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ORIGINAL RESEARCH

Predictors of Carotid Intima-Media Thickness Progression in Adolescents—The EVA-Tyrol Study

Sophia J. Kiechl, MD; Anna Staudt, MD; Katharina Stock, MD; Nina Gande, MD; Benoît Bernar, MD; Christoph Hochmayr, MD; Bernhard Winder, MD; Ralf Geiger, MD; Andrea Griesmacher, MD; Markus Anliker, MD; Stefan Kiechl, MD; Ursula Kiechl-Kohlendorfer, MD, MSc; Michael Knoflach, MD; Raimund Pechlaner, MD, PhD; for the Early Vascular Ageing (EVA) Study Group;*

BACKGROUND: Cardiovascular disease depends on the duration and time course of risk factor exposure. Previous reports on risk factors of progression of carotid intima-media thickness (cIMT) in the young were mostly restricted to high-risk populations or susceptible to certain types of bias. We aimed to unravel a risk factor signature for early vessel pathology based on repeated ultrasound assessments of the carotid arteries in the general population.

METHODS AND RESULTS: Risk factors were assessed in 956 adolescents sampled from the general population with a mean age of 15.8±0.9 years, 56.2% of whom were female. cIMT was measured at baseline and on average 22.5±3.4 months later by high-resolution ultrasound. Effects of baseline risk factors on cIMT progression were investigated using linear mixed models with multivariable adjustment for potential confounders, which yielded significant associations (given as increase in cIMT for a 1-SD higher baseline level) for alanine transaminase (5.5 µm; 95% CI: 1.5–9.5), systolic blood pressure (4.7 µm; 0.3–9.2), arterial hypertension (9.5 µm, 0.2–18.7), and non-high-density (4.5 µm; 0.7–8.4) and low-density lipoprotein cholesterol (4.3 µm; 0.5–8.1).

CONCLUSIONS: Systolic blood pressure, arterial hypertension, low-density and non-high-density lipoprotein cholesterol, and alanine transaminase predicted cIMT progression in adolescents, even though risk factor levels were predominantly within established reference ranges. These findings reemphasize the necessity to initiate prevention early in life and challenge the current focus of guideline recommendations on high-risk youngsters.

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Key Words: atherosclerosis ■ cardiovascular disease ■ intima-media thickness ■ risk factors

Early stages of atherosclerosis already manifest in childhood and may progress to advanced lesions in later life.[1] Atherosclerosis progression depends on the cumulative exposure to risk factors but also on the time course of exposure: high low-density lipoprotein-cholesterol (LDL-C) levels in early life confer a particularly high cardiovascular disease (CVD) risk independently of total exposure,[2] suggesting that risk factor management should already start in the young. Previous investigations in youngsters found associations of atherosclerosis with hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking and weaker or less consistently with physical activity and low high-density lipoprotein-cholesterol

Correspondence to: Raimund Pechlaner, MD, PhD, Department of Neurology, Medical University of Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria. E-mail: raimund.pechlaner@i-med.ac.ator Michael Knoflach, MD, Department of Neurology, Medical University of Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria. E-mail: michael.knoflach@i-med.ac.at

*A complete list of the EVA Study Group members can be found in the Appendix at the end of the article.

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CLINICAL PERSPECTIVE

What Is New?

- Previously reported associations between risk factors and early vessel pathology in adolescents as assessed by carotid intima-media thickness were either cross-sectional in design or restricted to high-risk populations; here, determinants of carotid intima-media thickness progression in community-dwelling adolescents were identified using repeated ultrasound measurements.
- Systolic blood pressure, arterial hypertension, low-density and non-high-density lipoprotein cholesterol, and alanine transaminase predicted increases in carotid intima-media thickness after ≈2 years.
- Risk factor levels were predominantly within reference ranges.

What Are the Clinical Implications?

- These findings suggest that primary prevention should start in adolescence and not be confined to high-risk subjects.

Nonstandard Abbreviations and Acronyms

cIMT	carotid intima-media thickness
NAFLD	non-alcoholic fatty liver disease

(HDL-C).[3] These investigations mainly focused on carotid intima-media thickness (cIMT) as a surrogate of early atherosclerosis. Barring studies in selected high-risk groups,[4,5] previous investigations were either cross-sectional in design[6] or related earlier risk factor levels to later assessments of cIMT.[7,8] The latter approach, however, cannot define whether changes in the outcome preceded assessment of risk factors and may overestimate effect sizes if risk profiles are stable over time.[3]

Here, we relate baseline levels of risk factors to progression of cIMT as ascertained by repeated assessments in the Early Vascular Ageing (EVA)-Tyrol study. cIMT progression has recently been firmly established as a surrogate of CVD risk in a large-scale meta-analysis.[9]

METHODS

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

Study Design and Participants

The EVA-Tyrol study is a prospective cohort study conducted throughout Tyrol, Austria and South Tyrol, Italy between May 2015 and July 2018 at local schools and companies. The number of students sampled from each school or company is shown in Table S1. All schools and larger companies throughout Tyrol were contacted. Because of regulatory and organizational issues, in South Tyrol only schools in Bruneck were invited to participate. Students attending 9th or 10th grade (target age 14–16 years) and apprentices of the same age were eligible for participation. Follow-up was performed ≈2 years after the baseline examination. Age range and duration of follow-up period were chosen to enable follow-up before graduation for most students. The EVA-Tyrol study investigates a health promotion intervention to improve lifestyle risk factors in White adolescents. All participants included in the current analysis received the same intervention, which included counseling on individual risk factors. A detailed description of the methods has been published.[10] The study was approved by the ethics committee of the Medical University of Innsbruck and all participants and their legal representatives gave informed consent.

Laboratory Analysis

Plasma samples were drawn in the morning after an overnight fast, cooled, and immediately delivered to the laboratory of the Medical University of Innsbruck, Austria for analysis. A detailed description of all laboratory analysis methods has been published.[10] The Homeostatic Model Assessment for Insulin Resistance index was calculated as fasting insulin (mIU/L) multiplied by fasting glucose (mmol/L) divided by 22.5. Elevated alanine transaminase (ALT) was defined as ≥22 U/L in girls and ≥26 U/L in boys.[11] The definitions of the 2018 American Heart Association/American College of Cardiology/American Association of Cardiovascular and Pulmonary Rehabilitation/American Academy of Physician Assistants/Association of Black Cardiologists/American College of Preventive Medicine/American Diabetes Association/American Geriatrics Society/American Pharmacists Association/American Society for Preventive Cardiology/National Lipid Association/Preventive Cardiovascular Nurses Association Guideline on the Management of Blood Cholesterol for low HDL-C (≤40 mg/dL), hypercholesterolemia (LDL-C ≥130 mg/dL), and hypertriglyceridemia (triglycerides ≥130 mg/dL) in adolescents were used.[12]

Assessment of Lifestyle Risk Factors and Socioeconomic Status

Behavioral risk factors were assessed by standardized medical interviews with questionnaires adapted from

the Atherosclerosis Risk-Factors in Male Youngsters, Atherosclerosis Risk-Factors in Female Youngsters, and Bruneck studies.[13–15] Smoking and physical activity were assessed in physician-guided interviews. Participants were categorized as smokers if they regularly smoked at least 1 cigarette per week. Physical activity was assessed as engagement in moderate- or vigorous-intensity sports (ie, leading to an increase in heart rate and/or sweating) in minutes per day. Alcohol consumption was assessed in a face-to-face interview, and alcohol intake in grams/week was obtained by summing, for each participant, the product of alcohol content and intake frequency for each alcoholic beverage type. Socioeconomic status was assessed by means of the Family Affluence Scale score,[16] a proxy for family wealth, ranging from 0 to 9 points.

Anthropometry

Participants wore light indoor clothes and no shoes for weight and height measurements. Weight was assessed using calibrated medical precision scales and height was determined using a Harpenden stadiometer (Holtain, Crymych, United Kingdom). Body-mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressure were calculated as the mean of 3 measurements on the left and right upper arm in a sitting position, recorded after a 5-minute seated rest (automated oscillometric device OMRON M4-I, Omron Healthcare Co., Lake Forest, IL). *Z* scores for blood pressures were calculated using a reference data set[17] and arterial hypertension was considered present if any of the following conditions applied: systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or any of the 2 at or above the age- and sex-specific 95th percentile.[18]

Based on a German reference data set *Z* scores for BMI and waist circumference were calculated (Table S2).[19,20] Overweight was defined as BMI ≥85th percentile, and obesity as BMI ≥95th percentile.[21] Central obesity was defined as waist circumference at or above the 90th age- and sex-specific percentile.[22,23]

High-Resolution Ultrasound

Ultrasound measurements were taken in the supine position using a 6.0 to 13.0 MHz linear probe (GE 12L-RS) on a Vivid q ultrasound device (both General Electric Healthcare, Chicago, IL). Carotid intima-media thickness (cIMT) was assessed on the far wall of the distal 4 cm of the common carotid arteries on both sides by identifying the greatest far-wall thickness in longitudinal images. Three representative measurements were taken per side and cIMT taken as the maximum of all 6 measurements in order to identify the area with the greatest focal thickening. The maximum cIMT represents the focal nature of atherosclerosis (early plaque precursors) better than mean IMT that is also subject to homogenous, adaptive changes especially in the young.[24,25] A single rater experienced in ultrasound techniques and blinded to the clinical characteristics of the study participants (A.S.) performed all measurements on digitally stored images. For 103 participants, repeated assessment was performed to obtain a measure of intraobserver reproducibility, which yielded a Pearson correlation coefficient of 0.634 and an agreement-based intraclass correlation of 0.621.

Statistical Analysis

Characteristics of the study cohort at baseline and at follow-up are shown as count (percentage), mean±SD, or median (interquartile range). Associations with cIMT progression were investigated by linear mixed models with random intercepts for individual schools and adjusted for baseline cIMT, age, and sex (Model 1) or for baseline cIMT, age, sex, and measurements of the following variables both at baseline and at follow-up: systolic and diastolic blood pressure, BMI *Z* score, LDL-C, fasting glucose, smoking status (ever versus never smokers), and Family Affluence Scale score (Model 2, termed "multivariable adjustment"). To avoid multicollinearity, LDL-C, high LDL-C, and non-HDL-C were not adjusted for LDL-C; arterial hypertension and systolic and diastolic blood pressure were not adjusted for systolic or diastolic blood pressure; smoking status (current and ever smoking) and pack years of smoking were not adjusted for smoking status (ever versus never smoker); fasting glucose, fasting glucose >100 mg/dL, insulin resistance and Homeostatic Model Assessment for Insulin Resistance >2.6 mIU×mmol were not adjusted for fasting glucose; and BMI Dr*Z* score, overweight, and obesity were not adjusted for BMI *Z* score. In each case, neither the baseline nor the follow-up measurement was adjusted for. Additionally, in analyses involving liver parameters, alcohol intake in grams/day was adjusted for. Only established and probable risk factors but not the adjustment variables of Model 1 and Model 2 are shown in Figure 1. Continuous variables were scaled to unit variance for this analysis, such that effects represent the difference in cIMT progression for a 1-SD higher level. Assessment of predictors (Figure 1) was 93.5% complete. For glucose, insulin, and triglyceride measurements, values of nonfasting participants were set to the median of fasting participants' values (3.6%, 4.5%, and 1.5% of values, respectively). For all other variables complete case analyses were performed. Analysis was conducted using R 4.0.1 (R Project for Statistical Computing, Vienna, Austria). All *P* values are 2 sided and an alpha level of 0.05 is used.

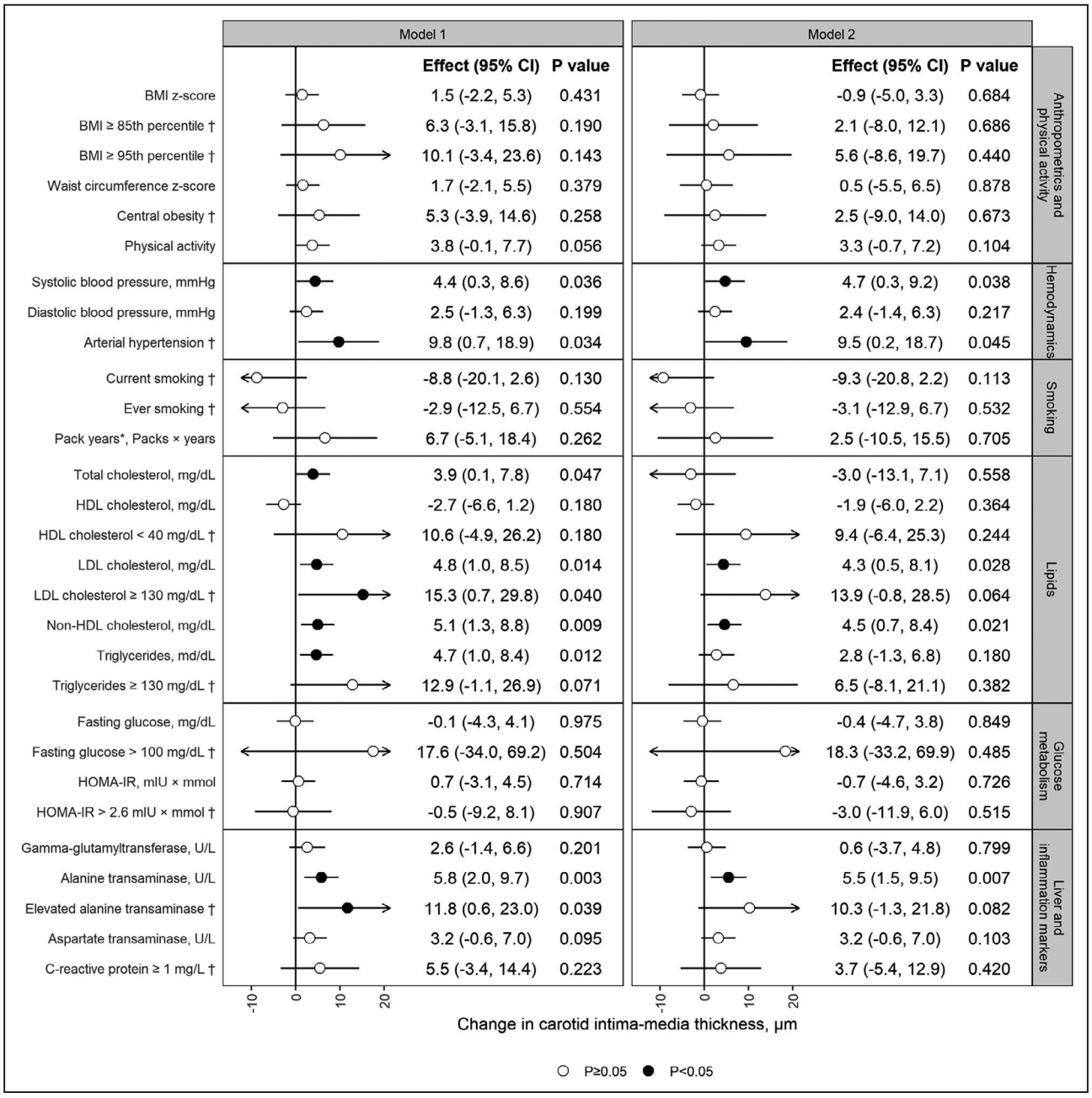

Figure. Predictors of carotid intima-media thickness progression in adolescents.
Predictors are shown on the y-axis and change in cIMT after 22.5 months of follow-up on the x-axis as points (main estimate) and horizontal ranges (95% CI). Effects are given for a 1-SD higher level for continuous variables and vs the reference category for categorical variables. Model 1: adjustment for baseline cIMT, age, and sex; Model 2: adjustment for baseline cIMT, age, sex, and for the following variables both at baseline and at follow-up: systolic and diastolic blood pressure, BMI *Z* score, LDL-cholesterol, fasting glucose, smoking status (never vs ever smoker) and Family Affluence Scale score (except for highly correlated variables, see Methods section for details), and alcohol consumption in grams/week (only for liver parameters). Only predictors but not the adjustment variables of Model 1 and Model 2 are shown on the y-axis. Under multivariable adjustment (Model 2), systolic blood pressure, arterial hypertension, LDL cholesterol, non-HDL cholesterol, and alanine transaminase were significantly associated with cIMT progression. Central obesity was defined as a waist circumference at or above the 90th age- and sex-specific percentile. Arterial hypertension was defined as a systolic blood pressure ≥130 mm Hg, a diastolic blood pressure ≥80 mm Hg, or any of the 2 at or above the age- and sex-specific 95th percentile. Elevated ALT was defined as an ALT ≥22 U/L in girls and ≥26 U/L in boys. *Never-smokers were excluded for this analysis. ALT indicates alanine transaminase; BMI, body mass index; cIMT, carotid intima-media thickness; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; and LDL, low-density lipoprotein. †Categorical variable.

RESULTS

A flow chart of the study population is shown in Figure S1. In brief, 1573 subjects participated in the baseline assessment, 1000 of them had a follow-up assessment, and complete data for cIMT measurements and adjustment variables were available for 956. Loss to follow-up was mostly because of graduating school, change of school, or illness on the day of examination. At baseline, participants who dropped out were on average older than participants who had a follow-up assessment (mean±SD; 16.2±1.2 versus 15.8±0.9 years), more often smokers (30.9% versus 13.2%) and apprentices (27.9% versus 5.5%), and had higher BMI *Z* scores (0.362±1.140 versus 0.173±0.999), whereas blood pressure, physical activity levels, liver enzymes, and lipid parameters were similar, as was baseline cIMT (473±54 and 473±54 µm).

Characteristics of the study population are shown in Table 1. The study participants were derived from 28 different schools and companies. Mean cIMT was 473 µm at baseline and 479 µm at follow-up 22.5±3.4 months later.

Systolic blood pressure, LDL-C, non-HDL-C, and ALT showed robust associations with cIMT progression under multivariable adjustment, with effect sizes of a 4.3 to 5.5 µm higher cIMT for a 1-SD higher level, and arterial hypertension (defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or any of the 2 at or above the age- and sex-specific 95th percentile) was associated with a 9.5 µm greater cIMT increase (Figure 1). Elevated ALT (defined as ALT ≥22 U/L in girls and ≥26 U/L in boys), LDL-C ≥130 mg/dL, and total cholesterol and triglyceride levels significantly predicted cIMT progression under adjustment for age, sex, and baseline cIMT but not under further multivariable adjustment. No significant associations with cIMT progression were detected for variables relating to body composition or overweight, smoking, physical activity, or glucose metabolism.

DISCUSSION

In community-dwelling adolescents, systolic blood pressure, arterial hypertension, LDL-C and non-HDL-C, and ALT predicted progression of cIMT, a measure of subclinical atherosclerosis and early vascular aging and a surrogate of CVD.[26] To the best of our knowledge, this is the first large community-based study investigating risk profiles for cIMT progression in adolescents. Previous longitudinal studies correlated earlier, childhood, or adolescent risk factor levels with later, adolescent, or adult cIMT measurements.[7,8] Other studies that prospectively assessed changes in cIMT were confined to high-risk groups and found systolic blood pressure and BMI predicting cIMT progression in children with type 1 diabetes mellitus[5] and lower cIMT progression during statin therapy in children with familial hypercholesterolemia.[4]

Among lipid parameters, LDL-C and non-HDL-C were directly associated with cIMT progression (Figure 1). LDL-C is among the most important predictors of cardiovascular events in adults, and strong evidence from intervention trials[27] and Mendelian randomization analyses[28] suggests that it is a causal risk factor. The small cholesterol-rich LDL particles penetrate the intima, where they ignite an inflammatory process that represents early atherosclerosis.[29] Non-HDL-C is the sum of LDL-C and remnant cholesterol, the cholesterol content of mostly delipidated triglyceride-rich lipoproteins. Remnant cholesterol has also been implicated as causative for ischemic heart disease,[30,31] and current guidelines recommend non-HDL-C for assessment of cardiovascular risk in standard lipid panels.[32]

Systolic blood pressure and arterial hypertension (defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or any of the 2 at or above the age- and sex-specific 95th percentile) were associated with cIMT progression, consistent with prior studies.[7,33] High blood pressure is the leading modifiable risk factor for premature CVD[34] and accounts for about half of the incidence of ischemic heart disease and stroke worldwide.[35] A causal relationship is highly probable,[36] and evidence is accumulating that blood pressure levels earlier in life and its cumulative burden are robust predictors of later CVD.[37,38] Therefore, blood pressure assessment and control starting early in life might be one of the most effective tools for preventing incident CVD. Some prior reports surmised that associations of cIMT with blood pressure in adolescents reflect physiological adaptations of the tunica media to hemodynamic stress[7] rather than subclinical atherosclerosis. However, we defined arterial hypertension according to age- and sex-standardized blood pressure *Z* scores,[16] making a purely physiological explanation for results found unlikely.

Liver enzymes are less established as cardiovascular risk markers in adults. Although a meta-analysis[39] and a Mendelian randomization study[40] reported a null association, a large high-quality analysis from the Framingham study found ALT to be directly associated with CVD[41] and this association was not confined to abnormally high ALT levels. ALT is considered to be linked to CVD because it is a sensitive marker of non-alcoholic fatty-liver disease (NAFLD).[42] NAFLD is associated with excess cardiovascular risk in adults because of its close association with metabolic abnormalities including hypertension, hypertriglyceridemia, and abnormalities of glucose homeostasis.[43] Although overweight and hypertension were prevalent in the current study (Table 1), insulin resistance, impaired fasting glucose, or diabetes mellitus were not, and none of these factors showed robust associations with cIMT progression on its own

Table. Baseline Characteristics of the Study Participants

	All	Men	Women
	956 (100%)	419 (43.8%)	537 (56.2%)
Demographics			
Age, y	15.8±0.9	16.0±0.9	15.7±0.8
Education			
General high-school	243 (25.4%)	60 (14.3%)	183 (34.1%)
Profession-oriented high-school	660 (69.0%)	323 (77.1%)	337 (62.8%)
Apprenticeship	53 (5.5%)	36 (8.6%)	17 (3.2%)
Family Affluence Scale score	6.24±1.59	6.32±1.57	6.17±1.60
Anthropometrics			
BMI, kg/m^2	21.5±3.2	21.6±3.4	21.4±3.1
BMI, *Z* score	0.173±0.999	0.212±1.010	0.143±0.989
BMI ≥85th percentile	186 (19.5%)	84 (20.0%)	102 (19.0%)
BMI ≥95th percentile	78 (9.2%)	35 (9.5%)	43 (9.0%)
Waist circumference, *Z* score	0.450±0.931	0.434±0.920	0.462±0.940
Central obesity	197 (20.6%)	82 (19.6%)	115 (21.4%)
Physical activity			
Physical activity, min/d	45.0 (30.0)	60.0 (60.0)	30.0 (40.0)
Hemodynamics			
Systolic blood pressure, mm Hg	123±12	128±11	119±10
Diastolic blood pressure, mm Hg	71±8	71±7	71±8
Arterial hypertension	208 (21.8%)	98 (23.4%)	110 (20.5%)
Smoking and alcohol intake			
Current smoker	126 (13.2%)	49 (11.7%)	77 (14.3%)
Ever smoker	190 (19.9%)	74 (17.7%)	116 (21.6%)
Pack-years*	0.124 (0.409)	0.150 (0.405)	0.106 (0.380)
Alcohol intake, g/wk	3.2 (25.0)	5.0 (32.8)	3.2 (22.5)
Lipids			
Total cholesterol, mg/dL	158±29	148±26	166±29
HDL cholesterol, mg/dL	58.3±13.2	53.7±11.5	61.8±13.3
HDL cholesterol <40 mg/dL	60 (6.3%)	46 (11.0%)	14 (2.6%)
LDL cholesterol, mg/dL	92.8±25.2	87.5±24.0	96.8±25.4
LDL cholesterol ≥130 mg/dL	67 (7.0%)	19 (4.5%)	49 (8.9%)
Non-HDL cholesterol, mg/dL	99.8±27.6	94.3±26.6	104.0±27.6
Triglycerides, mg/dL	68.0 (35.0)	67.0 (37.0)	69.0 (33.0)
Triglycerides ≥130 mg/dL	73 (7.6%)	30 (7.2%)	43 (8.0%)
Glucose metabolism			
Fasting glucose, mg/dL	75.8±9.9	78.7±9.5	73.6±9.7
Fasting glucose >100 mg/dL	5 (0.5%)	4 (1.0%)	1 (0.2%)
HOMA-IR, mIU×mmol	1.97 (1.14)	1.97 (1.21)	1.97 (1.07)
HOMA-IR >2.6 mIU×mmol	242 (25.3%)	112 (26.7%)	130 (24.0%)
Liver and inflammation markers			
Gamma-glutamyltransferase, U/L	14.0 (6.0)	16.0 (7.0)	12.0 (4.0)
Alanine transaminase, U/L	16.0 (7.0)	18.0 (8.0)	14.0 (6.0)
Elevated alanine transaminase†	122 (12.8%)	61 (14.6%)	61 (11.4%)
Aspartate transaminase, U/L	22.0 (6.0)	23.0 (8.0)	21.0 (6.0)
C-reactive protein >1.0 mg/L	223 (23.3%)	96 (22.9%)	127 (23.6%)

Values are given as mean±SD, median (interquartile range), or count (%). Missings were <2% except for fasting glucose (3.6%) and fasting insulin (4.5%) for which median imputation was performed. BMI indicates body mass index; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; and LDL, low-density lipoprotein.

*Never-smokers excluded.

†Defined as ≥22 U/L in girls and ≥26 U/L in boys.

(Figure 1). NAFLD may be a more proximate correlate of cardiovascular risk, reflecting the combined effects of these metabolic factors.

In our study, overweight or central obesity, physical activity, smoking, and abnormalities of glucose homeostasis were not associated with cIMT progression in adolescents (Figure 1) although these are established cardiovascular risk factors in adults.[44,45] This may partly be explained by a low prevalence or burden of some risk conditions such as impaired fasting glucose and pack years of smoking (Table 1) as well as the relatively short follow-up. Previous longer-term studies in adolescents and young adults with a higher burden of these risk factors have consistently shown associations with future CVD outcomes or subclinical CVD.[46,47]

The mean absolute cIMT increase over the course of ≈2 years was 6.08 µm (95% CI, 1.6–10.3), and risk factors showed effects of 4.3 to 5.5 µm higher cIMT progression per 1-SD higher baseline level (Figure 1). Direct translation of these effects into risks of incident CVD in community-dwelling adolescents is difficult because of very low event rates. In adults, a large meta-analysis reported a relative risk of 0.91 for incident CVD for each 10 µm/year slower progression of cIMT,[9] such that a 6.0 µm faster progression over 2 years would amount to a relative risk of 1.09, and 1-SD higher risk factor levels to relative risks between 1.04 and 1.07.

CONCLUSIONS

Efforts to prevent CVD already in childhood and adolescence are gaining traction because it is increasingly recognized that early atherosclerotic lesions are already present at this age.[48] Current American Heart Association guidelines do justice to this and recommend measurement of lipid profiles between ages 9 and 11 and again at ages 17 to 21 in children or adolescents irrespective of cardiovascular risk factors or family history of early CVD in order to detect moderate to severe lipid abnormalities.[12] Our results add to these recommendations by demonstrating a significant association of LDL-C with cIMT progression in adolescents from the general population, with generally low LDL levels (Table 1), suggesting that the "the lower the better" concept may apply to adolescents similarly as to adults.[49] Levels of both LDL-C and remnant cholesterol may be ameliorated by weight loss, management of hypertension,[29] and lifestyle-modification interventions in children and adolescents.[50,51]

Current guidelines of the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition recommend screening for NAFLD only in overweight children and adolescents or those with risk factors.[11] Our study revealed a significant association of ALT, a marker of NAFLD, with cIMT progression in healthy adolescents and, as in adults, this association was not confined to elevated ALT levels.[38] CVD is the leading cause of death in NAFLD and NAFLD is responsive to lifestyle changes and weight reduction.[52,53]

Strengths of our study include its large size, uniform assessment of cIMT by a single experienced rater, and the novelty of associating cardiovascular risk factors with cIMT progression in a sample representative of the adolescent general population. There are limitations as well: Data on pubertal stage were not available, although almost all participants are expected to have been in Tanner stage IV or V[54] and previous evaluations in 13-year-olds did not find an influence of Tanner stage on atherosclerosis.[55,56] ALT is inferior for detection of NAFLD to transient elastography, ultrasound, magnetic resonance imaging, or histopathology, which were not available in our study. However, ALT has been shown to predict coronary heart disease events and is preferred for NAFLD screening in children at risk according to the 2017 North American Society for Pediatric Gastroenterology, Hepatology & Nutrition guidelines.[11] Further limitations include that the health intervention participants received may have ameliorated risk factor levels after the baseline examination, that the follow-up period of 2 years was comparatively short, that prevalence or burden of some risk factors was low, and that a relevant portion of the study population that featured a less favorable cardiovascular risk profile dropped out of the study. Intraobserver reproducibility of cIMT measurements was modest with a Pearson correlation of 0.634 and an intraclass correlation of 0.621. This is consistent with known limited measurement precision of ultrasound for cIMT, and possibly limited our ability to detect true associations.

The study population consisted of adolescents of White descent in an economically developed country. Hence, findings may not be applicable to other ethnic groups or different economic backgrounds.

Future studies could extend the current study by considering alternative measures of early vascular pathology such as pulse-wave velocity[57] and by investigating the effects of early risk factor management on change in cIMT and on later life cardiovascular risk.

In summary, systolic blood pressure, arterial hypertension, LDL-C, non-HDL-C, and ALT already predicted cIMT progression in community-dwelling adolescents with risk factor levels predominantly within reference ranges, suggesting that preventative efforts should start in adolescence and should not be restricted to high-risk subjects.

APPENDIX

EVA Study Group Investigators

Markus Anliker, MD, Central Institute of Clinical Chemistry and Laboratory Medicine (ZIMCL), Medical University of Innsbruck, Innsbruck, Austria.

Mandy Asare, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria and VASCage, Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria.

Benoît Bernar, MD, Department of Pediatrics II and Department of Pediatrics III, Medical University of Innsbruck, Innsbruck, Austria.

Manuela Bock-Bartl, MSc, VASCage, Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria.

Maximilian Bohl, MD, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria.

Nina Gande, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Ralf Geiger, MD, Department of Pediatrics III, Medical University of Innsbruck, Innsbruck, Austria.

Andrea Griesmacher, MD, Central Institute of Clinical Chemistry and Laboratory Medicine (ZIMCL), Medical University of Innsbruck, Innsbruck, Austria.

Christoph Hochmayr, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Sophia J. Kiechl, MD, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria and VASCage, Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria.

Stefan Kiechl, MD, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria and VASCage, Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria.

Ursula Kiechl-Kohlendorfer, MD, Msc, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Julia Klingenschmid, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Michael Knoflach, MD, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria.

Martina Kothmayer, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Julia Marxer, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Raimund Pechlaner, MD, PhD, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria.

Maximilian Pircher, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Carmen Reiter, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Christina Schreiner, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Anna Staudt, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria.

Katharina Stock, MD, Department of Pediatrics III, Medical University of Innsbruck, Innsbruck, Austria.

Bernhard Winder, MD, Department of Pediatrics II, Medical University of Innsbruck, Innsbruck, Austria and VASCage, Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria.

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Affiliations

Department of Neurology (S.J.K., S.K., M.K., R.P.); Department of Pediatrics II (A.S., K.S., N.G., B.B., C.H., B.W., U.K.); Department of Pediatrics III (K.S., R.G.); Department of Pediatrics I (B.B.); and Central Institute of Clinical Chemistry and Laboratory Medicine (A.G., M.A.), Medical University of Innsbruck, Innsbruck, Austria; and VASCage, , Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria (S.J.K., B.W., S.K.).

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Disclosures

None.

Supplementary Material

Tables S1–S2
Figure S1

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Supplemental Material

Table S1. Distribution of participants over schools and companies.

School/company	N (%)
1	15 (1.6)
2	5 (0.5)
3	156 (16.3)
4	4 (0.4)
5	6 (0.6)
6	9 (0.9)
7	9 (0.9)
8	7 (0.7)
9	12 (1.3)
10	53 (5.5)
11	4 (0.4)
12	42 (4.4)
13	58 (6.1)
14	16 (1.7)
15	15 (1.6)
16	70 (7.3)
17	10 (1.0)
18	13 (1.4)
19	5 (0.5)
20	54 (5.6)
21	69 (7.2)
22	15 (1.6)
23	7 (0.7)
24	18 (1.9)
25	37 (3.9)
26	113 (11.8)
27	63 (6.6)
28	71 (7.4)

The study participants were recruited from 28 different schools and companies, with between 4 and 156 adolescents recruited from each.

Table S2. Reference percentiles for adolescent body-mass index.

Age [years]	85th percentile [kg/m^2]		95th percentile [kg/m^2]	
	boys	**girls**	**boys**	**girls**
14	22.66	23.04	25.56	25.75
14.5	22.99	23.35	25.87	26.03
15	23.31	23.60	26.16	26.24
15.5	23.61	23.80	26.42	26.39
16	23.89	23.95	26.67	26.50
16.5	24.16	24.08	26.91	26.57
17	24.43	24.19	27.14	26.63
17.5	24.68	24.29	27.36	26.68
18	24.92	24.39	27.56	26.73

Percentiles are age- and sex-specific. The following table shows the 85th and the 95th percentile BMI values for boys and girls as published by Kromeyer-Hauschild et al.[19] (here shown in half-year steps).

Figure S1. Study Flow Diagram.