

ORIGINAL RESEARCH

Preclinical Aortic Atherosclerosis in Adolescents With Chronic Disease

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BACKGROUND: Adolescents with chronic disease are often exposed to inflammatory, metabolic, and hemodynamic risk factors for early atherosclerosis. Since postmortem studies have shown that atherogenesis starts in the aorta, the CDACD (Cardiovascular Disease in Adolescents with Chronic Disease) study investigated preclinical aortic atherosclerosis in these adolescents.

METHODS AND RESULTS: The cross-sectional CDACD study enrolled 114 adolescents 12 to 18 years old with chronic disorders including juvenile idiopathic arthritis, cystic fibrosis, obesity, corrected coarctation of the aorta, and healthy controls with a corrected atrial septal defect. Cardiovascular magnetic resonance was used to assess aortic pulse wave velocity and aortic wall thickness, as established aortic measures of preclinical atherosclerosis. Cardiovascular magnetic resonance showed a higher aortic pulse wave velocity, which reflects aortic stiffness, and higher aortic wall thickness in all adolescent chronic disease groups, compared with controls ($P<0.05$). Age ($\beta=0.253$), heart rate ($\beta=0.236$), systolic blood pressure ($\beta=-0.264$), and diastolic blood pressure ($\beta=0.365$) were identified as significant predictors for aortic pulse wave velocity, using multivariable linear regression analysis. Aortic wall thickness was predicted by body mass index ($\beta=0.248$) and fasting glucose ($\beta=0.242$), next to aortic lumen area ($\beta=0.340$). Carotid intima-media thickness was assessed using ultrasonography, and was only higher in adolescents with coarctation of the aorta, compared with controls ($P<0.001$).

CONCLUSIONS: Adolescents with chronic disease showed enhanced aortic stiffness and wall thickness compared with controls. The enhanced aortic pulse wave velocity and aortic wall thickness in adolescents with chronic disease could indicate accelerated atherogenesis. Our findings underscore the importance of the aorta for assessment of early atherosclerosis, and the need for tailored cardiovascular follow-up of children with chronic disease.

Key Words: adolescents ■ atherosclerosis ■ children ■ chronic disease ■ cIMT ■ CMR

Atherosclerosis is a life-long disease that starts during childhood.¹ Adolescents with chronic disease are often exposed to long-term inflammatory, metabolic, or hemodynamic abnormalities, which can accelerate atherogenesis.² Over the past decades, follow-up studies of adolescents and young adults with chronic disorders such as obesity and rheumatoid disorders underscored their enhanced

cardiovascular risk.³⁻⁵ Nonetheless, detection of early atherosclerosis and identification of adolescents at risk remains challenging. A recent scientific statement from the American Heart Association therefore emphasized the need to develop and implement novel methods for the assessment of preclinical atherosclerosis, next to conventional carotid intima-media thickness (cIMT) measurements.²

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CLINICAL PERSPECTIVE

What Is New?

- The Cardiovascular Disease in Adolescents with Chronic Disease study used cardiovascular magnetic resonance imaging to study aortic stiffness and wall thickness, which are established measures of preclinical atherosclerosis in adults.
- Adolescents with cystic fibrosis, aortic coarctation, juvenile idiopathic arthritis, and obesity all showed enhanced aortic stiffness and wall thickness.

What Are the Clinical Implications?

- The enhanced aortic stiffness and wall thickness in adolescents with chronic disease could indicate accelerated atherogenesis, yet longitudinal studies are needed to assess the prognostic relevance.
- Our findings underscore the importance of the aorta for assessment of early atherosclerosis, and the need for tailored cardiovascular follow-up of children with chronic disease.

Nonstandard Abbreviations and Acronyms

AWT	aortic wall thickness
CDACD	Cardiovascular Disease in Adolescents with Chronic Disease study
cIMT	carotid intima-media thickness
CoA	coarctation of the aorta
PWV	pulse wave velocity

A promising location for the assessment of early atherosclerosis is the aorta. Postmortem studies have shown that atherogenesis starts in the aorta during childhood, and that the extent of aortic plaque formation correlates strongly with the severity of coronary atherosclerosis development.^{1,6} Aortic measures of preclinical atherosclerosis may therefore improve identification of adolescents at risk. Here, we report the CDACD (Cardiovascular Disease in Adolescents with Chronic Disease) study, which investigated preclinical aortic atherosclerosis in adolescents with chronic disease. Cardiovascular magnetic resonance (CMR) was used to assess aortic pulse wave velocity (PWV) and aortic wall thickness (AWT), which are established measures of preclinical atherosclerosis in adults.^{7,8} Conventional cIMT was assessed using ultrasonography, to compare aortic and carotid measures of preclinical atherosclerosis.

The CDACD study prospectively enrolled adolescents with various chronic disorders, to evaluate

different cardiovascular risk factor profiles. The study population included adolescents with cystic fibrosis (CF) and obesity, both characterized by metabolic and inflammatory risk factors, adolescents with juvenile idiopathic arthritis (JIA), primarily considered an inflammatory disorder, and adolescents with corrected coarctation of the aorta (CoA), which frequently coincides with hypertension.⁹ The CDACD study is the first to investigate aortic measures of preclinical atherosclerosis in adolescents with several chronic disorders, and to assess the association with chronic disease-associated risk factors.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

One hundred fourteen adolescents aged 12 to 18 years were enrolled in the cross-sectional, observational CDACD study at the Wilhelmina Children's Hospital in Utrecht, the Netherlands, between April 2017 and June 2019. The study population included patients with CF (n=24), corrected CoA (n=25), rheumatoid factor negative polyarticular or extended oligoarticular JIA (n=20), obesity (n=20), and healthy adolescents with a corrected atrial septal defect as control group (ASD, n=25). Obesity was defined as a body mass index (BMI) >30 kg/m² projected to the age of 18 years, according to the international Obesity Task Force.¹⁰ Exclusion criteria for all participants were acute illness, mental retardation, pregnancy, or contraindications for magnetic resonance imaging with gadolinium-based contrast agents. Medication use for diabetes and hypertension included insulin for CF-related diabetes (3 patients with CF), and antihypertensive medication (1 patient with CoA). Three patients with obesity reported smoking. Written informed consent was obtained from all participants or their parents/guardians. The study complied with the Declaration of Helsinki, and ethical approval was obtained from the institutional Medical Research Ethics Committee (protocol number 16–589).

Clinical Measurements

Waist and hip circumference were measured following established clinical standards.¹¹ Blood pressure was measured 3 times at the right arm after a 10-minute rest while seated. The lowest measurement of 3 readings was used.

CMR Imaging

CMR was performed on a Philips 3.0 T clinical MR system. Aortic PWV was assessed using velocity-encoded magnetic resonance imaging, obtaining 150 phases per cardiac cycle during free-breathing. Two through-plane phase-contrast measurements were obtained in the ascending aorta and in the abdominal aorta, planned perpendicular to the aortic central lumen line. Subsequent calculation of the PWV was performed after automatic detection of the pulse wave arrival time using Mass software (Medis, Leiden, the Netherlands) (Figure S1), as described previously.¹² Reliability of the aortic PWV measurements was excellent with an intrarater and interrater intraclass correlation coefficient of 0.99 (Table S1).

The thoracic and abdominal aortic wall were imaged using a fast 3D T1-weighted black blood spin echo (Volume ISotropic Turbo spin echo Acquisition; VISTA) sequence during 4 minutes of free-breathing without ECG gating, following a survey and B1 calibration scan. Analysis was performed by manual tracing of the inner and outer contours of the vessel wall with 0.6-mm increments and 1.2-mm slice thickness, analyzing 1 out of 5 slices using VesselMass software (Medis, Leiden, the Netherlands), following an established protocol (Figure S2).¹³ Thoracic and abdominal AWT measurements highly correlated (Figure S3), and reliability analyses showed a high intrarater and interrater reliability for the thoracic trajectory with an intraclass correlation coefficient >0.75. Considering the suboptimal reliability of the abdominal measurements, with an intrarater and interrater intraclass correlation coefficient of 0.72 and 0.54, respectively (Table S2), only thoracic measurements were used in subsequent analyses.

Ultrasonography (cIMT)

cIMT was measured in anterolateral, posterolateral, and mediolateral directions in both the right and left carotid artery 1 cm proximal to the carotid bulb, using a Philips EPIQ 5 clinical system and a 12.5 MHz broadband transducer. The leading edges of the lumen-intima and media-adventitia were automatically detected on an R-top frozen longitudinal image of the far wall using built-in software (Philips Qlab). The mean value of 6 measurements was used.

Statistical Analysis

In case of normally distributed variables, mean and SD were reported and groups were compared against controls (ASD group) using independent *t* tests. In case of nonnormality, median and interquartile range are shown and groups were compared against controls using Mann–Whitney *U* tests. Benjamini and Hochberg's correction for false discovery was applied to correct for multiple testing

when appropriate. For multivariable linear regression analysis, a maximum of 10 variables was subjected to backwards selection of variables, to prevent overfitting. These variables included age, sex, and established hemodynamic, inflammatory, and metabolic predictors, as detailed in the table legends. Outliers of predictor variables were removed if they were 3 interquartile ranges above the third quartile, or below the first quartile. Predictor variables were natural-logarithmically transformed if their skewness was >1. To prevent collinearity between predictor variables, 1 variable was selected in case of a correlation >0.5. Cases with missing values were excluded from analysis, resulting in analysis of 88 cases for PWV, 94 cases for AWT, and 102 cases for cIMT. Statistical analyses were performed using IBM SPSS Statistics 24.

RESULTS

Adolescents With Chronic Disease Show Distinct Risk Factor Profiles

Healthy adolescents who underwent elective ASD repair at a young age and showed normal cardiac dimensions and function during follow-up were included as controls (Table 1). Compared with the control group, patients with CF showed a pancreatic insufficiency phenotype with low cholesterol and insulin levels, in combination with elevated alanine aminotransferase levels. Furthermore, CF is associated with visceral adipose tissue accumulation, which was reflected by a high waist-to-hip ratio (WHR) (Table 1).¹⁴ Patients with CoA showed a characteristic elevation of their systolic blood pressure (SBP) and a higher waist-to-hip ratio, the latter of which may be explained by the male predominance in this group. Adolescents with JIA had a history of polyarticular or extended oligoarticular JIA, yet most patients with JIA were in remission during the study and did not show signs of active systemic inflammation (Table 1). Finally, obese adolescents showed characteristic features including a higher weight, body mass index (BMI), waist-to-hip ratio, lower insulin sensitivity (quantitative insulin sensitivity check index), dyslipidemia with high fasting triglycerides and low high-density lipoprotein cholesterol levels, and elevated high-sensitivity C-reactive protein levels reflecting low-grade systemic inflammation (Table 1).

Arterial Measures of Preclinical Atherosclerosis in Adolescents With Chronic Disease

Aortic PWV and AWT were higher in all adolescent chronic disease groups compared with controls, even when corrected for multiple testing (Figure 1, Table S3). Meanwhile, conventional cIMT measurements were only higher in adolescents with CoA, compared with controls (Figure 1, Table S3). While aortic PWV and AWT measurements

Table 1. Clinical Characteristics

	ASD	CF	CoA	JIA	OB
No. (male/female)	25 (3/22)	24 (13/11)**	25 (17/8)***	20 (6/14)	20 (8/12)*
Age (y)	14.32 (12.66–17.02)	15.92 (14.18–17.29)	14.55 (12.73–16.46)	16.10 (13.82–16.95)	14.61 (12.99–16.72)
Race (White/BAME)	25/0	24/0	23/2	24/2	10/10***
Puberty (pre-/puberty)	3/22	2/22	2/23	1/19	1/19
Height (m)	1.68 (1.55–1.70)	1.70 (1.62–1.74)*	1.71 (1.58–1.77)	1.68 (1.61–1.76)	1.67 (1.62–1.72)
Weight (kg)	51.7 (40.9–65.8)	54.6 (50.3–60.0)	57.2 (45.7–66.2)	57.7 (48.4–63.9)	89.4 (83.0–97.4)***
BMI (SD)	−0.15 ± 0.99	−0.36 ± 0.93	0.19 ± 1.26	0.07 ± 1.06	3.23 ± 0.33***
Waist-to-hip ratio	0.76 (0.73–0.79)	0.84 (0.78–0.89)**	0.81 (0.77–0.85)*	0.79 (0.73–0.83)	0.91 (0.83–0.96)***
Hemodynamic					
HR (bpm)	69.83 ± 6.72	77.29 ± 12.05*	68.76 ± 11.32	71.20 ± 12.18	74.45 ± 12.35
SBP (mm Hg)	114.28 ± 11.44	115.63 ± 11.35	122.20 ± 11.62*	114.45 ± 11.66	122.50 ± 9.76*
SBP percentile ¹⁵	62.00 (28.50–90.00)	55.5 (39.25–83.75)	91.00 (62.00–96.00)*	66.50 (22.50–85.00)	84.50 (77.75–92.50)
DBP (mm Hg)	64.00 (60.00–67.00)	65.00 (61.50–67.75)	66.00 (63.00–70.00)	66.00 (65.00–70.75)	65.50 (63.50–68.50)
DBP percentile ¹⁵	46.08 ± 26.11	45.38 ± 23.78	51.12 ± 20.20	54.25 ± 18.11	50.50 ± 20.17
Metabolic					
Fasting glucose (mmol/L)	5.00 (4.90–5.30)	5.25 (4.83–5.73)	5.20 (4.95–5.30)	5.10 (4.90–5.58)	5.20 (4.93–5.48)
Fasting insulin (mmol/L)	9.50 (8.05–14.00)	7.40 (5.60–9.80)*	9.30 (6.40–10.00)	9.85 (8.43–14.00)	21.00 (13.75–31.25)***
QUICKI	0.34 ± 0.02	0.35 ± 0.03	0.35 ± 0.02	0.33 ± 0.02	0.30 ± 0.02***
ALAT (U/L)	14.00 (10.00–19.00)	24.50 (16.00–39.25)**	13.00 (11.00–18.50)	13.00 (11.00–16.0)	22.00 (13.25–32.75)*
Total cholesterol (mmol/L)	4.06 ± 1.01	3.20 ± 0.82**	4.03 ± 0.52	3.92 ± 0.44	4.31 ± 0.58
LDL-cholesterol (mmol/L)	2.10 (1.70–3.10)	1.50 (1.13–2.08)	2.40 (1.90–2.70)	2.25 (1.93–2.50)	2.49 (2.20–3.10)
HDL-cholesterol (mmol/L)	1.37 ± 0.22	1.16 ± 0.22**	1.27 ± 0.23	1.28 ± 0.25	1.22 ± 0.21*
Triglycerides (mmol/L)	0.80 (0.50–0.90)	0.80 (0.60–0.90)	0.80 (0.65–1.05)	0.80 (0.60–1.00)	1.10 (1.00–1.40)***
Inflammatory					
Leukocytes (×10 ⁹ /L)	6.40 (5.30–7.65)	6.20 (4.68–7.80)	5.40 (4.60–6.95)	5.80 (5.00–6.98)	7.05 (5.68–8.58)
hs-CRP (mg/L)	0.86 (0.38–5.97)	3.94 (0.92–13.73)	1.14 (0.42–4.16)	1.16 (0.45–4.67)	9.24 (5.58–26.49)**

Original data without correction for age and sex. Mean±SD or median (lower quartile-upper quartile) were reported. All chronic disease groups were compared with healthy ASD controls.

ALAT indicates alanine-aminotransferase; ASD, corrected atrial septal defect (control group); BAME, Black, Asian, and minority ethnic: Turkish, Moroccan; BMI (SD), body mass index SD from the age- and sex-matched population mean; bpm, beats per minute; CF, cystic fibrosis; CoA, corrected coarctation of the aorta; DBP percentile, diastolic blood pressure percentile based on the age-, sex-, and height-matched population; HDL-cholesterol, high-density-lipoprotein cholesterol; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; JIA, juvenile idiopathic arthritis; LDL-cholesterol, low-density-lipoprotein cholesterol; OB, obesity; QUICKI, quantitative insulin sensitivity check index; and SBP percentile, systolic blood pressure percentile based on the age-, sex-, and height-matched population.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

correlated (Spearman $\rho = 0.220$), cIMT measurements neither correlated with aortic PWV nor AWT measurements (Figure S4). In summary, CMR revealed enhanced pre-clinical measures of aortic atherosclerosis in all adolescent chronic disease groups, while conventional cIMT measurements were only higher in the CoA group, compared with controls.

Identification of Disease-Associated Predictors for Preclinical Atherosclerosis

Studying hemodynamic, metabolic, and inflammatory risk factors associated with preclinical atherosclerosis

may aid identification of adolescents at risk for early atherosclerosis. Multivariable linear regression analysis identified age, heart rate, and diastolic blood pressure as significant predictors for PWV, while systolic blood pressure was a negative predictor for PWV (Table 2). AWT was significantly predicted by aortic lumen area, BMI (SD), and fasting glucose levels, even after exclusion of the obese population (Table 3, Table S4). Finally, cIMT was predicted by sex, systolic blood pressure, and low-density-lipoprotein cholesterol levels (Table 4). Taken together, PWV, AWT, and cIMT were predicted by different combinations of hemodynamic and metabolic parameters.

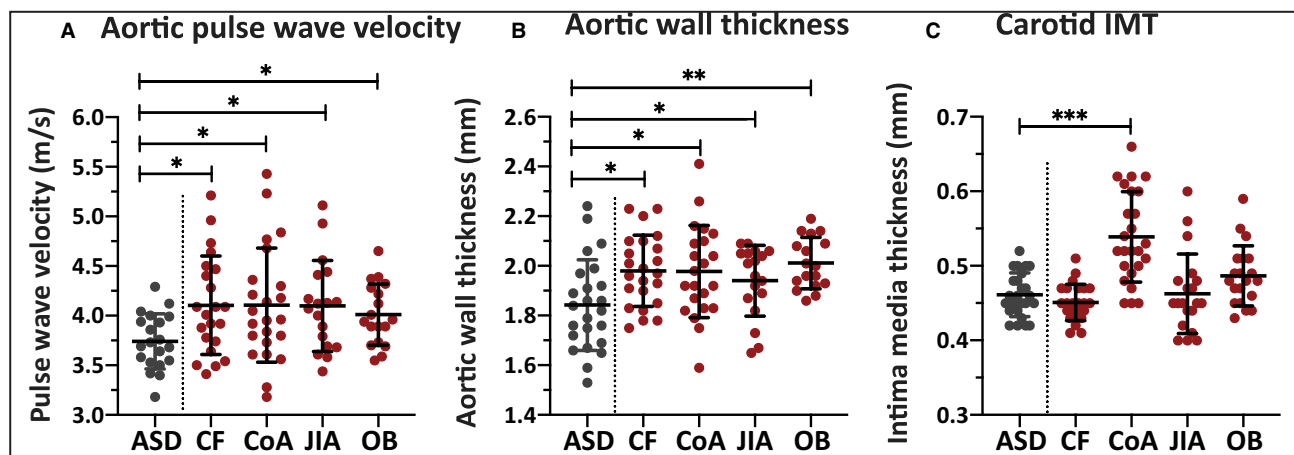


Figure 1. Arterial measures of preclinical atherosclerosis in adolescents with chronic disease

CMR-assessment of aortic pulse wave velocity (A) and aortic wall thickness (B), compared with conventional ultrasonography assessment of cIMT (C) of adolescents with chronic disease (red dots) and healthy ASD controls (gray dots). Analyses were corrected for multiple testing. ASD indicates corrected atrial septal defect (controls); CF, cystic fibrosis; cIMT, carotid intima-media thickness; CoA, corrected coarctation of the aorta; JIA, juvenile idiopathic arthritis; and OB, obesity. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

DISCUSSION

Adolescents with chronic disease are frequently exposed to inflammatory, metabolic, or hemodynamic abnormalities, which can accelerate atherogenesis. We investigated aortic and carotid measures of preclinical atherosclerosis in adolescents with various chronic diseases, including CF, JIA, CoA, and obesity. Aortic PWV and AWT are established measures of preclinical atherosclerosis in adults, and were assessed using CMR.^{7,8} All adolescent chronic disease groups showed enhanced aortic stiffness, reflected by a high aortic PWV, and a high AWT, compared with controls. The CDACD study thus revealed enhanced aortic measures of preclinical atherosclerosis in all adolescent disease groups. In contrast, conventional ultrasonography-based cIMT measurements were only higher in adolescents with CoA, compared with controls (Figure 2).

The CDACD study findings have several implications. First, the enhanced aortic stiffness and wall thickness in adolescents with chronic disease could indicate accelerated atherogenesis. In adults, aortic PWV is a strong predictor of atherosclerotic disease and cardiovascular events, independent of established cardiovascular risk factors.^{7,15,16} AWT is also considered a preclinical measure of atherosclerosis.^{8,17} The difference in aortic PWV between adolescents with chronic disease and controls in the CDACD study seems relatively small (4.0–4.1 m/s versus 3.74 m/s, Table S3), yet reflects ≈ 10 years of vascular aging, based on data in adults showing 0.3 m/s difference in mean PWV between healthy young adults < 30 years of age, and healthy adults 30 to 39 years of age.¹⁶ For the AWT measurements, the CDACD study reports ≈ 0.15 mm difference between adolescents with chronic disease and controls (1.95–2 mm versus 1.83 mm, Table S3).

Table 2. Multivariable Linear Regression of Hemodynamic, Metabolic, and Inflammatory Risk Factors for Aortic PWV

Aortic PWV	Standardized β	Unstandardized β (CI)	$R^2 = 0.269$
			P value
Age (y)	0.253	0.062 (0.014 to 0.110)	0.013*
HR (bpm)	0.236	0.010 (0.002 to 0.019)	0.016*
SBP (mm Hg)	-0.264	-0.011 (-0.020 to -0.001)	0.026*
DBP (mm Hg)	0.365	0.029 (0.011 to 0.048)	0.002**
Fasting glucose (mmol/L)	0.188	0.206 (-0.003 to 0.415)	0.053

Variables were selected using backwards selection. Variables added for selection: age, sex (0=female, 1=male), BMI (SD), heart rate, aortic lumen area, SBP (mm Hg), DBP (mm Hg), LDL-cholesterol, fasting glucose, high-sensitivity CRP (natural log). BMI indicates body mass index; bpm, beats per minute; CRP, C-reactive protein; DBP, diastolic blood pressure; HR, heart rate; LDL-cholesterol, low-density-lipoprotein cholesterol; SBP, systolic blood pressure; and PWV, pulse wave velocity.

* $P < 0.05$.

** $P < 0.01$.

Table 3. Multivariable Linear Regression of Hemodynamic, Metabolic, and Inflammatory Risk Factors for AWT

AWT	Standardized β	Unstandardized β (CI)	$R^2=0.332$
			P value
Aortic lumen area (cm ²)	0.340	0.170 (0.080–0.260)	<0.001**
HR (bpm)	0.149	0.002 (0.000–0.005)	0.095
BMI (SD)	0.248	0.027 (0.008–0.046)	0.007**
Fasting glucose (mmol/L)	0.242	0.094 (0.025–0.162)	0.008**

Variables were selected using backwards selection. Variables added for selection: age, sex (0=female, 1=male), BMI (SD), HR, aortic lumen area, SBP (mm Hg), DBP (mm Hg), LDL-cholesterol, fasting glucose, high-sensitivity CRP (natural log). AWT indicates aortic wall thickness; BMI, body mass index; bpm, beats per minute; CRP, C-reactive protein; HR, heart rate; and LDL-cholesterol, low-density lipoprotein cholesterol.

** $P<0.01$.

Studies on AWT in young adults are scarce, but a 0.15 mm difference in AWT also appears to reflect 5 to 10 years of vascular aging.^{17,18} Taken together, the enhanced aortic PWV and AWT in adolescents with chronic disease reflect \approx 5 to 10 years of vascular aging and could indicate clinically relevant acceleration of atherogenesis. Longitudinal studies are needed to investigate the prognostic relevance for clinical atherosclerosis later in life.

Second, the PDAY (Pathological Determinants of Atherosclerosis in the Young) study previously established that atherogenesis starts in the aorta during childhood.¹ We observed enhanced aortic PWV and AWT in all adolescent chronic disease groups, while cIMT measurements were only enhanced in adolescents with CoA. The CDACD findings thus align with the PDAY study, because they fit in the established sequence of atherosclerosis, which initiates in the abdominal aorta and gradually extends to higher regions of the arterial tree. The explicit cIMT changes in the CoA group are most likely explained by a combination of hypertension and developmental defects in the proximal aorta and its branches.^{9,19,20} The CDACD findings also align with studies in nonhuman primates, which showed that atherosclerosis initiates in the iliac

arteries and abdominal aorta, and subsequently develops in higher regions of the arterial tree including the coronary and carotid arteries.^{21,22} Alternatively, the absence of carotid abnormalities in most of the chronic disease groups could be explained by a lower sensitivity of ultrasonography to detect arterial changes, compared with CMR. Further studies are needed to compare the sensitivity of different imaging modalities in detecting aortic and carotid atherogenesis in adolescents with chronic disease. The CDACD study findings nonetheless underscore the relevance of the aorta for the assessment of preclinical atherosclerosis. As such, implementation of aortic measures of preclinical atherosclerosis in pediatric cardiovascular screening programs could improve the identification of children at risk.

Third, the CDACD study findings suggest that adolescents with obesity, CF, CoA, and JIA could indeed be at risk for early atherosclerosis. Numerous studies have established the detrimental effects of childhood obesity on atherosclerosis development, yet studies investigating the cardiovascular health of adolescents with CF, CoA, or JIA are scarcer. In patients with CF, the effects of chronic dyslipidemia and inflammation on cardiovascular health are cause for emerging concern as life expectancy increases.²³ Cardiovascular studies in patients with CF reported a lower aortic distensibility and higher aortic stiffness index, in line with the CDACD study findings.^{24,25} Arterial abnormalities in adolescents with CoA have also been reported. Children with CoA showed a higher carotid and femoral IMT and higher aortic stiffness.^{19,20} Finally, the enhanced cardiovascular risk of adults with rheumatoid arthritis is cause for concern in children with JIA.²⁶ The few available ultrasound and oscillometric studies have yielded contradictory results in children with JIA.²⁷ One study reported CMR-based assessment of aortic abnormalities in adolescents with JIA, and showed a higher PWV in adolescents with JIA, in line with the CDACD study results.²⁸ Taken together, the CDACD study findings add to the existing cardiovascular data on adolescents with obesity, CF, CoA, and JIA, and

Table 4. Multivariable Linear Regression of Hemodynamic, Metabolic, and Inflammatory Risk Factors for cIMT

cIMT	Standardized β	Unstandardized β (CI)	$R^2=0.196$
			P value
Sex	0.313	0.035 (0.014 to 0.056)	0.001**
SBP (mm Hg)	0.193	0.001 (0.000 to 0.002)	0.041*
LDL-cholesterol (mmol/L)	0.253	0.021 (0.006 to 0.037)	0.007**

Variables were selected using backwards selection. Variables added for selection: age, sex (0=female, 1=male), BMI (SD), heart rate, SBP (mm Hg), DBP (mm Hg), LDL-cholesterol, fasting glucose, high-sensitivity CRP (natural log). BMI indicates body mass index; cIMT, carotid intima-media thickness; CRP, C-reactive protein; DBP, diastolic blood pressure; LDL-cholesterol, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

* $P<0.05$.

** $P<0.01$.

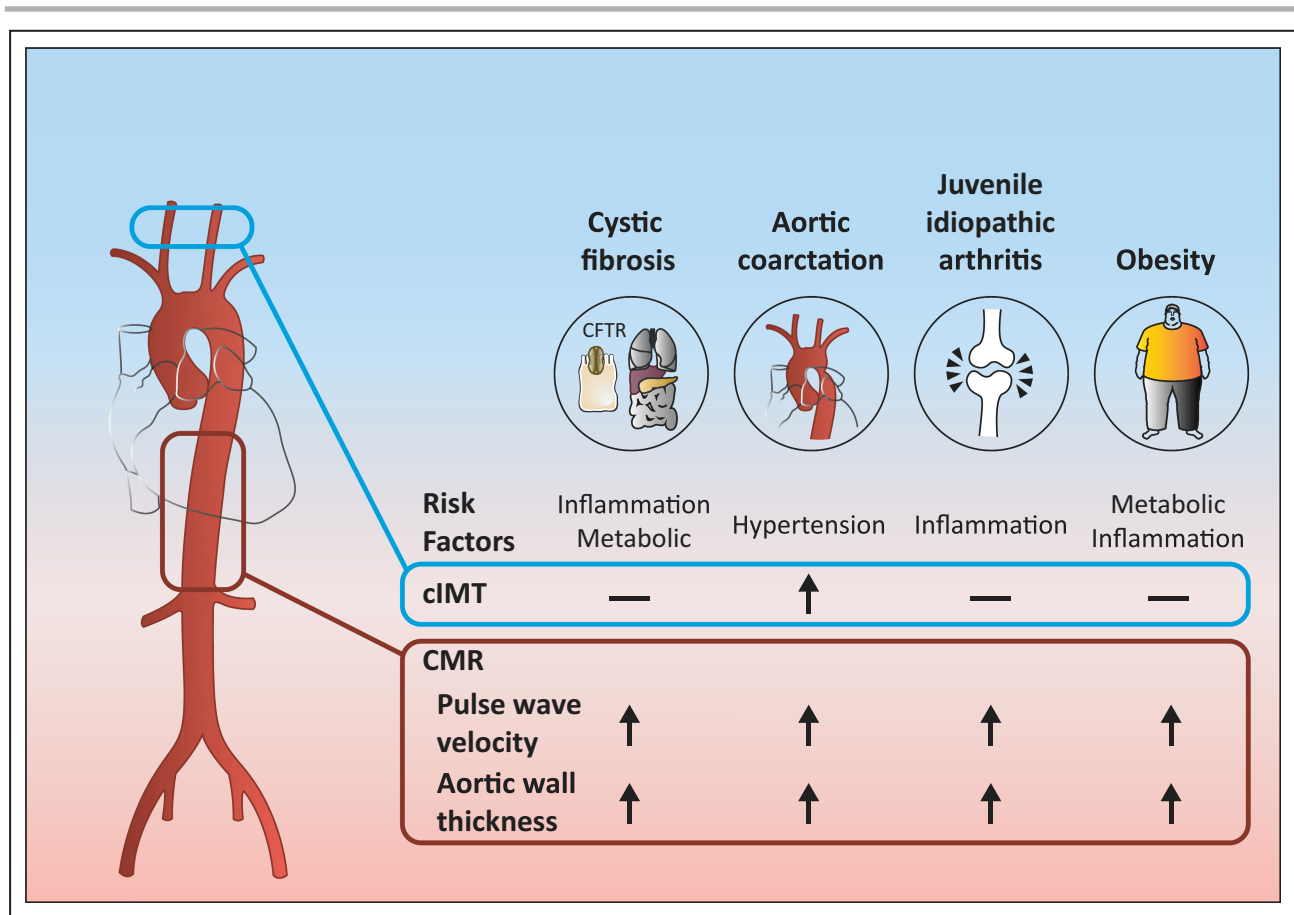


Figure 2. Measures of preclinical atherosclerosis in adolescents with chronic disease

Summary of the CDACD study findings following CMR assessment of aortic pulse wave velocity and aortic wall thickness, next to conventional carotid intima-media thickness measurements using ultrasonography, in adolescents with chronic disease. Upward arrows (↑) indicate an increase compared with the healthy controls and hyphens (—) indicate no difference. CDACD indicates Cardiovascular Disease in Adolescents with Chronic Disease study; CFTR, cystic fibrosis transmembrane conductance regulator protein; cIMT, carotid intima-media thickness; and CMR, cardiovascular magnetic resonance imaging.

suggest that they are at risk for early atherosclerosis. The CDACD study results cannot be generalized to all adolescents with chronic disease. Cardiovascular risk is a complex equation of disease-specific risk factors, comorbidities, and traditional cardiovascular risk and lifestyle factors, which requires careful evaluation in separate chronic disorders.² The CDACD study findings thus reinforce the emerging call for tailored cardiovascular follow-up and prevention studies in children with chronic disease.

Finally, chronic disease-associated predictors for preclinical atherosclerosis may help to identify adolescents at risk. Considering the relatively small sample size for predictor identification, the CDACD study should primarily be considered as hypothesis generating. Nonetheless, several interesting predictors were identified. First, previously established predictors for aortic PWV and AWT were confirmed in the CDACD study. Heart rate and diastolic blood pressure were identified as significant predictors for aortic PWV, in line

with previous studies.²⁹ Whether heart rate itself affects the viscoelasticity of the arterial wall, or its interaction with arterial stiffness is rather mediated by blood pressure, is debated.²⁹ Its interaction with aortic PWV seems particularly relevant for patients with CF, who showed a higher heart rate than the other chronic disease groups. The higher heart rate of adolescents with CF is in line with previous studies, and has been attributed to the cardiovascular effects of their lung disease, and to autonomic dysfunction.^{30,31} Their higher heart rate could affect arterial stiffness, even though adolescents with CF showed a normal diastolic and systolic blood pressure. Moreover, aortic lumen area was identified as a predictor for AWT. Aortic lumen area and AWT are both known to increase with age, although they develop in a distinct manner.^{13,17} From a theoretical perspective, aortic lumen area primarily depends on blood flow volumes, while AWT is determined by circumferential wall stress, which is, for example, related to blood pressure. Interestingly, circumferential wall stress also

increases with increasing lumen area, according to the law of Laplace.³² Next to their common dependence on growth, the interaction between aortic lumen area and AWT may therefore reflect a direct effect of aortic lumen area on circumferential wall stress. Furthermore, fasting glucose was identified as a predictor for AWT. The cardiovascular consequences of hyperglycemia are well established.³³ The underlying mechanisms linking glucose levels and aortic wall changes may include advanced glycation end products, which have been implicated in cross-linking collagen fibers, thereby decreasing distensibility of the arterial wall.³⁴ Inhibition of advanced glycation end products has been shown to reverse this pathophysiological process.³⁴ In addition, glucose may fuel vascular inflammation, as demonstrated by fluorodeoxyglucose–positron emission tomography studies in large vessel vasculitis.³⁵ Finally, BMI (SD) was identified as a predictor for AWT, and low-density-lipoprotein cholesterol was identified as a predictor for cIMT. Both BMI (SD) and low-density-lipoprotein cholesterol thus predicted arterial wall thickening rather than arterial stiffening, and may contribute to arterial lipid depositions, as suggested by studies involving patients with familial hypercholesterolemia.³⁶ Taken together, the identified predictors may provide insight into the early mechanisms driving atherogenesis. Follow-up studies are needed to validate the identified predictors, and to investigate whether additional modifiable risk factors are involved.

The CDACD study has several limitations. First, there were sex differences between groups. These sex differences are explained by disease epidemiology, because ASD is more common in females, and CoA is more common in males.³⁷ Our ASD control group therefore included a relatively high number of females, while the CoA group included a higher number of males. Multivariable regression analysis identified male sex as a positive predictor for cIMT, which may have contributed to the higher cIMT in the CoA group compared with ASD controls. At the same time, these sex differences cannot explain the lack of cIMT changes in the other disease groups, which counted a similar or higher number of males than the ASD control group. Second, our study included adolescents with corrected ASD as controls, rather than healthy controls without a medical history. The ASD controls underwent elective surgery early in life, and had normal cardiac dimensions and function during follow-up. Adolescents with corrected ASD and other minor cardiac repairs are frequently used as controls in pediatric cardiology studies. Studies that evaluated the long-term outcome after ASD repair confirm that these children are not at risk for developing atherosclerosis.³⁸ Nonetheless, the addition of a healthy control group without a medical history would have strengthened our study. Third, thoracic and abdominal AWT measurements highly correlated

(Figure S4), yet abdominal measurements showed sub-optimal intrarater and interrater reliability, in contrast to the thoracic measurements. The lower reliability of the abdominal measurements is most likely explained by abdominal aortic branching and lower signal-to-noise ratio because of closely surrounding organs and adipose tissue.¹³ Therefore, only thoracic measurements were reported and used in subsequent analyses. Finally, nutrition and lifestyle are important factors driving early atherosclerosis.³⁹ Adolescents with chronic disorders seem to engage in unhealthy lifestyles at similar or even higher rates than healthy peers.^{2,40} However, lifestyle factors have not been addressed in the current study. Further studies are needed to investigate the effect of nutrition and lifestyle factors on early aortic atherosclerosis in adolescents with chronic disease.

In conclusion, adolescents with chronic disease showed enhanced aortic PWV and AWT, compared with healthy ASD controls (Figure 2). The enhanced aortic PWV and AWT in adolescents with chronic disease could indicate accelerated atherogenesis, though longitudinal studies are needed to scrutinize their prognostic relevance for clinical atherosclerosis later in life. The CDACD study findings underscore the relevance of the aorta for assessment of early atherosclerosis in pediatric studies, and substantiate the emerging call for cardiovascular follow-up and prevention programs in children with chronic disease.

ARTICLE INFORMATION

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Acknowledgments

Author Contributions: FV coordinated the study and performed all laboratory work. FV, RN, GH, JK, IC, JD, LC, and YJ recruited and included patients and FV, GH, JK, IC, JD, LC, and YJ processed patient data. FV, GH, and IC analyzed magnetic resonance imaging data and performed reliability analyses. AE, HG, JW, and TL supported the magnetic resonance imaging measurements and analysis. FV and DK performed statistical analyses. FV and HS wrote the manuscript. HS designed and supervised the study as principal investigator. All authors provided valuable feedback and approved the manuscript for submission.

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Disclosures

Dr Kofink is a full-time employee of Abbott Laboratories. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4

Figures S1–S4

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Supplemental Material

Reliability analyses

In order to determine the intra-rater reproducibility, a random selection of scans was selected using an online random number generator and analyzed a second time by the same observer (Table S1 and S2). To reduce recall bias, there was at least a one-month interval between both analyses. For the assessment of the inter-rater reproducibility, a randomly selected set of 20 scans was analyzed by a second, independent observer.

Table S1. Reliability analysis for aortic pulse wave velocity measurements.

	ICC	95% CI	Mean difference (SD)	95% LOA
Intra-rater (n=10)	0.99	0.96- 1.00	0.0 (0.1)	-0.1- 0.2
Inter-rater (n=20)	0.99	0.96- 1.00	0.0 (0.1)	-0.1- 0.2

Table S2. Reliability analysis for aortic wall thickness measurements.

Thoracic aorta	ICC	95% CI	Mean difference (SD)	95% LOA
Intra-rater (n=20)	0.84	0.64- 0.94	0.03 (0.08)	-0.12- 0.19
Inter-rater (n=20)	0.79	0.55- 0.91	0.11 (0.13)	-0.14- 0.36

Abdominal aorta	ICC	95% CI	Mean difference (SD)	95% LOA
Intra-rater (n=20)	0.72	0.41- 0.88	0.02 (0.08)	-0.13- 0.17
Inter-rater (n=20)	0.54	0.13- 0.80	0.03 (0.12)	-0.22- 0.27

ICC: intraclass correlation coefficient (two-way mixed effects model assessing consistency of agreement between single measures), CI: confidence interval, SD: standard deviation, LOA: limits of agreement

Table S3. Aortic and carotid measures of preclinical atherosclerosis.

	ASD	CF	CoA	JIA	OB
Aortic pulse wave velocity (m/s)	3.74 ± 0.28	4.10 ± 0.50*	4.11 ± 0.58*	4.10 ± 0.46*	4.01 ± 0.31*
Aortic wall thickness (mm)	1.83 (1.70-1.95)	1.97 (1.85-2.10)*	1.95 (1.83-2.11)*	1.99 (1.86-2.06)*	2.00 (1.93-2.11)**
Carotid intima media thickness (mm)	0.46 (0.44-0.49)	0.45 (0.43-0.47)	0.52 (0.49-0.60)***	0.45 (0.42-0.48)	0.48 (0.45-0.51)

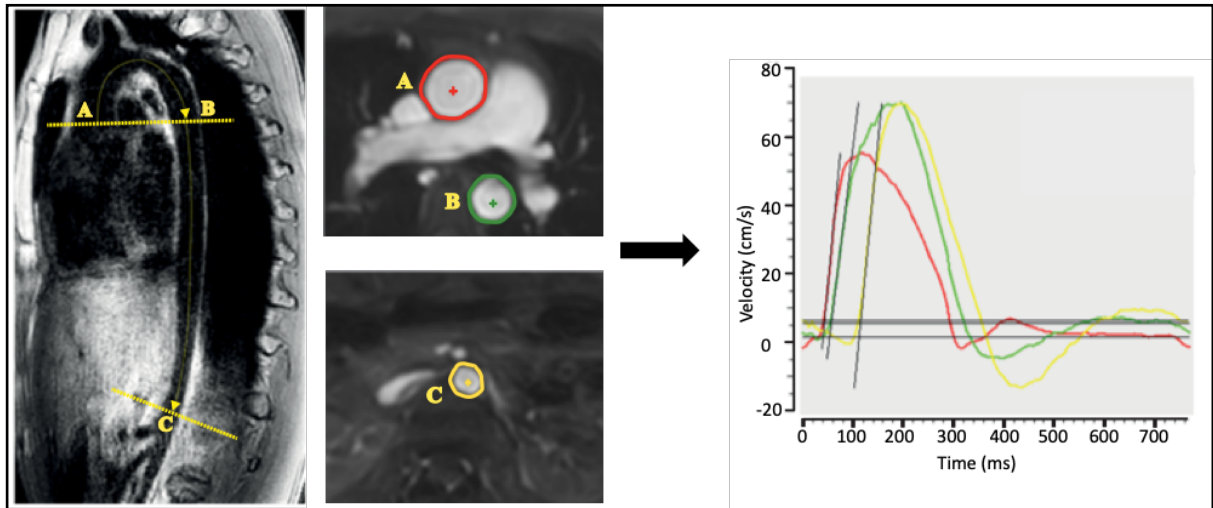
Original data, represented in the main manuscript in figure 1. All chronic disease groups were compared with healthy ASD controls, and analyses were corrected for multiple testing. *p<0.05, **p<0.01, ***p<0.001.

Table S4. Multivariable regression analysis after exclusion of obese adolescents.

Aortic wall thickness			R² = 0.36
	Standardized β	Unstandardized β (CI)	P-value
Heart rate (beats per minute)	0.195	0.003 (0.000- 0.006)	0.043*
Aortic lumen area (cm ²)	0.263	0.134 (0.035- 0.233)	0.009**
BMI (SD)	0.284	0.046 (0.015- 0.078)	0.005**
Fasting glucose (mmol/L)	0.297	0.120 (0.043- 0.198)	0.003**

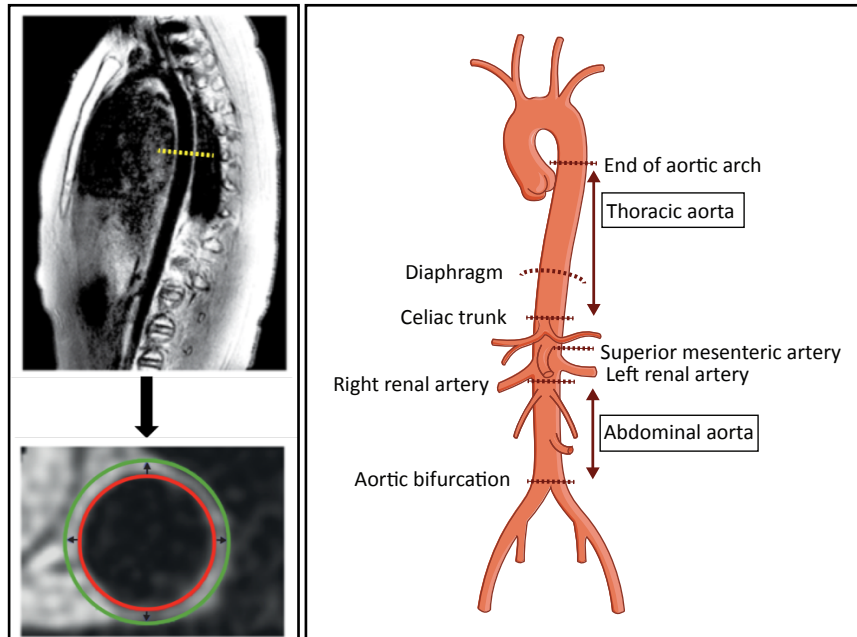
Variables were selected using backwards elimination. Variables added for selection: age, sex (0=female, 1=male), BMI-SD, heart rate, aortic lumen area (only for PWV and AWT, not for cIMT), SBP, DBP, LDL-cholesterol, fasting glucose, high-sensitivity CRP (natural log). CI: confidence interval, BMI (SD): body mass index standard deviation from age-and sex matched population mean. *p<0.05, **p<0.01.

Figure S1. Pulse wave velocity measurement.



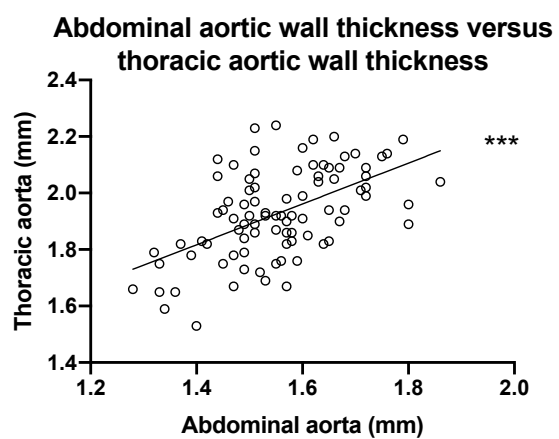
Pulse wave velocity measurement. Red contour (A): ascending aorta, green contour (B): descending aorta, yellow contour (C): abdominal descending aorta. The pulse wave arrival time was measured at A, B, and C and the pulse wave velocity was calculated between A and C (total trajectory).

Figure S2. Aortic wall thickness measurement.



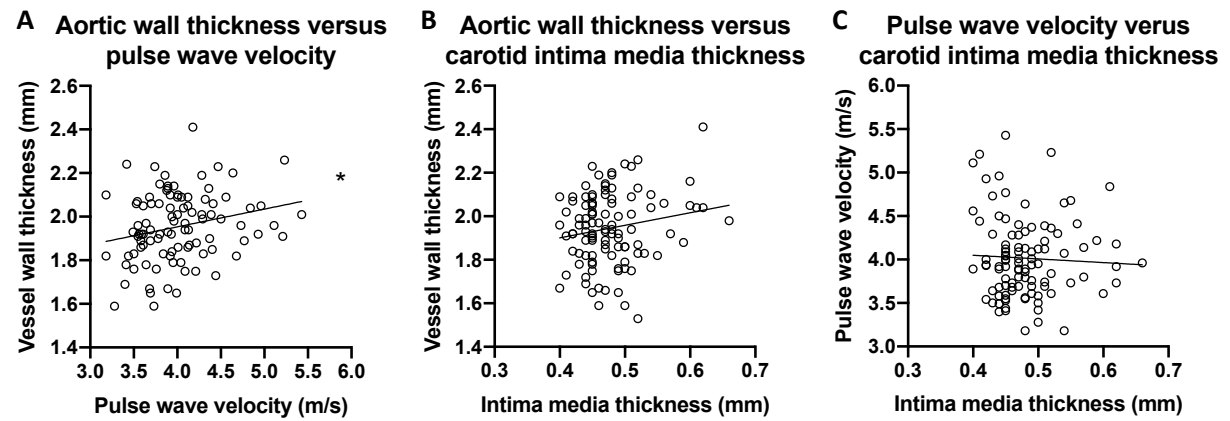
Green contour: outer contour of aortic wall, red contour: inner contour of aortic wall. The thoracic trajectory spans from the end of the aortic arch until the celiac trunk, the abdominal trajectory spans from below the renal arteries until the aortic bifurcation.

Figure S3. Abdominal aortic wall thickness versus thoracic aortic wall thickness.



Pearson's $R = 0.548$. *** $p < 0.0001$.

Figure S4. Correlation analysis of separate preclinical measures of atherosclerosis.



Spearman's rho = 0.220 (A). *p<0.05.