European Journal of Pediatrics (2018) 177:699–707
https://doi.org/10.1007/s00431-018-3107-0

ORIGINAL ARTICLE

Is there a gender-specific association between asthma and carotid intima media thickness in Swiss adolescents?

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Received: 29 September 2017 / Revised: 21 January 2018 / Accepted: 23 January 2018 / Published online: 6 February 2018

Abstract

Respiratory diseases are associated with increased cardiovascular risk in adults, but little is known on the early impact on the vasculature in youth. The SAPALDIA Youth study, the offspring study of the Swiss Study on Air Pollution and Lung and Heart Disease In Adults (SAPALDIA), investigated the association between physician-diagnosed asthma status and common carotid artery intima media thickness (CIMT). Offspring underwent standardized clinical protocols and provided information on early life factors, health, and lifestyle. The association between per subject averages of CIMT and asthma was estimated using mixed linear regression analyses adjusting for main confounders, testing for interaction with gender and age. Of 257 offspring (mean age 15 years, 53% female), 11.5% reported doctor-diagnosed asthma (male 17%, female 7%). Mean CIMT was significantly different by gender (male 0.53 mm (± 0.045), female 0.50 mm (± 0.048); $p < 0.001$). Interaction was highly significant by gender ($p = 0.001$) with significantly increased CIMT in asthmatic vs. non-asthmatics boys (difference 0.023 mm, 95% CI 0.003; 0.043), as compared to girls.

Conclusion: Our study suggests an increased risk for early vascular change in adolescent asthmatic boys. Whereas the small number of girls limits the interpretation, the result necessitates further research into sex-specific atherosclerotic burden related to respiratory health in adolescence.

What is Known:
- *Evidence points to a significant impact of adult respiratory disease on cardiovascular health indicators as well as on endpoints.*
- *Inflammation is a key pathway in vascular change across the life course.*

Communicated by Peter de Winter

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What is New:

- *We observe an adverse association between physician-diagnosed asthma and carotid intima media thickness in adolescent boys.*
- *Albeit a limited number of asthmatic girls, we hypothesize the gender typical timing of asthma or a higher male cardiovascular vulnerability as possible explanations for the gender-specific results.*

Keywords Asthma · Atherosclerosis · Epidemiology · Carotid intima media thickness

Abbreviations

BMI	Body mass index
CIMT	Carotid artery intima media thickness
FEV_1	Forced expiratory volume
SAPALDIA	Swiss Study on Air Pollution and Lung and Heart Disease In Adults

Introduction

Respiratory health and cardiovascular health are the leading causes of morbidity globally [32]. Cardiovascular disease is projected to increase globally, while increase in asthma prevalence seems to have stabilized in many countries. In Swiss children, the prevalence is about 10% [19], but prevalence reaches far higher values in other European countries [3].

Clinical manifestation of asthma occurs early in life (early onset) as well as later in life (late onset), while cardiovascular diseases usually become symptomatic in adulthood. Non-invasive diagnostic methods, however, can evidence early subclinical changes of the vasculature associated with cardiovascular health later in life, as has been shown for numerous known cardiovascular risk factors [9, 16, 30, 38]. Epidemiological studies agree on a general association between asthma and cardiovascular disease, but do not provide consistent results across the range of cardiovascular end points [34, 39, 44], and very few have studied children and adolescents [6, 41]. Systematic inflammation is considered an important pathway between the two disease entities [6, 27]. From a life course perspective on health and disease, the question on how early in life respiratory health impacts on cardiovascular health and which risk factors the disease entities have in common is of interest to clinicians and public health alike. The non-invasive ultrasound measurement of carotid intima media thickness (CMT) is accepted as a subclinical biomarker of vascular damage and is predictive of cardiovascular outcomes in adults [28]. Furthermore, research has consistently shown the association of metabolic and pro-inflammatory risk factors in childhood with a higher CIMT both in children and adults [23], while the cardiovascular cohorts investigating childhood CIMT are still too young to assess the predictive value.

The SAPALDIA Youth study concurrently collected various data on respiratory health and physician-diagnosed asthma status and carotid intima media thickness (CIMT). Hence, the study offers the ideal situation to investigate the association between asthma status and early indicators of ateriosclerogenesis and to investigate some of the hypothesized pathways.

Patients and methods

Study design and study sample

The SAPALDIA Youth Study is a cross-sectional offspring study nested into the Swiss Study on Air Pollution And Lung and Heart Disease In Adults (SAPALDIA). The SAPALDIA cohort was recruited as a population-based, random sample of adults (18–60 years) from eight study areas in Switzerland in 1991, representing both rural and urban and a broad range of environmental conditions [1]. The SAPALDIA Youth methodology [11] and the validation for intra- and inter-reader variability of the applied ultrasound method [45] have been described in detail elsewhere. In short, all offspring born to participants between the first two adult surveys (1990–2001) in the German-speaking study areas were eligible, of which 67% participated ($N = 356$). Two hundred eighty-eight participated in the full clinical examination. High-quality CIMT data were available in 281 youth. After excluding children with heart malformations, renal disease, or missing parental data, the analytic sample counted 257 youth (Fig. 1). Written informed consent was given by the participant's parent, and as of 15 years of age, adolescent were asked to

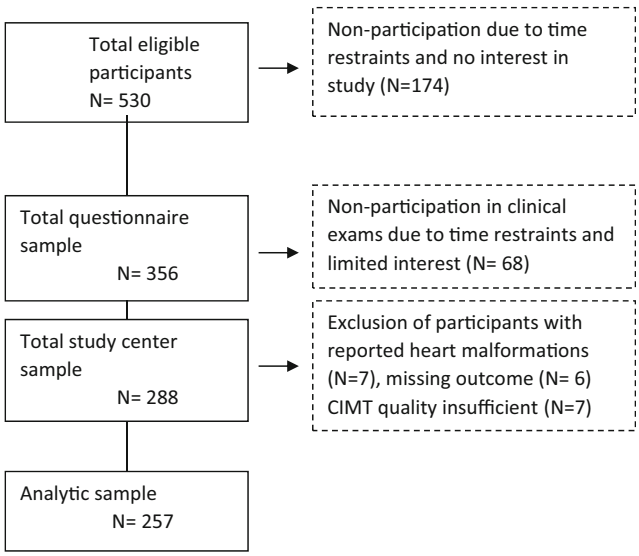

Fig. 1 SAPALDIA Youth study participation flow chart

provide written informed consent. Ethical clearance was obtained from the respective cantonal Ethical Review Boards.

The ultrasound detection program showed a high precision with bias of ± SD of 0.002 ± 0.010 mm (T1) and 20.004 ± 0.008 mm (T2) for completely automatic detections for average CIMT in the Bland-Altman analysis.

Trained and certified field workers visualized the common carotid bilaterally in two angles (longitudinal and ear to ear) according to a validated study protocol. An automatic contour detection program measured CIMT measured over a 1-cm segment proximal to the carotid bulb across several heart cycles calculating the individual's end-diastolic average and maximum CIMT combining all images [45]. Asthma status "ever-asthma" was assigned if the participant had answered "yes" to the question "Have you ever have had asthma?" and "physician-diagnosed asthma" when this asthma diagnosis had been confirmed by a physician. Offspring performed spirometry with the help of trained field workers using the EasyOne Spirometer (NDD, Zürich, Switzerland) in a sitting position wearing nose clips. At least three and up to maximal eight forced expiratory lung function maneuvers were performed to obtain an acceptable results for both FEV1 and FVC and the forced expiratory flows. Percent predicted values were calculated using the Global Lung Function Tables 2012 [37]. Blood draw, blood pressure measurements, and anthropometric measures followed standard protocols. All other information on health or childhood exposures was self-reported. Further information on study design and protocol is provided in the online repository.

Statistical analyses

Descriptive statistics of the study population and group differences by asthma status are presented in Table 1. A mixed linear regression, taking clustering by study area and family into account, was applied to investigate the association between the main exposure of interest physician-diagnosed asthma and CIMT. Given the complexity of the potential confounding factors, four potential confounder groups were identified: (1) birth and pregnancy-related outcomes, (2) adolescent lifestyle, (3) other early childhood inflammatory exposures, and (4) parental factors (covariates see online repository). Participants with high-sensitive C-reactive protein (hs-CRP) > 10 mg/l risk were excluded from the regression analyses ($N = 6$) since we were interested in the chronic inflammatory effects, even though analyses in the full sample resulted in similar associations. Confounder groups were added in a step-wise forward process. Covariates significant at a p value < 0.2 were included in the final gender stratified model. The models were defined and main analyses performed gender-stratified, after interaction was confirmed in a full sample analyses in the primary and final model. Sensitivity analyses were performed in children without any history or evidence of cardiometabolic disease based on reported cardiometabolic disease status (physician-diagnosed diabetes, dyslipidemia, or arterial hypertension) and biomarkers (HDL, LDL, HbA1C) and adjusting for parental cardiometabolic history. Further analyses were performed to investigate potential pathways, as suggested by literature, including lung function, history of respiratory infections (bronchitis and pneumonia) and asthma medication, hs-CRP, and mean arterial blood pressure (diastolic blood pressure + pulse pressure/3) (Table 2).

All analyses were performed using the statistical software STATA (StataCorp, Release 12. Statistical Software, College Station, TX, USA). p values < 0.05 were considered as statistically significant.

Results

Among the 257 offspring, 15% had reported ever having had asthma and 11% a physician diagnosis of asthma. Significantly more boys than girls reported asthma, both ever ($p = 0.039$) and physician diagnosed ($p = 0.045$). Asthma medication was taken by 9% overall. More than half of the offspring reporting ever-asthma (55%) and physician-diagnosed asthma (58%) had taken medication in the recent 12 months. We observed no significant gender difference with respect to medication intake. Approximately 40% of the asthmatics had experienced an attack in the past 12 months (43% of asthma-ever, 39% physician-diagnosed asthma).

With respect to basic cardiovascular parameters, boys presented with significantly higher percentage of high blood pressures than girls (> 95 percentile 19 vs. 8%, $p = 0.006$) and a thicker CIMT of 0.529 mm (± SD 0.045) vs. 0.502 mm (± SD 0.048; $p < 0.001$, Fig. 2). Unadjusted CIMT as well as metabolic parameters were not significantly different between asthmatics and non-asthmatics.

Given the significant interaction terms in the overall sample analyses (interaction term ever-asthma × gender $p = 0.003$; physician-diagnosed asthma × gender $p = 0.032$), the multilevel regression analyses were performed gender-stratified separately for ever-asthma and physician-diagnosed asthma and results presented gender-stratified. Since the results for ever-asthma were similar in direction of association and significance to the results for physician-diagnosed asthma, only the results of the latter are presented in this manuscript.

In boys, the association was statistically significant in the basic and most of the consecutive models (Table 3), yielding an increased CIMT in asthmatics as compared to non-asthmatics. The models including potential respiratory pathway variables (percent predicted lung function, reported respiratory infections, or asthma medication) yielded no major changes in effect estimates or significance of the associations. Results were also similar when adding mean arterial blood pressure or hs-CRP to the model (Table 3). The confidence interval of the

Table 1 Study participants' characteristics by asthma status

	No physician-diagnosed asthma[e]	Physician-diagnosed asthma		
	N = 229	*N* = 28	Total N	*p* value
Age (in years)	15.4 (sd 3.6)	14.56 (sd 3.4)		0.930
FEV1, percent predicted[a]	96.82 (sd 12.2)	95.83 (sd 12.9)		0.689
	%	%		
Sex male	44.1	67.9	120	
Female	55.9	32.1	137	0.017
Born preterm	10.0	10.7	26	0.184
Maternal smoking in utero	10.9	10.7	28	0.974
Pregnancy complications	7.0	10.7	19	0.477
Puberty staging				
Tanner 0	15.7	10.7	39	
Tanner 1	12.2	17.9	33	
Tanner 2	7.4	14.3	21	
Tanner 3	19.2	21.4	50	
Tanner 4	45.4	35.7	114	0.548
Physical activity[b] low	31.6	32.1	80	
Middle	31.1	17.9	7	
High	37.3	50.0		0.286
Weekly smoker	9.6	10.7	25	0.852
ETS exposed, last 12 months	24.0	25.0	62	0.909
Ever atopy/atopic eczema	9.2	14.3	25	0.389
Respiratory infection in childhood[c]	21.0	39.3	59	0.030
Father asthma	4.4	0.0	10	0.176
Mother asthma	6.6	25.0	22	0.001
Parental cardiometabolic disease[d]	19.7	14.3	49	0.495
Parental smoking current	19.2	35.7	54	0.028
SAPALDIA parent smoking status				
Never/before 1991	72.5	57.1	182	
Between 1991 and 2001	11.4	7.1	28	
After 2001/currently	16.2	35.7	47	0.040

p value comparison asthma vs. non-asthma using chi2 test or ANOVA as applicable

ETS environmental tobacco smoke

[a] Based on the Global Lung Function reference values [37]

[b] Physical activity defined based on school and free-time physical activity (low < 3 h, middle 3 h, high > 3 h per week)

[c] Bronchitis or pneumonia reported by parents

[d] Hypertension, heart diasease, diabetes, hypercholesteremia

[e] Includes 10 children, who report asthma, but not physician diagnosed

Table 2 Cardiometabolic parameters by asthma status

Cardiometabolic parameters	No physician-diagnosed asthma	Asthma, physician diagnosed	
	N = 229	*N* = 28	*p* value
IMT (mm)	0.513 (sd 0.046)	0.527 (sd 0.063)	0.151
Blood pressure ≥ 95th P	14.4	3.6	0.259
BMI ≥ 90th P	12.7	14.3	0.899
High cholesterol	6.7	8.7	0.727
Hb1Ac > =5.8	5.7	7.1	0.952

p value comparison asthma vs. non-asthma group using chi2 test or ANOVA as applicable

P percentile, cutoffs based on the laboratory reference values and pediatric guidelines [11] [10]

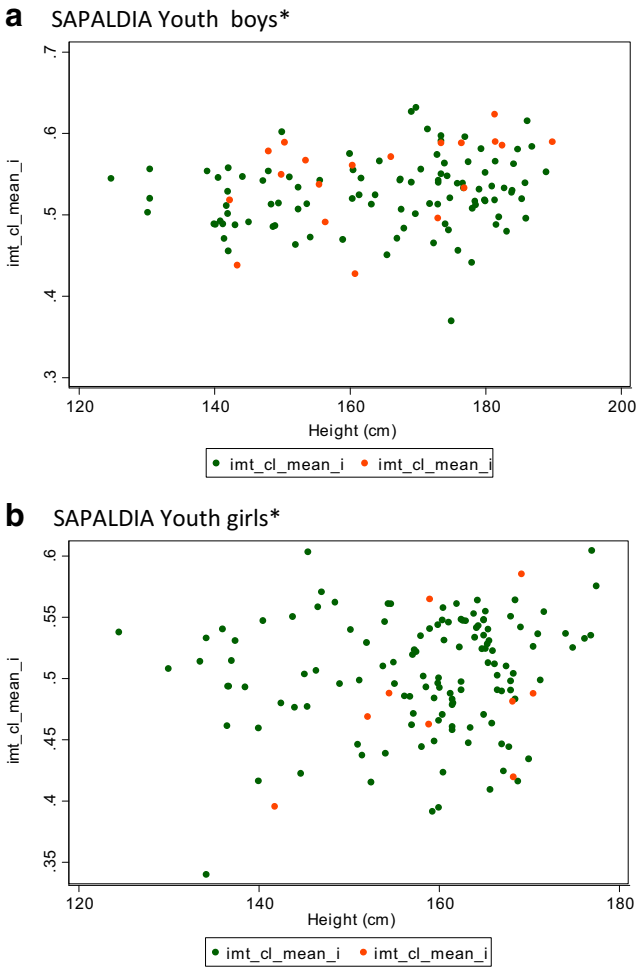

Fig. 2 Scatter plots of CIMT and height by sex and asthma status*. **a** SAPALDIA Youth boys*. **b** SAPALDIA Youth girls*. *Asthma status indicated by red dots

sensitivity analyses in participants without additionally reported cardiometabolic risks pointed to a similar direction, albeit of borderline significance (Table 3). In girls, none of the models or additional analyses yielded statistical significant associations between asthma status and CIMT; however, the small number of asthmatic girls might have limited the power of detecting a significant effect.

Discussion

The analyses of the SAPALDIA Youth study yield significant associations between asthma status and increased CIMT in boys, while we observe no significant effect in girls. Given the literature in adults on the association between respiratory and cardiovascular health but only few studies in children, we expected a small albeit significant impact of childhood asthma on CIMT in this adolescent population. In addition, our results suggest a higher male vulnerability of the vasculature already at young age. While the small number of girls in our study population limits the conclusion, that asthma has no effect on female adolescent CIMT, the finding generates questions about the sex specificity of cardiovascular risk factors and health in adolescence. Neither Cakmak et al. [6] who investigated oxidative stress and CIMT in asthmatics and clinical controls nor Steinman et al. [41] or Öskan et al. [36] in their case-control studies on asthma and arterial stiffness in school-aged children had investigated gender differences, possibly due to too small numbers. Studies on CIMT in childhood and youth, however, document early vascular gender differences. In general, CIMT in boys is found to be thicker than in girls, which corresponds to observations in adults with thicker CIMT in men compared to pre-menopausal women also after adjusting for cardiovascular risk factors [12, 42]. The difference becomes most evident around puberty. The male growth spurt and increase in blood pressure with age may play a role [4, 7]. Our analyses allowed for adjustment by age, anthropometrics, and blood pressure in both gender; thus, we are confident that the observed results are independent of these factors. In children, Böhm et al. provides evidence for other sex-specific risk predictors of increased CIMT: BMI in girls and SBP in boys [5]. Gender differences in relation to prevalence and impact of cardiovascular risk factors, also for asthma, on atherosclerosis are known in adults [18, 25, 34, 43].

Our finding may result from a higher vulnerability to infectious agents in boys [29, 31]. In fact, in a previous analysis on infectious childhood disease and CIMT, boys were also at higher risk compared to girls [13]. When the model was additionally adjusted for self-reported bronchitis and pneumonia in childhood, the effect in boys was indeed attenuated. Respiratory infections might be an underlying pathway of the observed association. Lower respiratory infections occur more frequent and are more severe in asthmatic children than in non-asthmatics [8], and often trigger asthma exacerbations [14]. This observation is supported by studies in adult populations. The Brunek study, for example, found strong association with new atherosclerotic lesions in participants who experienced chronic infections, predominantly respiratory infections [22]. However, since asthma occurs at younger age in boys than in girls, who more frequently experience first asthma symptoms after puberty [48], the observed association might only become evident at a later time point in girls.

Our data allowed studying potential pathways between asthma status and CIMT, but none of the investigated pathways proved relevant in our sample. A recent study by Steinmann [41] provided a weak inverse association between lung function and arterial stiffness in asthmatic children and adolescents, but did not investigate lung function in the healthy controls. The only other study in this age group, to our knowledge, observed an opposite association with increased stiffness associated with higher lung function [15], partly explained by anthropometry. In our data, we can neither confirm nor reject lung function being a pathway. Given the

Table 3 Association between doctor-diagnosed asthma and carotid artery intima media thickness (CIMT)

Boys	CIMT difference in mm	*p* value	95% Confidence interval		Number
Ref. non-asthmatic	0				
Basic model[a]	0.022	0.035	0.0016	0.042	119
Final model[b]	0.024	0.020	0.004	0.044	119
Pathway models[c]					
+Respiratory infections	0.018	0.074	−0.002	0.037	119
+CRP	0.023	0.029	0.002	0.043	119
+Asthma medication	0.021	0.078	−0.002	0.044	97
Mad	0.023	0.025	0.004	0.043	119
FEV1%predicted	0.026	0.009	0.007	0.045	112
Sensitivity analysis[e]	0.019	0.095	−0.003	0.041	84
Girls					
Basic model[a]	−0.027	0.100	−0.059	0.005	132
Final model[f]	−0.015	0.338	−0.046	0.016	127
Pathway models[c]					
+Respiratory infections	−0.016	0.312	−0.047	0.015	127
+CRP	−0.015	0.346	−0.045	0.016	132
+Asthma medication	−0.009	0.684	−0.052	0.034	127
Mean arterial pressure[d]	−0.013	0.415	−0.044	0.018	126
FEV1%predicted	−0.012	0.458	−0.044	0.020	119
Sensitivity analysis[e]	−0.008	0.699	−0.046	0.031	106

[a] Adjusted for age and puberty stage

[b] Adjusted for covariates of the basic model plus additional covariates: height, weekly smoker, environmental tobacco exposure (last 12 months), physical activity, parental educational status, parental CVD, pregnancy complications, atopy

[c] Adjusted for covariates of the final model plus additional potential pathway variables: respiratory infections in childhood (yes/no), hs-CRP, asthma medication (yes/no), mean arterial pressure, or percent-predicted lung function [37]

[d] Mean arterial pressure: diastolic blood pressure + 1/3 (systolic blood pressure − diastolic blood pressure)

[e] Adjusted for covariates of final model in participants without cardiometabolic history or current metabolic risk (BMI ≥ 97 percentile, hypercholesteremic, Hb1AC > 5.8, blood pressure ≥ 95th percentile)

[f] Model covariates plus height, environmental tobacco exposure (last 12 months), physical activity, parental educational status, parental CVD, term birth, birth weight, and maternal asthma

small discriminatory value of lung function to define severity in childhood and adolescence [24], this result was expected. Fifty percent of the asthmatics reported taking asthma medication, among them corticosteroid. Corticosteroids have been discussed as risk factor for cardiovascular diseases due to their adverse metabolic side effects. However, inhaled corticosteroids may affect the metabolism less, instead decrease systemic inflammation [35, 46, 47]. We observed no effect of asthma medication, possibly because different anti-asthmatic medication was aggregated into one variable. The study by Cakmak et al. found oxidative stress to be associated with CIMT in a clinically based study population of asthmatics [6]. Others identified hs-CRP among other inflammatory biomarkers to be associated with CIMT in youth [20, 40]. In our study, adjusting for hs-CRP did not affect the observed association. Neither did overweight and obesity, metabolic risk factors for both cardiovascular and respiratory health [2, 17], show a significant association with asthma diagnosis or CIMT. Nor did we find BMI to mediate the association observed in boys. Blood pressure is considered to play a role in atherosclerosis [12, 26], an observation which we could not confirm for our SAPALDIA offspring. However, the prevalence of increased blood pressures was low, and the association between blood pressure and atherosclerosis seems to relate to persistence of high blood pressure into adulthood [21].

The presented results are somewhat limited by the self-reported asthma status and small number of asthmatics. However, validity of reported disease prevalence is high (sensitivity 97%, specificity 91%) [33], when asking for physician-diagnosed diseases, and participants were asked on additional aspects of their asthma to increase the validity of the reported diagnosis. Unfortunately, due to missing information, the time since first asthma attack or diagnosis could not be investigated.

The SAPALDIA Youth study increases the evidence and supports the two relevant existing studies on respiratory health and CIMT in children. It also adds a new hypothesis, a potential sex specificity, to the scientific discussion. The small number of asthmatics, especially asthmatic girls, demands caution in the interpretation of the results, and cross-sectional study cannot provide evidence on causation nor the long-term relevance of the observed association. The hypothesis of a gender specificity of the association requires confirmation in subsequent studies, and further studies are needed to understand the lifelong impact this early respiratory risk factor may have. Our observations indicate that asthma in childhood may be associated with early structural changes of the vasculature. Identifying a potentially vulnerable subgroup of children and possibly a time window in which cardiovascular risk can be prevented or modified is of high relevance, given the high asthma prevalence in children and adolescents [3].

Acknowledgements We thank Prof. Christian Schindler for his statistical support and critical input and the SAPALDIA Youth study participants for providing data and trust in our research.

Authors' contributions Julia Dratva is the primary investigator of the SAPALDIA Youth study. She developed the study protocol and supervised the data collection, has developed the hypotheses and analytic plan presented in this paper, conducted the analyses, interpreted the data in conjunction with all authors, and was responsible for writing the first and all consecutive drafts and the submitted paper.

Seraina Caviezel was involved in the CIMT data collection and management, provided analytic support and contributed in the interpretation of the presented results in conjunction with all authors, and participated in the drafting of the manuscript.

Emmanuel Schaffner is involved in the CIMT data management, provided analytic support and contributed in the interpretation of the presented results in conjunction with all authors, and participated in the drafting of the manuscript.

Daiana Stolz was involved in the SAPALDIA Youth data collection as study center physician and pneumologist. She contributed in the interpretation of the presented results in conjunction with all authors, and participated in the drafting of the manuscript.

Thomas Rothe was involved in the SAPALDIA Youth data collection as study center physician and pneumologist. He contributed in the interpretation of the presented results in conjunction with all authors and participated in the drafting of the manuscript.

Nino Kuenzli is a longstanding member of the SAPALDIA cohort study, in which the SAPALDIA Youth study is nested. He oversaw the SAPALDIA 3 survey and the development of the SAPALDIA CIMT protocol and provided methodological support in the development of the SAPALDIA Youth study. He contributed in the interpretation of the presented results in conjunction with all authors and participated in the drafting of the manuscript.

Arno Schmidt-Trucksäss was involved in the SAPALDIA CIMT protocol development, data collection and analyses, contributed to the interpretation of results in conjunction with all authors, and participated in drafting the paper.

Elisabeth Zemp provided methodological support in the development of the SAPALDIA Youth study and contributed in the interpretation of the presented results in conjunction with all authors and participated in the drafting of the manuscript.

Nicole Probst-Hensch is the primary investigator of the SAPALDIA cohort study, in which the SAPALDIA Youth study is nested. She implemented into the SAPALDIA cohort the comorbidity framework between inflammation-related diseases. She provided methodological support in the development and data collection of the SAPALDIA Youth study and contributed in the interpretation of the presented results in conjunction with all authors, and participated in the drafting of the manuscript.

Funding information The SAPALDIA Youth study was funded by the Swiss National Science Foundation (PMPDP3_129021/1, PMPDP3_141671/1) and supported financially by the canton's Lung League of Basel Stadt/Basel Landschaft and Graubünden and the Stiftung ehemals Bündner Heilstätten.

The SAPALDIA cohort study, from which offspring were recruited, is funded by the Swiss National Science Foundation (grant no. 33CSCO-134276/1, 33CSCO-108796, 3247BO104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200042532, 4026-028099). For additional information on funding bodies, please refer the homepage: www.sapaldia.ch/en/.

Compliance with ethical standards

Parents signed written informed consent for adolescent < 18 years; as of 15 years of age, adolescent were asked to provide written informed consent. The study protocol was approved by the respective cantonal Ethical Review Boards.

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

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