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Cardiometabolic determinants of aortic and carotid intima-media thickness in adolescence

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ABSTRACT

Background and aims: Comprehensive longitudinal data in healthy populations on cardiometabolic determinants of arterial intima-media thickness (IMT), especially aortic IMT, in adolescence are lacking. We aimed to examine in detail how cardiometabolic risk factors associate with aortic and carotid intima-media thickness (IMT) in adolescence.

Methods: Participants (n = 522) were healthy individuals from Special Turku Coronary Risk Factor Intervention Project. IMT of the abdominal aorta and common carotid artery was measured repeatedly with ultrasonography at the age of 11, 13, 15, 17 and 19 years. Data on cardiometabolic risk markers were available beginning from early childhood.

Results: Between ages 11 and 19 years, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, serum total cholesterol, non-HDL-cholesterol, and apolipoprotein B levels, insulin and insulin resistance indicated by homeostasis model of insulin resistance (HOMA-IR), C-reactive protein, and smoking associated directly with aortic IMT. For carotid IMT, a direct association was found with BMI, waist circumference, systolic blood pressure and smoking. In multivariate analyses, BMI($\beta = 5.49$, SE = 1.01, $P < 0.0001$) and HOMA-IR ($\beta = 16.79$, SE = 7.45, $P = 0.02$) remained as determinants of aortic IMT. Correspondingly, BMI($\beta = 1.78$, SE = 0.42, $P < 0.0001$) and systolic blood pressure ($\beta = 0.38$, SE = 0.10, $P = 0.0001$) determined carotid IMT. Participants with longitudinal aortic or carotid IMT above/equal the 80th percentile had higher BMI measured from infancy than their peers with longitudinal IMT below the 80th percentile.

Conclusions: In adolescence, several cardiometabolic risk factors associate with aortic IMT while these links are less evident for carotid IMT. Aortic IMT may serve as a more sensitive marker than carotid IMT of early vascular remodeling.

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1. Introduction

Although cardiovascular diseases caused by atherosclerosis typically manifest after middle age, the disease process has its roots in childhood [1,2]. The key strategy to prevent atherosclerosis is thus the promotion of protective cardiovascular health factors and concomitant prevention of risk factor development beginning at an early age [3–5].

Ultrasonically measured arterial intima-media thickness (IMT) is shown to be a useful marker of vascular remodeling and morphologic adaptations in children and adolescents [6,7]. Previous studies have suggested that first atherosclerotic lesions begin to emerge in the aorta [8,9]. We have previously shown that children with hypercholesterolemia and type 1 diabetes show increased aortic and carotid IMTs compared with healthy controls, with a relatively greater increase in the aortic IMT than in the carotid IMT [10]. In the Muscatine Offspring Study, both aortic and carotid IMT were associated with BMI and blood pressure in adolescents, whereas the association of total cholesterol and low-density lipoprotein cholesterol (LDL-C) with carotid IMT was only seen later in young adulthood (age 18–34 years). [11]· We have previously reported in this same cohort, the longitudinal Special Turku Coronary Risk Factor Intervention Project (STRIP), that physical activity, fitness, and healthy diet were favorably associated with aortic, but not carotid, IMT in adolescence. [12–14]. However, comprehensive longitudinal data in healthy populations on cardiometabolic determinants of arterial IMT, especially aortic IMT, in adolescence are lacking.

Therefore, we examined the associations of several cardiometabolic risk markers with abdominal aortic and carotid IMT measured repeatedly from ages 11 (n = 430) to 19 years (n = 450). We sought to explore whether the cardiometabolic risk markers associate differentially with the aortic than carotid IMT.

2. Methods

For detailed methods, please see the online only supplement.

2.1. Study design and participants

The STRIP study, a prospective, randomized, controlled trial to prevent atherosclerosis beginning in infancy, recruited families with 5-month-old infants at well-baby clinics in Turku, Finland from 1990 to 1992 (Supplemental Fig. S1). At the age of 7 months, 1062 infants (56.5 % of the eligible age cohort) were randomly allocated to dietary intervention (n = 540) or control (n = 522) groups. The intervention group received individualized dietary counseling at least biannually beginning at the age of 8 months until the age of 20 years. The control group was seen biannually until the age of 7 years and annually thereafter until 20 years of age [15,16].

The STRIP study is conducted according to the guidelines of the Declaration of Helsinki and the study protocol was approved by the local ethics committee. Written informed consent was obtained from parents and from the children at age 15 and 18 years. The present study comprised adolescents who provided arterial ultrasound data. at ages 11 (n = 430), 13 (n = 510), 15 (n = 522), 17 (n = 494), or 19 years (n = 450).

2.2. Ultrasonic assessment of arterial IMT and distensibility

IMT and distensibility of abdominal aorta and common carotid artery were studied with ultrasonography (Acuson Sequoia 512 mainframe; Acuson, Mountain View, CA) at ages 11, 13, 15, 17, and 19 years, as previously described [15].

2.3. Anthropometric measurements and laboratory methods

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured

Table 1
Characteristics of the study cohort at the age of 11 and 19 years.

		11y		19y
	n	mean ± SD[a]	n	mean ± SD[a]
Height, cm				
Females	203	148.27 ± 7.38	230	167.37 ± 6.13
Males	237	147.28 ± 6.26	221	181.22 ± 6.23
Weight, kg				
Females	203	40.45 ± 8.99	229	62.97 ± 11.89
Males	237	38.51 ± 6.97	222	73.82 ± 11.92
BMI, kg/m^2				
Females	203	18.25 ± 3.03	229	22.44 ± 3.93
Males	237	17.68 ± 2.54	221	22.48 ± 3.49
Waist circumference, cm				
Females	203	63.92 ± 7.69	228	74.27 ± 9.61
Males	234	64.29 ± 7.08	222	80.67 ± 8.63
Systolic blood pressure, mmHg				
Females	203	106.92 ± 10.26	230	114.20 ± 11.54
Males	237	105.89 ± 9.54	221	127.52 ± 12.55
Diastolic blood pressure, mmHg				
Females	203	58.20 ± 5.85	230	64.70 ± 7.32
Males	237	58.97 ± 6.48	221	66.03 ± 7.94
Total cholesterol, mmol/L				
Females	202	4.53 ± 0.76	225	4.55 ± 0.76
Males	235	4.44 ± 0.71	222	4.06 ± 0.76
LDL cholesterol, mmol/L				
Females	201	2.85 ± 0.67	225	2.59 ± 0.65
Males	235	2.75 ± 0.61	221	2.41 ± 0.66
Non-HDL cholesterol, mmol/L				
Females	201	3.25 ± 0.72	225	3.09 ± 0.71
Males	235	3.11 ± 0.64	221	2.88 ± 0.70
HDL cholesterol, mmol/L				
Females	201	1.28 ± 0.24	225	1.45 ± 0.30
Males	235	1.33 ± 0.29	221	1.17 ± 0.24
Triglycerides, mmol/L				
Females	202	0.75 (0.39)[a]	225	1.00 (0.60)[a]
Males	235	0.65 (0.39)[a]	222	1.00 (0.50)[a]
Apo-A1, mmol/L				
Females	200	1.38 ± 0.19	225	1.65 ± 0.26
Males	231	1.41 ± 0.23	222	1.39 ± 0.19
ApoB, mmol/L				
Females	200	0.85 ± 0.19	225	0.84 ± 0.20
Males	231	0.81 ± 0.18	222	0.79 ± 0.20
Lp(a), mg/dL				
Females	202	11.95 (16.76)[a]	n/a	n/a
Males	235	10.12 (11.34)[a]	n/a	n/a
Glucose, mmol/L				
Females	n/a	n/a	225	4.73 ± 0.32
Males	n/a	n/a	222	4.95 ± 0.39
Insulin, mmol/L				
Females	n/a	n/a	223	7.17 ± 3.23
Males	n/a	n/a	218	7.30 ± 3.48
HOMA-IR				
Females	n/a	n/a	223	1.52 ± 0.75
Males	n/a	n/a	218	1.63 ± 0.84
CRP, mg/L				
Females	202	0.29 (0.59)[a]	225	1.11 (2.78)[a]
Males	236	0.23 (0.59)[a]	222	0.57 (1.29)[a]
Regular smoker, %				
Females	n/a	n/a	191	12.6
Males	n/a	n/a	192	15.1
Overweight, %[b]				
Females	203	17.3	229	9.6
Males	237	13.9	221	15.8
Obesity, %[b]				
Females	203	3.0	229	6.1
Males	237	1.3	221	3.2
Borderline high total cholesterol, %[c]				
Females	202	37.1	225	39.1
Males	235	40.4	222	23.0
High total cholesterol, %[c]				
Females	202	20.3	225	17.8
Males	235	13.2	222	7.2
Elevated blood pressure, %[d]				
Females	203	8.4	230	16.5
Males	237	4.6	221	27.2
Hypertension, %[d]				

(continued on next page)

Table 1 (*continued*)

		n	11y	n	19y
			mean ± SD[a]		mean ± SD[a]
Females	203	11.3	230	11.7	
Males	237	10.1	221	43.0	

BMI, body mass index; n/a, not available; HDL, high-density lipoprotein; Apo, apolipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; CRP, C-reactive protein.

[a] Data are median (interquartile range) for triglycerides, insulin, HOMA-IR, and CRP.

[b] Overweight and obesity status at the age of 11 years was defined according to the extended international (International Obesity Task Force) cutoffs for BMI (Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012; 7 (4):284–294). At the age of 19, overweight status was defined by having BMI ≥25.0–29.99 and obesity status was defined by having BMI ≥30.

[c] Dyslipidemia status was defined according to the NHLBI guidelines (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011; 128(Suppl 5): S213–S256) as having plasma total cholesterol ≥4.40–5.17 mmol/l (borderline high) and ≥5.18 mmol/l (high).

[d] Blood pressure status at the age of 11 years was defined according to the American Academy of Pediatrics guideline (Flynn JT, Kaelber DC, Baker-Smith CM et al. Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017; 140 (3): e20171904). At the age of 19, blood pressure status was defined according to the American College of Cardiology/American Heart Association guideline (Whelton PK, Carey RM, Aronow WS et al., 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Hypertension. 2018; 71 (6):e13-e115).

throughout the study with an oscillometric device. Venous blood samples were taken after an overnight fast. Standard methods were used to determine total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations. Low-density lipoprotein cholesterol was calculated indirectly using the Friedewald formula.

2.4. Statistical methods

Cardiometabolic determinants of arterial IMT were studied with linear mixed-effects models for repeated measures using compound symmetry covariance structure. All models included age and sex as covariates. The continuous cardiometabolic markers were standardized (*z* scored) by age and sex for the analyses to allow comparisons between exposures. To study lifetime trajectories of the significant cardiometabolic risk markers, participants were categorized as those with longitudinal IMT above/equal the 80th percentile (high IMT) and longitudinal IMT below to the 80th percentile (moderate/low IMT). Longitudinal associations of cardiometabolic risk markers starting from infancy with arterial IMT categories were studied with linear mixed-effects models for repeated measures using compound symmetry covariance structure adjusted by age and sex. Results were considered statistically significant at values of $P < 0.05$. Analyses were performed with the SAS 9.4 (SAS Institute, Cary, NC).

3. Results

Characteristics of the participants at age 11 and 19 years are shown in Table 1.

3.1. Determinants of aortic and carotid IMT

In longitudinal age and sex adjusted analyses, BMI, waist circumference, and systolic blood pressure were directly associated with aortic and carotid IMT between ages 11 and 19 years (Fig. 1, Supplemental Table S1). Additionally, diastolic blood pressure and concentrations of total cholesterol, non-HDL-cholesterol, triglycerides, ApoB, insulin, HOMA-IR, and CRP were directly associated with aortic IMT. In line, there was a direct association between the concentration of glucose and aortic IMT, but it failed to reach conventional statistical significance (P = 0.06). Additionally, regular smoking associated directly with aortic (β = 22.99, SE = 10.94, *P* = 0.04) and carotid (β = 11.33, SE = 5.05, *P* = 0.03) IMT.

To further explore determinants of aortic and carotid IMT, the cardiometabolic risk markers that significantly (using conventional p-value threshold of 0.05) associated with aortic or carotid IMT in the age and sex adjusted analyses (Fig. 1, Supplemental Table S1) were introduced to multivariate analysis. Due to expected multicollinearity between the risk markers, we applied VIF in the models (Supplemental Tables S2 and S3). This inspection resulted in the final multivariate models (Tables 2 and 3). In these analyses, BMI and HOMA-IR were both independently associated with aortic IMT (Table 2), whereas BMI and systolic blood pressure were both independently associated with carotid IMT (Table 3). The results were not altered after additional adjustment with parental socioeconomic status (data not shown). When smoking was additionally added to the multivariable models, it's associations with aortic (β = 16.42, SE = 10.89, *P* = 0.13) or carotid (β = 9.36, SE = 5.00, *P* = 0.06) IMT failed to reach conventional statistical significance.

Due to collinearity issues, total cholesterol was the only lipid variable that was selected in the final multivariate models. Therefore, we additionally tested the associations between IMT's and other lipid markers in multivariate models adjusted with age, sex and BMI. After these adjustments, none of the tested lipid parameters, including ApoB, non-HDL-cholesterol and triglycerides, associated with either aortic or carotid IMT (data not shown). The only exception was serum triglycerides, which showed borderline significant (P = 0.058) association with aortic IMT after adjustments with age, sex, and BMI.

BMI, HOMA-IR and systolic blood pressure trajectories beginning in infancy in individuals stratified by aortic and carotid IMT values measured in adolescence.

To depict links between the identified key risk markers - BMI, systolic blood pressure and HOMA-IR - with the aortic and carotid IMT, Fig. 2 shows the risk marker trajectories in individuals with high aortic IMT compared with peers who have moderate/low aortic IMT (A, BMI; B, HOMA-IR). Fig. 3 shows the risk marker trajectories in individuals with high carotid IMT compared with peers who have moderate/low carotid IMT (A, BMI; B, systolic blood pressure). Individuals with high aortic or carotid IMT in adolescence had higher BMI from infancy compared with those who had moderate/low aortic or carotid IMT. Furthermore, HOMA-IR in adolescence was systematically lower in individuals with moderate/low aortic IMT compared with those who had high aortic IMT. Correspondingly, systolic blood pressure from infancy onwards was higher in individuals who had high carotid IMT compared with their peers who had moderate/low carotid IMT.

4. Discussion

The present study shows the longitudinal associations of several cardiometabolic risk markers with longitudinally measured aortic and carotid IMT between ages 11–19 years. The data demonstrate that several risk markers associate with aortic IMT at this early age while less associations are evident with carotid IMT. In age and sex adjusted analyses, body size, blood pressure, serum total cholesterol, non-HDL-cholesterol, triglycerides and ApoB levels, insulin resistance, CRP level, and smoking associated directly with aortic IMT. For carotid IMT, age and sex adjusted direct associations were found with body size,

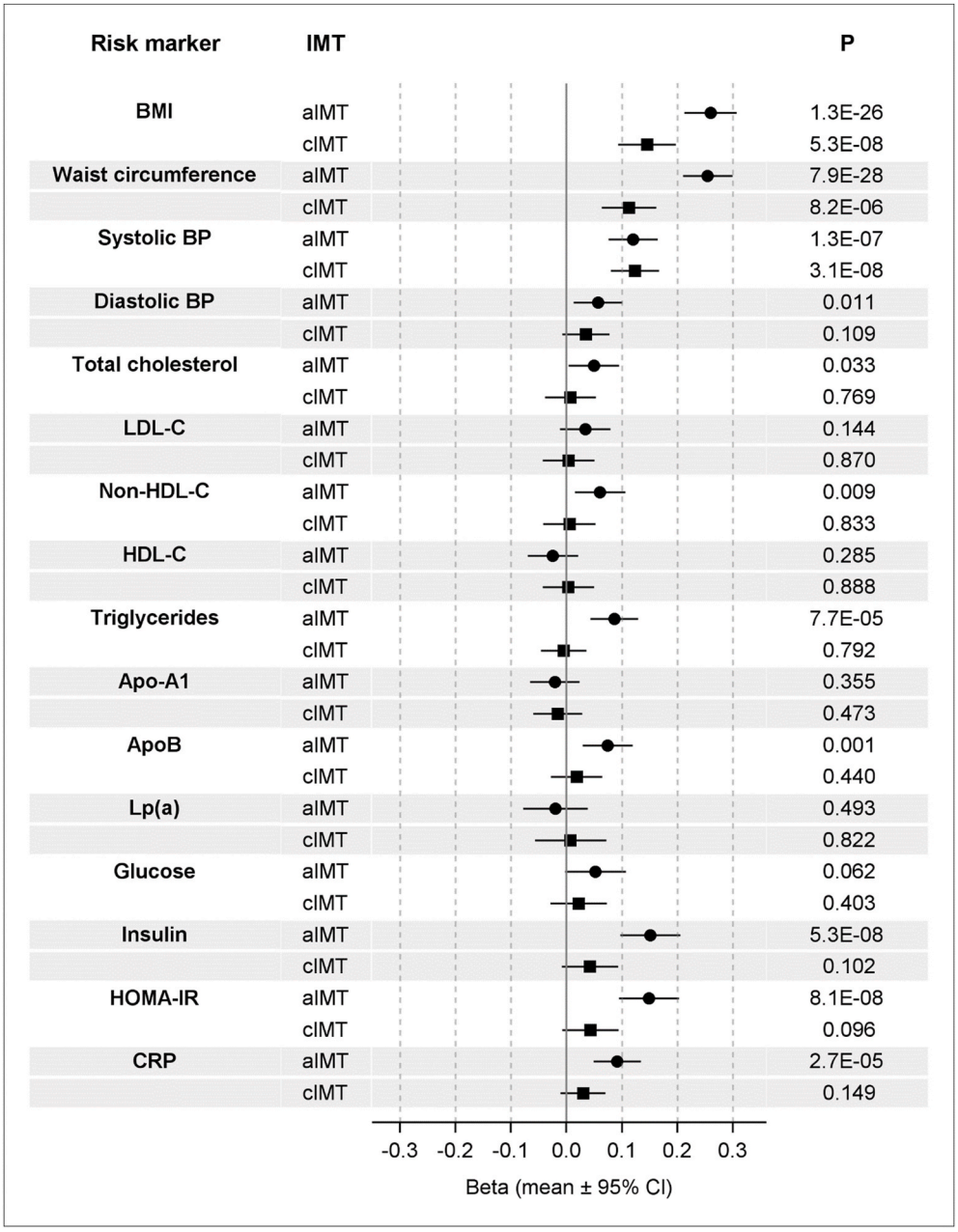

Fig. 1. Results of age- and sex-adjusted longitudinal association analyses of standardized cardiometabolic risk markers with standardized aortic IMT (aIMT) and carotid IMT (cIMT). Apo indicates apolipoprotein; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model of insulin resistance; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a).

systolic blood pressure, and smoking. Multivariate models revealed BMI and insulin resistance as the key determinants of aortic IMT, and BMI and systolic blood pressure as the key determinants of carotid IMT. Longitudinal data demonstrated that participants with high aortic or carotid IMT (≥80th percentile) had higher BMI measured since infancy compared to their peers with IMT<80th percentile. These data are unique because of the exceptional risk marker data meticulously collected since infancy and the concurrent assessment of arterial, especially aortic IMT.

Studies investigating the determinants of IMT, especially aortic IMT, at a young age in healthy individuals in a longitudinal setting are scarce. In the present study, BMI was an independent determinant of both aortic and carotid IMT. In our prior study investigating the associations of physical activity and aortic IMT, we similarly found that higher BMI and a wider waist circumference associate with higher aortic IMT in adolescents aged 13–17 years [12]. In line, children with overweight or obesity have increased carotid IMT compared with their normal weight counterparts in some earlier studies [10,17], but not in all [18]. Taken together, we found that body size, indicated by BMI, appear as a key cardiometabolic determinant of both aortic and carotid IMT during adolescence. BMI tracks from childhood to adulthood, and children with overweight or obesity have increased risk for cardiometabolic outcomes in adulthood, including high carotid IMT [19]. However, although BMI does track over time, some children and adolescents with a high BMI become non-obese as adults, and this change is associated with a reduction in the risk [19]. Therefore, health care providers should work to improve health behaviors especially among obese children and adolescents and recognize that cardiovascular risk may be substantially reduced if childhood and adolescent overweight/obesity is successfully prevented or treated.

Table 2
Results of longitudinal multivariate linear regression analyses. Cardiometabolic risk marker associations with aortic IMT (μm) (adjusted for age and sex). R^2 for the model: 0.072. Regression coefficient (standard error, SE) for a 1-unit change in a predictor variable.

Aortic IMT		
Risk marker	β/SE	*P*
BMI, kg/m^2	5.49/1.01	6.30×10^{-7}
Systolic blood pressure, mmHg	0.12/0.33	0.72
Diastolic blood pressure, mmHg	−0.36/0.51	0.49
Total cholesterol, mmol/L	4.50/4.52	0.32
Triglycerides, mmol/L[a]	7.36/8.50	0.39
HOMA-IR[a]	16.79/7.45	0.02
CRP, mg/L[a]	1.85/2.74	0.50

IMT, intima-media thickness; BMI, body mass index; HOMA-IR, homeostasis model of insulin resistance; CRP, C-reactive protein.
[a] log-transformed variable.

Table 3
Results of longitudinal multivariate linear regression analyses. Cardiometabolic risk marker associations with carotid IMT (μm) (adjusted for age and sex). R^2 for the model: 0.18. Regression coefficient (standard error, SE) for a 1-unit change in a predictor variable.

Carotid IMT		
Risk marker	β/SE	*P*
BMI, kg/m^2	1.78/0.42	1.90×10^{-5}
Systolic blood pressure, mmHg	0.38/0.10	0.0001

*log-transformed variable.
IMT, intima-media thickness; BMI, body mass index.

In addition to markers of body size, we found that systolic blood pressure associated with aortic and carotid IMT, whereas diastolic blood pressure associated only with aortic IMT. Similar results were reported from the previous cross-sectional Muscatine Offspring Study that studied determinants of aortic (n = 220) and carotid (n = 228) IMT in children and adolescents aged 11–17 years [11]. Echoing our present results, that study showed that BMI and systolic blood pressure associate with IMT of both arteries, and diastolic blood pressure had significantly stronger associations with aortic IMT than with carotid IMT [11]. Complementing the findings related to aortic IMT, autopsy studies have shown early atherosclerotic changes of the aorta to associate with hypertension in young people, particularly after age 25 years [8,20]. Our longitudinal results also further confirm previous findings from the ALSPAC Study in healthy children and adolescents aged 9–17 years showing that higher systolic blood pressure associated with increased carotid IMT at the age of 17 years [21]. Of note is that in our study, the association of systolic blood pressure with aortic IMT was not independent of other risk markers included in the multivariable model, suggesting that the other risk markers may play a more pronounced role on aortic IMT. We found direct and independent associations of systolic blood pressure and BMI with carotid IMT. On the other hand, there has also been some evidence that BMI might not affect carotid IMT directly as its influence would rather be mediated through other risk factors, such as systolic blood pressure [22]. It should be noted, however, that the cohort (784 subjects aged 10–24 years) applied by Gao et al. was enriched with type 2 diabetics, and therefore, the results may not be generalizable to other, more general populations.

We found that in age and sex adjusted models, serum total cholesterol, non-HDL-cholesterol, triglycerides and ApoB concentrations associated directly with aortic IMT but not with carotid IMT. In multivariate models for aortic IMT, however, the effects of these lipid markers were diluted to non-significant, especially after adjustment for BMI. Only serum triglycerides showed borderline significant (P = 0.058) association with aortic IMT after the adjustment. Similarly, the Muscatine Offspring Study observed an association between triglycerides and aortic IMT in adolescence aged 11–17 years but did not find associations between lipids and carotid IMT [11]. Our longitudinal results thus suggest that between the ages of 11–19 years, carotid IMT is not determined by the measured lipid and apolipoprotein concentrations. Furthermore, while higher serum total cholesterol, non-HDL cholesterol, triglyceride and ApoB concentrations associate with higher aortic IMT, these associations may not be independent of BMI - reflecting either confounding or shared causal pathways of body size and lipoprotein metabolism influencing vascular phenotypes. The observations from our study and the Muscatine Offspring Study may be in line with the findings of post-mortem studies performed in adolescents that have died from accidents or suicide, which have demonstrated that ante-mortem dyslipidemias associate with atherosclerotic lesions in the aorta during the first two decades of life [19,23].

Elevated Lp(a) is a strong and causal risk factor for cardiovascular outcomes [24], but it's role in the development of early atherosclerotic lesions is less well understood. We found virtually no associations between Lp(a) and IMT measures. This observation is in line with the recent findings in the Young Finns cohort, where we showed that Lp(a) measured in youth is strongly associated with cardiovascular events in adulthood, but not with the occurrence of carotid artery plaques or high carotid IMT [25]. These observations may suggest the importance of other potential pathological mechanisms of Lp(a) such as antifibrinolytic and proinflammatory properties rather than the initiation of atherosclerosis [24,26].

We observed that insulin resistance, as indicated by HOMA-IR, was directly associated aortic IMT but not carotid IMT. In line with our results, glucose and insulin levels were not associated with carotid IMT in adolescents aged 17 years in the ALSPAC Study [21]. We have previously shown that in children with diabetes but not in control subjects, LDL oxidizability correlated with carotid IMT [27]. Therefore, it has been suggested that in hyperglycemia, LDL particles may become more easily oxidized leading to increased foam cell formation and accelerated atherogenesis [27,28]. Alternatively, other mechanisms that have been proposed to underlie hyperglycemia induced atherogenesis are decreased nitric oxide bioavailability, including endothelial dysfunction, as well as increasing local activity of the renin–angiotensin–aldosterone system and elevation of the expression of angiotensin II receptors in the arterial tissue leading to arterial wall hypertrophy and fibrosis [29–31]. Further, hyperglycemia may exert its deleterious effects by leading to glycosylation of LDL, thus increasing its atherogenicity [32].

Findings from autopsy studies have shown that the earliest morphological changes in the arterial wall appear in the abdominal aorta [33]. Furthermore, cardiovascular risk factors have been associated more strongly with aortic IMT in adolescents (aged 11–17 years) while the associations with carotid IMT emerge later in young adults (aged 18–34 years) [11]. Our study among apparently healthy adolescents showed that several risk markers determine aortic IMT whereas fewer associations were found with carotid IMT. Our data thus support the previous findings that the cardiometabolic risk burden is reflected at earlier age on aortic IMT than on carotid IMT. It should, however, be noted that the resolution of ultrasonography is limited and differences in and changes of IMT over time in adolescents are small. Moreover, since the participants represent a general population cohort, in contrast to e.g. cohorts concentrated with a high proportion of individuals with overweight/obesity, presumably even more evident associations would be seen among high-risk adolescent populations with more obesity and hence more risk factors.

This study has limitations. The IMT measurements used in this study represent combined assessment of both the intimal and medial layers of the arterial wall. Therefore, it is not possible to differentiate whether the observed changes in IMT reflect early atherosclerotic alterations within the intimal layer, a remodeling response within the medial layer, or a combination of both. Whether increased IMT reflects atherosclerosis or

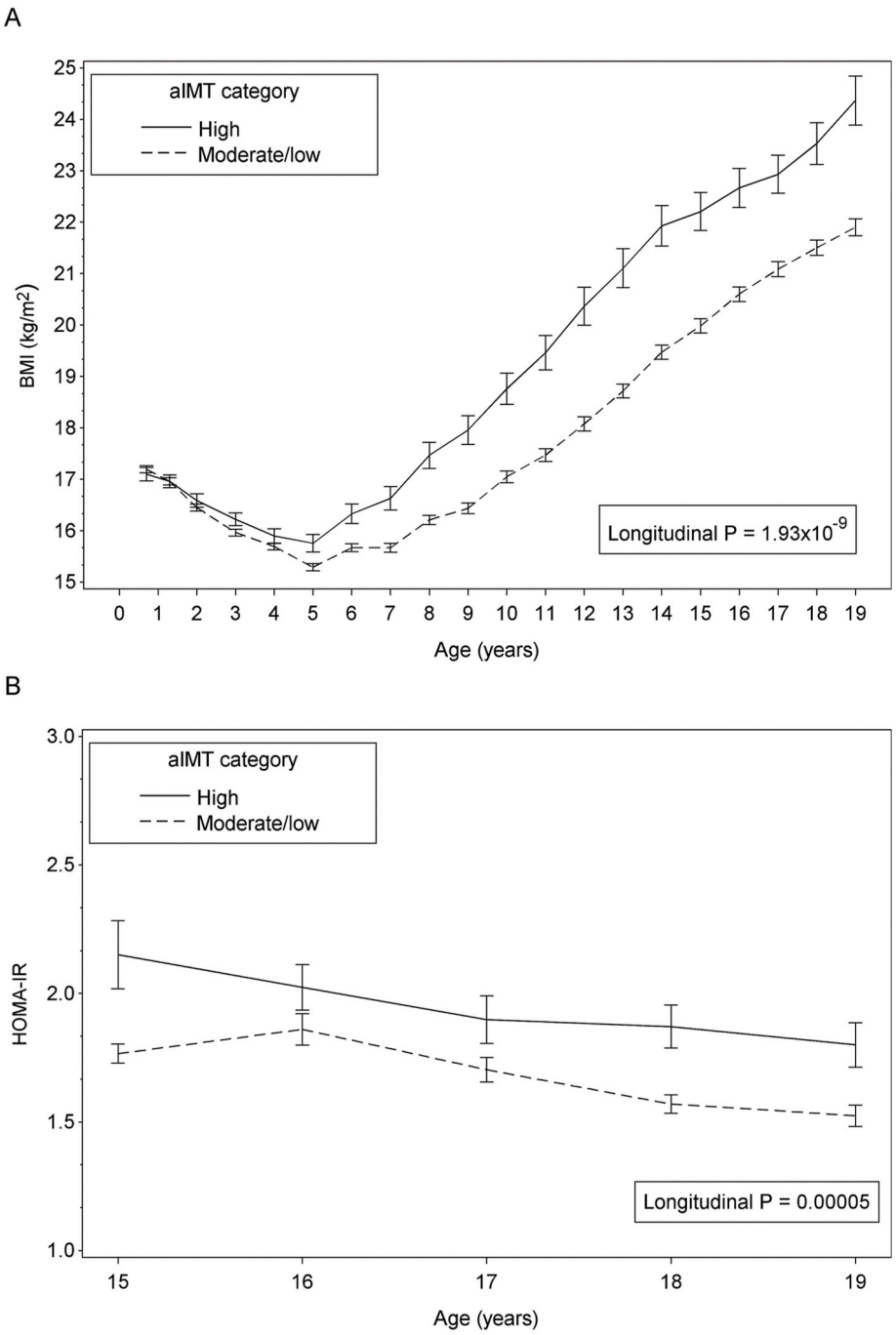

Fig. 2. Trajectories of A) body mass index (BMI) measured from early childhood to the age of 19 years and B) HOMA-IR measured from the age of 15–19 years in the participants with high or moderate/low aortic IMT (aIMT). High aIMT was defined as the highest 20th percentile of the age- and sex-standardized mean values (solid line). Participants with aIMT<80th percentile were determined as having moderate/low aIMT (dashed line). Whiskers represent ±standard error of the mean. Longitudinal P values are from repeated measures mixed models adjusted by age and sex. Log-transformed values were used for the analysis of HOMA-IR.

merely represents vascular adaptation that predisposes to atherosclerosis is not fully understood. However, recent data showed that screening for high carotid IMT in young adults may help identify individuals at high risk for future atherosclerotic cardiovascular disease [34]. In addition, Bao et al. reported data from the large Malmö Study that carotid IMT significantly added predictive information to conventional risk factors for atherosclerotic cardiovascular disease events in individuals aged 46–68 years followed up to 10 years [35]. Another potential limitation of the STRIP study is the likely unavoidable selection bias in the initial recruitment of participants; families that took part in the trial might have been more interested in health-related issues than families which did not participate. Moreover, half of the participants have received systematic counseling on a heart-healthy diet since infancy, and although the control group children did not receive the dietary counseling, they probably were more aware of their health-related behaviors and factors than typical Finnish children. They e.g. completed food records similar to the intervention peers and were informed of their serum cholesterol values, which could have inadvertently caused them to modify their behavior and diet. Given that belonging to the trial likely has led the STRIP participants to have healthier lifestyles than their peers, our results may underestimate rather than overestimate the true associations between cardiometabolic risk markers and IMT. Further

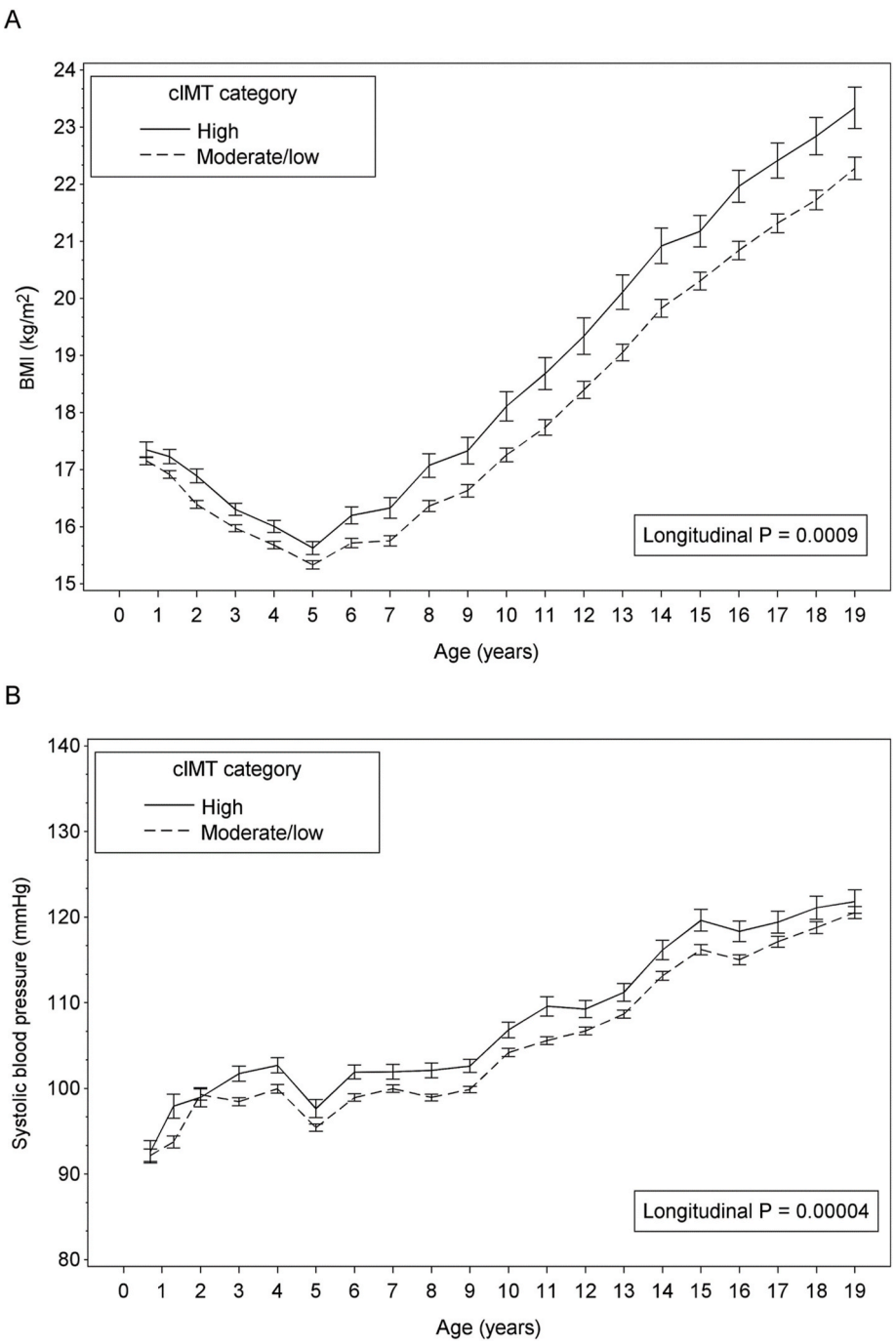

Fig. 3. Trajectories of A) body mass index (BMI) and B) systolic blood pressure measured from early childhood to the age of 19 years in the participants with high or moderate/low carotid IMT (cIMT). High cIMT was defined as the highest 20th percentile of the age- and sex-standardized mean values (solid line). Participants with cIMT<80th percentile were determined as having moderate/low cIMT (dashed line). Whiskers represent ±standard error of the mean. Longitudinal P values are from repeated measures mixed models adjusted by age and sex.

limitations of the study include loss-to-follow-up, which is inevitable in such a long-term study as the STRIP. Of the original 1062 participants who entered the study in 1990–1992, 522 (49.2 %) had the requisite information to conduct the present study. The characteristics of those participating in the study and those lost to follow-up have been compared repeatedly and no major differences have been found e.g. with regard to body weight, BMI, serum total cholesterol or saturated fat intake [15]. In addition, loss-to-follow-up analyses regarding components of a cardiometabolic risk factor cluster, the metabolic syndrome, and the STRIP study group showed that discontinuation in the study was not affected by these characteristics [36]. Moreover, those subjects who attended the ultrasound studies did not differ from the subjects in the entire STRIP study cohort with respect to their cardiometabolic risk factors. [37]. In addition, due to the long time period during which the IMT measurements were done in this study, the measurements were not conducted by a single observer. Also, as children in the STRIP study are all Caucasian the results may not be generalizable to other ethnicities. Major strengths of the study include the exceptionally long follow-up period, beginning in infancy; the large number of repeatedly studied participants and frequent follow-ups (at least one a year); as well as the use of well-established methods, including the repeated in vivo assessment of arterial IMT.

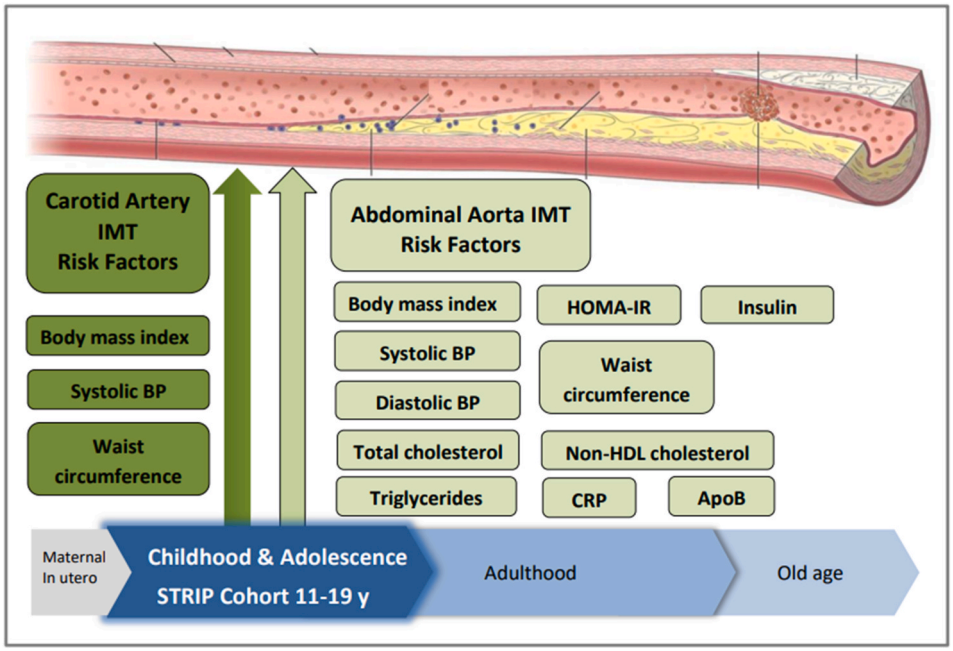

Fig. 4. Graphical abstract.

In conclusion, several cardiometabolic risk markers associate with aortic IMT already in adolescence while these links are less evident for carotid IMT. These observations suggest that aortic IMT is a more sensitive marker than carotid IMT of early vascular remodeling. These findings suggest that compared to carotid IMT, aortic IMT is more susceptible to the effects of cardiometabolic risk markers, and more priorly affected by them (Fig. 4).

CRediT authorship contribution statement

Tomi T. Laitinen: Conceptualization, Methodology, writing the manuscript. **Hanna Mikola:** Conceptualization, Methodology, writing the manuscript. **Katja Pahkala:** Conceptualization, Project administration, Methodology, data collections, statistical consulting, commenting and writing the manuscript. **Juha Mykkänen:** Conceptualization, Methodology, data collections, statistical consulting, commenting and writing the manuscript. **Suvi P. Rovio:** data collections, commenting and writing the manuscript. **Harri Niinikoski:** data collections, commenting and writing the manuscript. **Tapani Rönnemaa:** data collections, commenting and writing the manuscript. **Jorma S.A. Viikari:** data collections, commenting and writing the manuscript. **Antti Jula:** data collections, commenting and writing the manuscript. **Hanna Lagström:** data collections, commenting and writing the manuscript. **Pia Salo:** data collections, commenting and writing the manuscript. **Joel Nuotio:** commenting and writing the manuscript. **Mika Ala-Korpela:** data collections, commenting and writing the manuscript. **Markus Juonala:** data collections, commenting and writing the manuscript. **Costan G. Magnussen:** data collections, commenting and writing the manuscript. **Olli T. Raitakari:** Conceptualization, Project administration, Study design, data collections, commenting and writing the manuscript.

Disclosure of interest

None declared.

Data sharing statement

Data access may be permitted on a case-by-case basis upon request only. Investigators can submit an expression of interest to the chairman of the STRIP steering group (Prof. Olli Raitakari).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120218.

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