Association between impaired lung function and carotid intima-media thickness in children

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To the Editor:

Cardiovascular disease (CVD) is a leading cause of mortality and a major contributor to the economic burden and healthcare utilisation globally [1]. In adults, a robust association between reduced lung function with poor CVD outcomes has been described, even in lifetime nonsmokers [2]. Low-grade systemic inflammation has been proposed to underpin the link between chronic lung diseases with endothelial dysfunction [3], arterial stiffness [4] and CVD events [5]. However, neither systemic inflammation nor traditional cardiometabolic adult risk factors have been shown to fully explain these clinical associations in adulthood [6]. This raises questions regarding the importance of early-life factors, particularly shared early risk factors and common pathways [6, 7]. The objective of this study was to examine the association between lung function with carotid intimal thickness (cIMT), a valid measure of CVD risk, at age 10 years. All associations were adjusted for potential confounders, and secondary analyses stratified by sex, household income, second-hand smoke exposure and obesity.

The Family Atherosclerosis Monitoring in Early Life (FAMILY) study is a longitudinal birth cohort study with 857 families (901 newborns) enrolled from 2002 and 2009 from three hospitals in Ontario, Canada. Details of the study have been published [8]. The study was approved by the ethics committee of each participating hospital. The present cross-sectional analysis included 394 children, who had complete data on high-quality lung function measurements and cIMT at age 10 years. The highest forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were selected for analysis. These were selected from a minimum of two acceptable and highly reproducible (<200 mL difference in FEV_1 and FVC) forced expiratory manoeuvres using a portable spirometer (EasyOne; NDD Medical Technologies, Switzerland). Spirometry variables were expressed as z-scores compared to the Global Lung Initiative normative values for age, sex, height and ethnicity. Carotid B-mode ultrasonography was conducted using Panasonic Diagnostic Ultrasound System (GM-72P00A) at a high resolution, with 7.5–10 MHz linear array transducer. A standardised protocol was used to obtain six well-defined measurements (1 cm longitudinal section) on the posterior wall of the right and left carotid artery at 1 cm proximal to the carotid bifurcation. Multivariable linear regression was used to examine the association between spirometry variables with cIMT adjusting for sex, annual household income (below/above CAD 50 000), second-hand smoke exposure (SHS), asthma status, body mass index (BMI) z-score, height z-score, systolic and diastolic blood pressure and preterm status. Secondary analyses were stratified by sex, SHS, household income and obesity status (z-score >2 SD on the World Health Organization growth reference) to examine the impact of these factors.

The cohort had a mean±SD age 10.66±1.07 years, 51% males, 89% Europeans, 82% with household income >CAD 50 000, 4% asthmatics and 12% SHS exposure. The mean±SD FEV_1 was 2.06±0.49 L, FVC 2.48±0.63 L, FEV_1/FVC 0.84±0.09 and cIMT 0.43±0.03 mm. There was significant inverse association between the FEV_1/FVC ratio z-scores and cIMT (b=−0.004, 95% CI −0.01–−0.00; p=0.0054) after adjusting for covariates (table 1), but no significant association between FEV_1 or FVC with cIMT. Males on average had higher cIMT compared to females (b=0.01, 95% CI 0.00–0.02; p=0.0044). Stratified analyses showed a similar inverse association in children with obesity (BMI z-score >2 SD), females and high-income households, while similar associations did not reach statistical significance in children with normal weight, males and low-income households. Lastly, a consistent inverse association was observed across children with or without exposure to SHS.

Shareable abstract (@ERSpublications)
Association between obstructive lung function impairment with higher cIMT is present in childhood after accounting for common risk factors. This suggests that a developmental link between obstructive lung diseases and CVD may have its origin in early life. https://bit.ly/4657s2b

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TABLE 1 Association of forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC), FEV_1 and FVC with carotid intima-media thickness (cIMT) overall and stratified by sex, household income, second-hand smoke and obesity status

	Subjects n	FEV_1/FVC z-score		FEV_1 z-score		FVC z-score	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Overall model after adjustment for covariates[#]		−0.004 (−0.01–−0.00)	**0.0054**	−0.00 (−0.00–0.00)	0.49	0.00 (−0.00–0.01)	0.07
Stratified analysis by sex[¶]							
Males	185	−0.004 (−0.01–0.01)	0.0816	−0.00 (−0.01–0.00)	0.8579	0.004 (−0.00–0.01)	0.0771
Females	171	−0.01 (−0.01–−0.00)	**0.0257**	−0.00 (−0.01–0.00)	0.3947	0.002 (−0.00–0.01)	0.4992
Stratified analysis by household income[+]							
>CAD 50 000	294	−0.006 (−0.01–−0.00)	**0.0005**	−0.00 (−0.01–0.00)	0.1926	0.00 (−0.00–0.01)	0.1009
⩽CAD 50 000	61	−0.00 (−0.01–0.01)	0.9782	0.00 (−0.01–0.01)	0.3437	0.01 (−0.01–0.02)	0.3459
Stratified analysis by second-hand smoke exposure[§]							
Yes	44	−0.009 (−0.02–−0.00)	**0.0168**	0.001 (−0.00–0.02)	0.1957	0.008 (0.00–0.01)	**0.0023**
No	312	−0.003 (−0.01–0.00)	**0.0342**	−0.00 (−0.01–0.00)	0.3885	0.00 (−0.00–0.01)	0.4673
Stratified analysis by obesity status[ƒ,##]							
Obese	54	−0.01 (−0.02–−0.00)	**0.0163**	−0.00 (−0.01–0.01)	0.7787	0.007 (0.00–0.02)	0.0625
Normal weight	302	−0.00 (−0.01–0.00)	0.0599	−0.00 (−0.00–0.00)	0.5753	0.00 (−0.00–0.01)	0.2874

Bold type represents statistical significance. [#]: each model was adjusted for sex, household income, second-hand smoke exposure, asthma, World Health Organization (WHO) body mass index (BMI) z-score, WHO height z-score, systolic blood pressure, and diastolic blood pressure; [¶]: each model was adjusted for household income, second-hand smoke exposure, asthma, WHO BMI z-score, WHO height z-score, systolic blood pressure, and diastolic blood pressure; [+]: each model was adjusted for sex, second-hand smoke exposure, asthma, WHO BMI z-score, WHO height z-score, systolic blood pressure, and diastolic blood pressure; [§]: each model was adjusted for sex, household income, asthma, WHO BMI z-score, WHO height z-score, systolic blood pressure, and diastolic blood pressure; [ƒ]: each model was adjusted for sex, household income, second-hand smoke exposure, asthma, WHO height z-score, systolic blood pressure, and diastolic blood pressure; [##]: obesity status was defined as BMI z-score >2 SD.

In this study, we found a significant inverse association between the FEV_1/FVC ratio and cIMT, suggesting that an obstructive ventilatory impairment at 10 years was already associated as a marker for elevated CVD risk. The mechanism(s) by which cIMT increases with lower lung function is not well understood, but alterations to elastin and collagen production and composition within the airway and the vasculature may be important [7, 9, 10]. Our findings align with other studies in children that have shown an association between lower lung function with increased arterial stiffness [7, 9, 10], even in much earlier age groups, suggesting an underlying developmental link. In addition, our stratified analyses demonstrated a stronger association in obese children than normal-weight children, raising the possibility of mediating adiposity-associated pathways. Indeed, in adults with asthma, obesity has been shown to be associated with higher systemic interleukin-6 inflammation [11], more impaired lung function and asthma exacerbations [11, 12]. Alternatively, obesity can have an immune-modulatory effect and dysregulation of airways responses to allergens and other environmental inhaled irritants [13], leading to an increased risk of lung function impairment. Furthermore, in a systematic review, the association between increased cIMT and adiposity was only observed at later time points in childhood and adolescence [14]. This suggests that there may be a lag between early-life obesity and the development of vascular changes that can be detected. Therefore, we cannot dismiss the possibility that obesity in early life may predispose to the development of both low lung function (obstructive) and higher cIMT.

Consistent with our findings, studies in adults have demonstrated an association between reduced lung function with increased cIMT among nonsmokers after adjusting for SHS [15]. However, we did not assess the intensity, frequency or duration of SHS exposure, all of which may have variable effects and may explain the statistically nonsignificant impact of this exposure in our study, especially in the early stages of life. Lastly, we observed a significant inverse association between lung function with cIMT in high-, but not low-household-income families. Unhealthy behaviours such as SHS exposure, physical inactivity, poor sleep quality and unhealthy diet are more prevalent in children from lower socioeconomic households, and may be more strongly related to cIMT than low lung function. This may explain the nonsignificant findings in the lower socioeconomic stratum.

This study has a number of limitations. The cross-sectional study design prevents us from drawing any conclusion on causality between lung function and cIMT. Exposure to SHS was self-reported and thus

prone to misclassification bias. Our cohort was predominantly of European ethnicity, which limits the generalisability of our findings to other ethnic groups. Finally, even though we accounted for many important covariates, our study may be susceptible to residual confounding.

In conclusion, our study provides evidence that the association between obstructive lung function impairment with higher cIMT is present in childhood, even after accounting for common risk factors. This adds to the evidence of possible early-life shared risk factors that may promote the development of cardiovascular and lung diseases later in life. Public health strategies targeting these early-life factors can mitigate the burden of cardiorespiratory diseases later in life.

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