche < 12 years at either S2 or S3. The percentage of women defined as having early menarche was considerably lower for the definition of < 2SD of mean age (2.3%). The highest percentage was seen when using 1SD below language region specific mean (19.1%). The percentage of women presenting new-onset of asthma at least 1 year after menarche was 10.0%.

3.3. Determinants of asthma incidence

The crude odds ratio (OR) for asthma incidence in women with menarche < 12 years compared to women with menarche ≥ 12 years was 1.50 (95% CI 1.05–2.15). In the fully adjusted analysis, the OR for early menarche was 1.23 (95% CI 0.85–1.80) (Table 3). To examine why our crude OR became statistically insignificant in our fully adjusted model, we added our covariates in a stepwise manner (Table S3a/S3b), selecting the order of variables for a priori reasons. The addition of urbanity, study area, BMI and atopy into our model decreased the odds ratio and the OR became statistically non-significant when entering study area.

3.4. Stratified analyses

When stratifying by atopy (Fig. 2), non-atopic women with menarche < 12 years had an OR for new-onset of asthma of 1.11 (95% CI 0.63–1.95), whereas atopic women had a OR of 1.36 (0.81–2.27).

When stratifying by BMI categories (Fig. 2), estimates for asthma-onset in overweight/obese women with early menarche were slightly higher (OR 1.51, 95% CI 0.76–3.00) than in normal weight women (OR 1.27, 95% CI 0.80–2.02), though CI's were overlapping. Underweight women had an OR 0.45 (95% CI 0.32–6.27), however the wide and overlapping CI's indicate a lack in power.

3.5. Sensitivity analyses

Running analyses with varying definitions of asthma did not change results (data not shown). When running the overall model using varying definitions of early menarche, the OR for asthma incidence in those having early menarche did not change much, varying from 1.23 (95% CI 0.85–1.80) to 1.25 (95% CI 0.90–1.73) (Table 3). When grouping early menarche into a categorical variable of whole years and comparing the risk of new-onset of asthma in women with menarche at 10

Table 2

General characteristics of study population and those excluded by age at menarche.

Adult characteristics	Study population ^a (N = 2,492)							Women excluded ^b (N = 2,414)						
	Total		Menarche < 12 yrs.		Menarche ≥ 12 yrs.		P-value	Total		Menarche < 12 yrs.		Menarche ≥ 12 yrs.		P-value ^c
	N	%	N	%	N	%		N	%	N	%	N	%	
Overall	2,492	100	300	12	2,192	88.0	–	2,414	100	119	12.2	853	87.8	–
Age							< 0.01							0.11
≤ 30	488	19.6	70	23.3	418	19.1		465	19.3	21	17.7	156	18.3	
31–45	1,036	41.6	134	44.7	902	41.2		920	38.1	57	47.9	311	36.5	
46–60	968	38.8	96	32.0	872	39.8		1,029	42.6	41	34.5	386	45.3	
Atopy	752	30.2	107	35.7	645	29.4	0.03	588	32.7	23	32.9	205	36.8	0.60
Smoking ^d							0.82							0.59
Never-smoker	1,287	51.7	150	50.0	1,137	51.9		318	46.8	27	45.8	163	47.4	
Former-smoker	813	32.6	102	34.0	711	32.4		222	32.7	18	30.5	118	34.3	
Current-smoker	392	15.7	48	16.0	344	15.7		140	20.6	14	23.7	63	18.3	
BMI							1.00							1.00
Underweight	144	5.8	12	4.0	132	6.0		153	6.5	9	7.9	57	6.8	
Normal weight	1,802	72.3	205	68.3	1,597	72.9		1,513	64.5	62	54.4	570	67.9	
Overweight/obese	546	21.9	83	27.7	436	21.1		679	30.0	43	37.7	212	25.3	
Parental asthma	286	11.5	38	12.7	248	11.3	0.50	271	11.2	16	13.6	108	12.7	0.77
Urban	1,208	48.5	168	56.0	1,040	47.5	< 0.01	1,391	57.6	81	68.1	470	55.1	0.01
Education ^e							0.34							0.15
Low	215	8.6	26	8.7	189	8.6		87	12.5	7	11.5	24	6.8	
Intermediate	1,789	71.8	206	68.7	1,583	72.2		482	69.1	37	60.7	255	71.8	
High	488	19.6	68	22.7	420	19.2		129	18.5	17	27.9	76	21.4	

^a Study Population: Women who provided information on age at menarche in either SAPALDIA 2 (S2) or SAPALDIA 3 (S3), provided information on doctor-diagnosed asthma in at least SAPALDIA 1 (S1), S2 or S3, reported onset of asthma at least one year after menarche, and had complete covariate information.

^b Women excluded: Women having no information on age at menarche (N = 1442), having asthma onset before menarche (N = 81), or having missing covariate information (N = 891).

^c Using *t*-test for variables early menarche, age and BMI, and Fischer exact test for variables smoking, parental asthma, early-life respiratory infection, education, atopy and urbanity.

^d Smoking: Cumulative smoking at SAPALDIA 3 (S3), never-smokers being consistent never smokers across all three surveys, current smokers being smokers at S3, and ex-smokers being people who were smokers at S1 and/or S2, but not at S3.

^e Education: Cumulative education at SAPALDIA 3 (S3) (the highest educational level reported at S1/S2).

years to women with menarche at the mean age of menarche, as done by Macsali et al. (2011) [8], did not change results (data not shown).

When splitting occurrence of asthma into 3 groups: results did not change nor reach statistical significance. The OR for asthma-onset occurring 1–3 years after menarche was 1.61 (95% CI 0.52–4.99) and 1.22 (95% CI 0.81–1.85) 10 years after menarche.

When restricting our analysis to those ≤ 30 years at baseline, we found a higher OR for asthma incidence in those with early menarche, especially in the area specific definition (OR 1.63 (95% CI 0.84–3.15)

(Table S1 in online supplement). When running our stratified analysis by atopy and BMI in those age < 30 years at baseline we saw an increase in the OR for asthma incidence in young atopic women (OR 2.21, 95% CI 0.90–5.43) (Table 4). When defining early menarche using S2 information only, we found a slightly lower OR 1.13 (95% CI 0.75–1.72) for asthma incidence in those with early menarche compared to our definition using S2 or S3 information (Table S2 in online supplement).

The kappa statistic for agreement between reported age at me-

Table 3

Determinants of new-onset asthma using different definitions of early menarche.

Variables	Overall study population			
	Early menarche ≤ 12 ^a OR (95% CI) (N = 2,492)	Early menarche 1SD ^b OR (95% CI) (N = 2,492)	Early menarche 2 SD ^c OR (95% CI) (N = 2,492)	Early menarche Area ^d OR (95% CI) (N = 2,492)
Early menarche	1.23 (0.85–1.80)	1.23 (0.85–1.80)	1.12 (0.51–2.46)	1.25 (0.90–1.73)
Age (yrs.)	0.99 (0.98–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Atopy	2.75 (2.10–3.62)	2.75 (2.10–3.62)	2.77 (2.11–3.63)	2.75 (2.10–3.61)
Never-smoker (reference)	1	1	1	1
Former-smoker	1.45 (1.08–1.94)	1.45 (1.08–1.94)	1.45 (1.08–1.94)	1.45 (1.08–1.94)
Current-smoker	1.01 (0.67–1.51)	1.01 (0.67–1.51)	1.01 (0.67–1.51)	1.01 (0.67–1.52)
BMI	1.06 (1.03–1.10)	1.06 (1.03–1.10)	1.07 (1.03–1.10)	1.06 (1.02–1.10)
Parental asthma	1.66 (1.15–2.37)	1.66 (1.15–2.37)	1.66 (1.16–2.38)	1.66 (1.11–2.30)
Urban	1.05 (0.64–1.71)	1.05 (0.64–1.71)	1.34 (0.63–1.70)	1.02 (0.62–1.67)
Intermediate education (reference)	1	1	1	1
Low education	0.73 (0.43–1.26)	0.73 (0.43–1.26)	0.73 (0.43–1.26)	0.74 (0.43–1.26)
Higher education	1.02 (0.72–1.43)	1.02 (0.72–1.43)	1.02 (0.73–1.43)	1.01 (0.72–1.42)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area.

^a Definition early menarche < 12: age of menarche reported as < 12 years of age at either in SAPALDIA 2 or SAPALDIA 3.

^b Definition early menarche < 1SD: age at menarche reported as < 1 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3.

^c Definition early menarche < 2SD: age at menarche reported as < 2 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3.

^d Definition early menarche area: age at menarche reported as < 1SD below language region specific mean (German, French, Italian) at either SAPALDIA 2 or SAPALDIA 3.

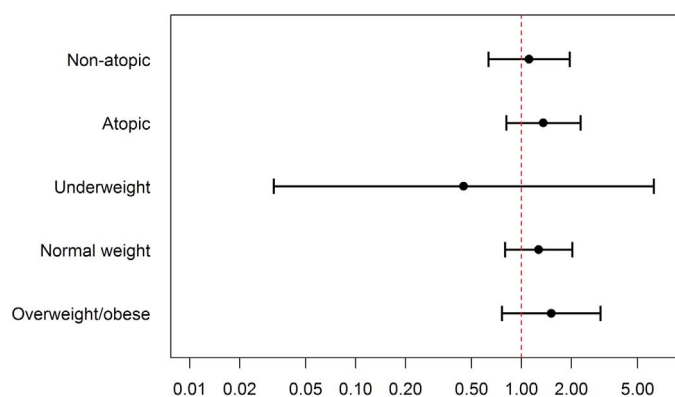


Fig. 2. Associations of early menarche and asthma incidence in analyses stratified by atopy and BMI. Data are presented as odds ratios (OR) and 95% confidence intervals (CI) for early menarche (age at menarche < 12 years of age as reported in SAPALDIA 2 or SAPALDIA 3). Stratified models for non-atopic/atopic: based on logistic regression adjusting for age, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area. Stratified models for underweight/normal weight/overweight/obese: based on logistic regression adjusting for age, atopy, cumulative smoking, parental asthma, urbanity, cumulative education and study area. Underweight (BMI < 18.5), normal weight (BMI 18.50–24.99), overweight/obese (BMI ≥ 25).

narche at S2 and S3 overall was 0.46. In those ages ≤30 years at baseline the kappa statistic for agreement for reported age at menarche between S2 and S3 was 0.49, and 0.46 in those aged 31–45 years, and 0.46 in those aged 46–60 years at baseline. Results did not differ (data not shown) when excluding women reporting early menarche only in S2 or S3 ($N = 107$), nor when running our analysis excluding women who reported a difference in age of menarche in the two follow-ups of ≥1 year ($N = 374$) or ≥2 years ($N = 85$).

To account for potential bias in loss to follow up inverse probability weighting was done which yielded largely the same results (data not shown). In addition, when excluding covariates with the most amount of missing information (smoking $N = 559$, education $N = 547$, atopy $N = 335$), associations stayed similar (data not shown).

4. Discussion

4.1. Main findings

In our population-based cohort, 250 (10.0%) women newly reported doctor-diagnosed asthma at least one year after menarche. In our fully adjusted analysis, we could not substantiate an association between early menarche and new-onset of asthma in women aged

18–60 years at baseline. Young atopic women with early menarche appeared to have an increased risk of asthma-onset (OR 2.21, 95% CI 0.90–5.43) (Table 4), although the association was not statistically significant.

This study is among the few to investigate the impact of early menarche on asthma incidence in women in later adulthood.

4.2. Comparison with other studies

Most recently in the review by Lieberoth et al. (2014) [3], they found a pooled OR of 1.37 (95% CI 1.15–1.64) for new-onset of asthma among women with menarche before the age of 12. However, the majority of studies included in this review who found a significant association of early menarche with asthma incidence, only followed-up women to the age of 30 years [14,15,23,24]. With the exception of five studies [4,6,9,10,8], early menarche and asthma incidence has not been investigated in adults > 30 years. From these five studies, three found a significant association of early menarche with asthma [4,9,8] whereas two did not [6,10]. Lieberoth et al. (2015) [4], in ages 12–41 years, found the eight-year cumulative incidence of asthma was higher in girls with early menarche compared to girls without early menarche, (OR 1.53, 95% CI 1.15–2.04). In the Omega study, Fida et al. (2012) [9], in ages 18–35 years, found that women who had early menarche (< 12 years old) had a 60% higher risk of being diagnosed with adult asthma as compared with women who did not have early menarche (aRR 1.59, 95% CI 1.19–2.13). Macsali et al. (2011) [8], in ages 27–57 years, found that women with early menarche had lower lung function and more asthma in adulthood. In contrast, Jartii et al. (2009) did not find early menarche to be associated with asthma at ages 24–39 years, and neither did Gnatiuc et al. (2013) [10] at age 33.

Similar to Jartii et al. (2009) [6] and Gnatiuc et al. (2013) [10], we did not see a significant association between early menarche and new-onset of asthma in our study population aged 18–60 at baseline. Jartii et al. (2015) [6], who also had a slightly older study population (24–39 years) reported that age at menarche was not associated with prevalent asthma among participants, so possibly older age partly explains our findings. One possible reason that we may not find a significant association is that our study population was older (18–60 at baseline), implying a longer recall period for the age of menarche. However, when restricting our analysis to those aged ≤30 years at baseline, although the OR for asthma incidence in women with early menarche slightly increased, it still did not reach statistical significance (Table S1 in online supplement). To try to account for potential recall bias we also restricted our analysis to using S2 information only (the earliest time point when participants gave information on menarche). However, the

Table 4

Determinants of new-onset asthma stratified by atopy and BMI restricted to those age < 30 at baseline.

Variables	Early menarche < 12 ^a OR (95% CI)				
	Non-atopic (N = 261)	Atopic (N = 180)	Underweight ^b (Omitted)	Normal weight ^c (N = 393)	Overweight/obese ^b (N = 48)
Early menarche	0.23 (0.28–1.95)	2.21 (0.90–5.43)	–	1.28 (0.57–2.87)	1.77 (0.04–69.79)
Age (yrs.)	1.09 (0.93–1.27)	1.05 (0.94–1.16)	–	1.03 (0.94–1.12)	1.08 (0.81–1.45)
Atopy	–	–	–	3.75 (1.98–7.12)	6.26 (0.29–136.25)
Never-smoker (reference)	1	1	1	1	1
Former-smoker	1.93 (0.66–5.60)	2.06 (0.89–4.78)	–	2.87 (1.41–5.86)	0.10 (0.00–4.33)
Current-smoker	1.00 (0.28–3.60)	0.64 (0.21–1.95)	–	1.23 (0.51–2.98)	0.35 (0.01–12.56)
BMI	1.02 (0.86–1.22)	0.97 (0.85–1.12)	–	–	–
Parental asthma	1 (omitted)	1.18 (0.35–3.97)	–	0.54 (0.17–1.69)	1.22 (0.06–25.85)
Urban	2.11 (0.42–10.55)	1.71 (0.48–6.09)	–	1.94 (0.68–5.48)	4.22 (0.03–550.02)
Intermediate education (reference)	1	1	1	1	1
Low education	1 (omitted)	1.82 (0.24–13.57)	–	1.37 (0.13–13.96)	3.19 (0.21–47.94)
Higher education	0.68 (0.22–2.12)	0.63 (0.25–1.57)	–	0.68 (0.32–1.44)	0.41 (0.00–34.38)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area.

^a Definition early menarche < 12: age of menarche reported as < 12 years of age at either in SAPALDIA 2 or SAPALDIA 3.

^b Underweight (BMI < 18.5), normal weight (BMI 18.50–24.99), overweight/obese (BMI ≥ 25).

OR for asthma incidence in women with early menarche actually slightly decreased (Table S2 in online supplement).

We saw a tendency among young atopic women with early menarche to have increased risk of asthma-onset, which is consistent with, and may partly explain, our previous findings [1] that young atopic women have the highest risk of newly developing asthma after the age of 18 (OR 3.21, 95% CI 2.12–4.85). To the best of our knowledge, other studies have not taken atopy into account when investigating the association with early menarche and asthma incidence, including studies which informed the meta-analysis by Lieberoth et al. (2014) [3]. If atopy was more prevalent in other study populations, we cannot exclude that this might have increased their probability to find an association. Furthermore, if atopic women are aware of their asthma risk, and they are also more overweight (associated with earlier age at menarche), they may have more complaints when asthma develops and may tend to visit the doctor earlier. This may partly explain why our crude odds ratio was similar to that of Lieberoth et al. (2014) [3], however, after taking further covariates into account, including atopy, our results became statistically insignificant (Table S3a & S3b).

4.3. Strengths and limitations

The strengths of this study is its large database representing the general Swiss population from urban, rural and mountainous areas with different environmental exposure characteristics, with standardised health assessment and a women's health questionnaire that was developed alongside the ECHRS [11,13].

A limitation of this study is that women were 18–60 years at baseline and therefore had to recall their age at menarche and age of first asthma attack retrospectively. This may have introduced some recall bias [25] as possibly reflected in the insignificant odds ratios and moderate agreement between reported age at menarche in the two surveys (S1 & S2). We observed that 107 (14%) women reported early menarche only once in the two follow-up periods. Although analyses excluding these women did not change our results, we believe that this non-differential misclassification may have biased our associations towards the null. This is also consistent with our finding that we had a higher kappa statistic for agreement and slightly higher odds ratios in those ages ≤ 30 years at baseline. Although studies looking at recall of early menarche have generally found a quite good correlation between recoded and recalled menarche in women both close to and distant from the event [25,26], future studies may need to prospectively follow girls from the time of their transition into puberty up to adulthood to really assess whether early menarche is also a risk factor for asthma developing in later adulthood. Another limitation is that BMI at baseline was used which does not take into account BMI at menarche nor adiposity.

5. Conclusion

In this Swiss population-based cohort we could not substantiate an association between early menarche and asthma-onset in women aged 18–60 years at baseline. Future studies may need to prospectively assess the age of menarche and – besides assessing BMI or more appropriate measures of adiposity – take into account atopic status.

Contributors

SH was responsible for study conception and design, analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript. NP-H was responsible for study conception and design, analysis and interpretation of data, and critical revision of the manuscript. RB was responsible for critical revision of the manuscript. MP was responsible for analysis and interpretation of data, and critical revision of the manuscript. BL was responsible for analysis and

interpretation of data, and critical revision of the manuscript. FGR was responsible for analysis and interpretation of data, and critical revision of the manuscript. TR was responsible for critical revision of the manuscript. JD was responsible for analysis and interpretation of data, and critical revision of the manuscript. CS was responsible for critical revision of the manuscript. DK was responsible for study conception and design, analysis and interpretation of data, and critical revision of the manuscript. CS was responsible for study conception and design, analysis and interpretation of data, and critical revision of the manuscript. EZ was responsible for study conception and design, analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript. The SAPALDIA team (see Appendix A) was responsible for acquisition of data.

Competing interest

The authors declare that they have no conflict of interest.

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Ethical approval

Ethical approval was obtained from the Swiss Academy of Medical Sciences, the regional committees, and written informed consent was obtained from all participants.

Provenance and peer review

This article has undergone peer review.

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Appendix A

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.maturitas.2017.04.012>.

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Supplementary Material

Title: Early menarche and new-onset of asthma: results from the SAPALDIA cohort study

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Table S1: Determinants of new-onset asthma using different definitions of early menarche

Restricted to those ages <30 at baseline

<u>Variables</u>	<u>Early Menarche <12*</u> OR (95% CI) (N=488)	<u>Early Menarche 1SD†</u> OR (95% CI) (N=488)	<u>Early Menarche 2 SD‡</u> OR (95% CI) (N=488)	<u>Early Menarche Area§</u> OR (95% CI) (N=488)
Early menarche	1.42 (0.68 – 2.97)	1.42 (0.68 - 2.97)	0.79 (0.16 - 3.91)	1.63 (0.84 - 3.15)
Age (yrs.)	1.05 (0.96 - 1.14)	1.05 (0.96 - 1.14)	1.05 (0.96 - 1.14)	1.05 (0.96 - 1.14)
Atopy	3.77 (2.10 - 7.01)	3.77 (2.10 - 7.01)	3.80 (2.12 - 6.83)	3.75 (2.08 - 6.74)
Never-smoker (reference)	1	1	1	1
Former-smoker	1.94 (1.03 - 3.66)	1.94 (1.03 - 3.66)	1.98 (1.04 - 3.75)	1.94 (1.03 - 3.67)
Current-smoker	0.79 (0.34 - 1.80)	0.79 (0.34 - 1.80)	0.78 (0.34 - 1.78)	0.81 (0.35 - 1.85)
BMI	0.98 (0.90 - 1.09)	0.98 (0.90 - 1.09)	0.99 (0.89 - 1.10)	0.98 (0.88 - 1.09)
Parental asthma	0.60 (0.21 - 1.68)	0.60 (0.21 - 1.68)	0.59 (0.21 - 1.67)	0.59 (0.21 - 1.67)
Urban	1.88 (0.71 - 4.95)	1.88 (0.71 - 4.95)	1.83 (0.70 - 4.79)	1.81 (0.69 - 4.75)
Intermediate education (reference)	1	1	1	1
Low education	1.74 (0.31 - 9.65)	1.74 (0.31 - 9.65)	1.83 (0.34 - 9.98)	1.73 (0.31 - 9.75)
Higher education	0.66 (0.33 - 1.32)	0.66 (0.33 - 1.32)	0.65 (0.32 - 1.30)	0.67 (0.33 - 1.34)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area

*Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

†Definition early menarche <1SD: age at menarche reported as < 1 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3

‡Definition early menarche <2SD: age at menarche reported as < 2 standard deviation of mean age at menarche at either SAPALDIA 2 or SAPALDIA 3

§Definition early menarche area: age at menarche reported as <1SD below language region specific mean (German, French, Italian) at either SAPALDIA 2 or SAPALDIA 3

Table S2: Determinants of new-onset asthma
Early Menarche <12 years (S2 information only)*

<u>Variables</u>	<u>OR (95% CI)</u> (N=2,492)
Early menarche	1.13 (0.75 - 1.72)
Age (yrs.)	0.99 (0.98 - 1.00)
Atopy	2.76 (2.10 - 3.63)
Never-smoker (reference)	1
Former-smoker	1.45 (1.08 - 1.94)
Current-smoker	1.01 (0.67 - 1.51)
BMI	1.06 (1.03 - 1.10)
Parental asthma	1.66 (1.16 - 2.38)
Urban	1.04 (0.63 - 1.70)
Intermediate education (reference)	1
Low education	0.73 (0.43 - 1.26)
Higher education	1.02 (0.73 - 1.43)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Based on logistic regression adjusting for age, atopy, cumulative smoking, BMI, parental asthma, urbanity, cumulative education and study area

*Definition early menarche <12: age of menarche reported as <12 years of age in SAPALDIA 2

Table S3a: Step-Wise Addition of Variables

<u>Variables</u>	<u>Crude model</u> OR (95% CI) (N= 2,492)	<u>Model 1†</u> OR (95% CI) (N= 2,492) age	<u>Model 2‡</u> OR (95% CI) (N= 2,492) education	<u>Model 3§</u> OR (95% CI) (N= 2,492) smoking	<u>Model 4 </u> OR (95% CI) (N= 2,492) Parental asthma
Early menarche <12*	1.50 (1.05 - 2.15)	1.47 (1.02 - 2.10)	1.46 (1.02 - 2.10)	1.45 (1.01 - 2.09)	1.44 (1.01 - 2.07)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Bold indicated significance at $p \leq 0.05$.

*Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

†Model 1: based on logistic regression adjusting for age

‡Model 2: based on logistic regression adjusting for age and cumulative education

§Model 3: based on logistic regression adjusting for age, cumulative education and cumulative smoking

|| Model 4: based on logistic regression adjusting for age, cumulative education, cumulative smoking and parental asthma

Table S3b: Step-Wise Addition of Variables

<u>Variables</u>	<u>Model 5††</u> OR (95% CI) (N= 2,492) urban	<u>Model 6‡‡</u> OR (95% CI) (N= 2,492) area	<u>Model 7§§</u> OR (95% CI) (N= 2,492) atopy	<u>Model 8 </u> OR (95% CI) (N= 2,492) BMI	<u>Model 9***</u> OR (95% CI) (N= 2,492) Full
Early menarche <12**	1.41 (0.98 - 2.03)	1.40 (0.97 - 2.01)	1.34 (0.92 - 1.94)	1.29 (0.89 - 1.87)	1.23 (0.85 - 1.80)

Data are presented as odds ratios (OR) and 95% confidence intervals (CI). Bold indicated significance at $p \leq 0.05$.

**Definition early menarche <12: age of menarche reported as <12 years of age at either in SAPALDIA 2 or SAPALDIA 3

††Model 5: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, and urbanity

‡‡Model 6: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, and study area

§§Model 7: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, study area and atopy

|||| Model 8: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, study area and BMI

***Model 9: based on logistic regression adjusting for age, cumulative education, cumulative smoking, parental asthma, urbanity, study area, BMI and atopy