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Original article

Cardiovascular Risk in Childhood is Associated With Carotid Intima-Media Thickness and Stiffness in Adolescents and Young Adults: The KiGGS Cohort

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A B S T R A C T

Purpose: Cardiovascular risk factors are widespread among children and adolescents and may lead to accelerated vascular aging in middle adulthood. However, data are scarce on shorter-term consequences, for example, on associated distinctive vascular properties before age 30 years. This study analyzes the association of childhood exposure to cardiovascular risk factors with carotid properties in adolescents and young adults.
Methods: Four thousand thirty one participants from the population-based German Health Interview and Examination Survey for Children and Adolescents cohort (aged 3–17 years) had carotid intima-media thickness (CIMT) and distensibility coefficient (DC) measurements at the second follow-up (aged 14–28 years). The assessment of cardiovascular risk factors at baseline included information about arterial hypertension, obesity, dyslipidemia, and passive smoking.
Results: Single risk factors and the exposure to multiple cardiovascular risk factors were associated with elevated CIMT and decreased DC. Relative risks for CIMT $\geq$ 90th centile and/or DC $\leq$ 10th centile were increased in participants exposed to two ($RR_{CIMT} = 1.45$ [95% confidence interval 1.11–1.91], $p < .05$; $RR_{DC} = 1.37$ [1.02–1.84], $p < .05$) and $\geq$ three risk factors ($RR_{CIMT} = 1.66$ [1.05–2.62], $p < .05$; $RR_{DC} = 1.25$ [0.71–2.21], $p > .05$).
Discussion: Exposure to multiple cardiovascular risk factors starting in childhood is associated with measurably increased CIMT and carotid stiffness in late adolescence and early adulthood. These findings underline the importance of population-wide preventive measures to promote optimal cardiovascular health.

IMPLICATIONS AND CONTRIBUTION

This study demonstrates subclinical atherosclerosis in adolescents and very young adults who were exposed to multiple cardiovascular risk factors during childhood. It closes a gap in the existing literature, demonstrating a much earlier presence of these alterations. Therefore, the study emphasizes the importance of population-wide preventive efforts to promote upstream determinants of cardiovascular health such as physical activity, healthy nutrition, and reduction of inequalities in children.

The burden of cardiovascular risk factors is increasing in children and adolescents and recent studies found that only one-third of children at age five years have ideal cardiovascular health metrics [1,2]. The American Heart Association recommends the

Conflicts of interest: The authors have no conflicts of interest to declare.

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monitoring of Life's Essential 8 including four health behaviors and four easily measurable intermediate health factors (body mass, blood lipids, blood glucose, and blood pressure) [3]. Not only adults but also children and adolescents exposed to cardiovascular risk factors are at risk for accelerated pathological vascular remodeling and early vascular aging (EVA) [4], which ultimately leads to a higher lifetime-burden of cardiovascular morbidity and mortality [5]. However, the trajectories from cardiovascular risk exposure to subclinical changes and to manifest cardiovascular disease take several decades and are a challenge for epidemiological research. Nevertheless, childhood cardiovascular risk factors have been linked to adult cardiovascular events after a mean follow-up of 35 years [5].

To investigate more short-termed consequences of childhood risk factor exposure, carotid intima-media thickness (CIMT), a biomarker of subclinical atherosclerosis [6], and measures of carotid stiffness [7] are of interest because they have been shown to predict clinical cardiovascular events in middle-aged adults [8,9]. However, most previous studies were either cross-sectional [10–13] or studied only individual risk factors instead of risk factor combinations which reflect the overall cardiovascular risk [14–18], or they left the question unanswered as to what cardiovascular consequences arise in adolescence and young adulthood [7,14,19–21].

The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) cohort characterizes cardiovascular aging from childhood until young adulthood in an unselected general population sample. This study analyzes the effects of multiple cardiovascular risk factors during childhood on carotid properties in adolescents and young adults, including CIMT and carotid stiffness [6]. Thereby, it aims to close a significant gap in the investigation of short-termed to middle-termed EVA in this age group. The hypothesis is that childhood exposure to multiple cardiovascular risk factors is associated with increased CIMT and carotid stiffness in late adolescence and young adulthood.

Methods

This prospective study was approved by the German Federal Commissioner for Data Protection and Freedom of Information. Approval was given by the Ethics committees of Medizinische Hochschule Hannover (No. 2275-2014). Informed consent was obtained from all participants in advance.

Study sample

Being the first nationwide representative health survey among German children and adolescents, KiGGS ("German Health Interview and Examination Survey for Children and Adolescents") [22,23] was initially conducted in 167 communities between 2003 and 2006. The second follow-up, KiGGS-2, was conducted from 2014 until 2017. Four thousand four hundred eighteen healthy young subjects aged 14–28 years, who had initially participated as children in the baseline assessment (KiGGS-0), and who qualified for carotid ultrasound measurement at the follow-up assessment (KiGGS-2) were eligible for this study. Data from 4,031 participants who had a valid CIMT measurement and a complete baseline risk profile were used for statistical analyses (Figure 1).

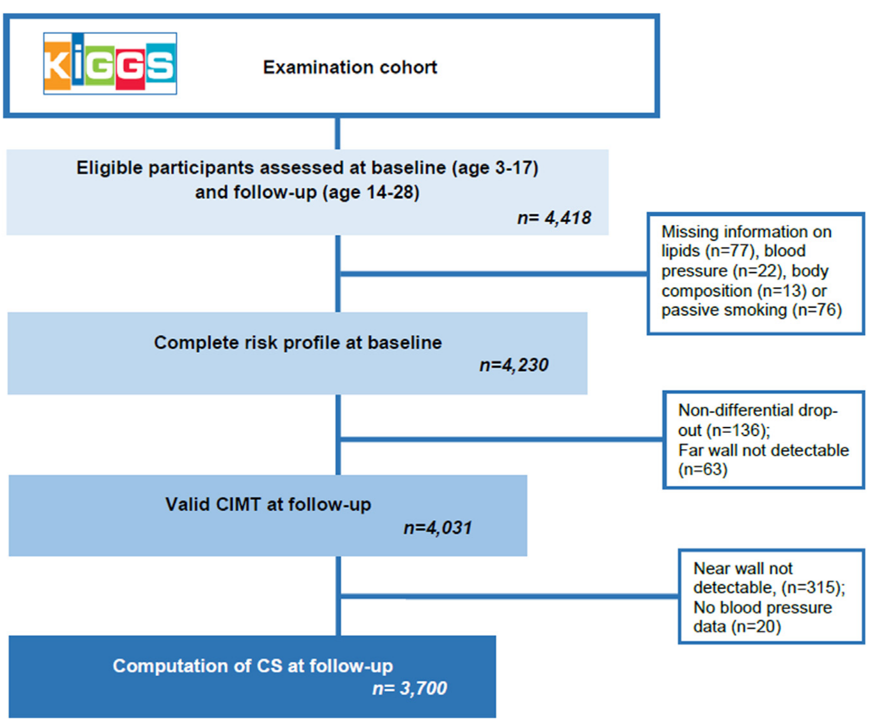

Figure 1. Flowchart of data collection and cleaning (n unweighted).

Measurement of carotid intima-media thickness and stiffness

Seven centrally trained, certified, and repeatedly retrained physicians conducted the ultrasound examinations. Ultrasound examinations and data acquisition were performed semi-automatically using a portable state-of-the-art ultrasound system (UF-760AG, Fukuda Denshi Co Ltd, Tokyo, Japan). Standard operating procedures, including measurement of CIMT and computation of carotid stiffness, adhered to current guidelines [24,25] and have been previously described in detail [6]. Far wall common CIMT and outer lumen diameter were measured bilaterally in two planes each (ear-to-ear and horizontal) within a 10-mm segment 10–15 mm proximal to the carotid bifurcation. The measurement was considered valid, if CIMT was detected in at least one plane for two consecutive heart cycles according to the quality criteria [6]. All valid values were averaged to a participant-specific CIMT. Carotid stiffness was expressed as distensibility coefficient (DC):

$$DC = \left(2 * \Delta LD * dLD + \Delta LD^2\right) \Big/ \left(\Delta P * dLD^2\right) * 7501 \; [l0-3\,kPa]$$

with ΔLD = systolic–diastolic outer lumen diameter, dLD = diastolic outer lumen diameter, and ΔP = systolic–diastolic blood pressure.

Measurement of cardiovascular risk factors

All participants had extensive cardiovascular and metabolic phenotyping at baseline and follow-up assessment based on interviews and medical examinations, including risk behavior and metabolic characteristics such as measurement of blood lipids, blood glucose, and HbA1c [23]. The mean of two readings of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was obtained after a 5-minute rest at a 2-minute interval with an automated upper arm oscillometric device (DatascopeAccutorr Plus, Mahwah/NJ) and appropriately sized cuffs [26]. Sex-specific, age-specific, and height-specific blood pressure reference centiles from KiGGS were used to classify hypertension in children and adolescents. Portable stadiometer devices (baseline: Holtain Ltd., Crymych/UK; follow-up: seca274, seca, Hamburg/Germany) were used to measure height to the nearest 0.1 cm. Weight was measured with a calibrated scale (baseline: electronic scale type seca; follow-up: seca mBCA 515/514, seca, Hamburg/Germany) in minimal clothing to the nearest 0.1 kg. Body mass index (BMI) was calculated as the ratio of body weight to the square of height (kg/m^2).

Statistical analyses

Analyses were conducted using STATA, Version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Descriptive data were presented as either proportions or means (± standard deviation). For categorical indicators, a Chi-Square Goodness of Fit Test was performed to determine whether the proportion was equal between the groups. To test for statistically significant differences between the groups in continuous indicators, the F-test was used.

Details about the procedure of variable selection according to representative population-based centiles [27–29] can be found in the supplementary materials.

Previously published reference centiles were used to ascribe an individual age-specific, sex-specific, and height-specific value and corresponding z-score for CIMT and DC to each participant [7,30]. CIMT ≥ 90th centile and DC ≤ 10th percentile were defined as 'high-risk' according to the increased likelihood of future atherosclerotic diseases [8,9,30]. Associations between these z-scores and single z-standardized cardiovascular risk factors were analyzed using multivariate linear regression. The resulting standardized effect estimates (± 95% confidence intervals) per change of one standard deviation allowed us to compare the strengths of these associations.

Relative risks for high-risk CIMT and DC were stratified according to the number of cardiovascular risk factors apparent at baseline using log-binomial regression. Logistic regression was not used as odds ratios overestimate the relative risk when outcomes are common [31]. Sensitivity analyses on the effect of the inclusion of active teen smoking and HbA1c were performed (supplementary materials, Tables S1 and S2).

Results

Data of 4,031 subjects (50.7% male) were finally included in the statistical analyses (Table 1). At baseline, 52.5%, 34.1%, 10.6%, and 2.8% of all subjects (3–17 years) were exposed to zero, one, two, or ≥ three cardiovascular risk factors. Mean CIMT of the whole sample was 0.54 ± 0.05 mm and mean DC was 47.77 ± 12.03 10^{-3} kPa. Groups with higher numbers of cardiovascular risk factors had higher CIMT and lower DC (Table 1).

Figure 2 compares the associations of individual risk factors with elevated CIMT (Figure 2A) and decreased DC (Figure 2B). These analyses take into account age and sex by using z-scores from specific percentile modelling. Blood pressure was additionally adjusted for height. Furthermore, standardized coefficients as shown in Figure 2 allow a comparison of the order of magnitude of the associations of individual risk factors with CIMT and DC. For CIMT, unfavorable alterations of all variables were significantly associated with higher CIMT at follow-up. As for DC, similar observations were made for SBP and DBP, BMI, and high-density lipoprotein–cholesterol, but no association was observed for total cholesterol and passive tobacco smoking.

Figure 3 demonstrates relative risks for elevated CIMT ≥ 90th percentile (3a) and decreased DC ≤ 10th percentile (3b) stratified by the number of cardiovascular risk factors. Using the group with zero risk factors as a reference (RR_{CIMT} = 1.0), no significant increase in relative risk for elevated CIMT was found for those exposed to one risk factor (RR_{CIMT} 1.90 [95% confidence interval {CI}: 0.89–1.33], *ns*). However, a significantly higher relative risk was found in those exposed to two (RR_{CIMT} = 1.45 [1.11–1.91], $p < .05$) and ≥ three risk factors (RR_{CIMT} = 1.66 [1.05–2.62], $p < .05$). Relative risks for decreased DC were also higher with higher numbers of risk factors: RR_{DC} = 1.17 [95% CI 0.95–1.44], *ns*, for one; RR_{DC} = 1.37 [1.02–1.84], $p < .05$, for two; and RR_{DC} = 1.25 [0.71–2.21], $p < .05$, for ≥ three risk factors.

Relative risks for elevated CIMT were even higher in the older subgroup of 1,545 participants aged 10–17 years at baseline: RR_{CIMT} = 1.45 [1.04–2.03], *ns,* for one risk factor; RR_{CIMT} = 1.89 [1.23–2.91], $p < .05$, for two risk factors; and RR_{CIMT} = 1.83 [0.95–3.52], *ns,* for ≥ three risk factors. Similar observations were made for the relative risks for decreased DC in tendency: RR_{DC} = 0.92 [0.65–1.32], *ns,* for one risk factor; RR_{DC} = 1.27 [0.79–2.06], *ns,* for two risk factors; and RR_{DC} = 1.76 [0.93–3.32], *ns,* for ≥ three risk factors. This analysis could not be conducted

Table 1
Sample characteristics of the 4,031 KiGGS cohort participants with complete risk profile at baseline and successful carotid sonography at follow-up

N		Number of risk factors at baseline[b]				p
	Total	0	1	2	3–4	
	4,031	2,119	1,376	428	108	
At baseline						
Female sex, No. (%)	1,989 (49.34)	1,012 (47.78)	723 (52.51)	225 (52.57)	56 (51.85)	< .05
Age, mean (SD)	8.59 (3.98)	8.21 (3.85)	8.91 (4.09)	9.07 (4.10)	10.18 (3.73)	< .05
SBP in mmHg, mean (SD)	104.40 (11.06)	101.16 (9.09)	105.95 (11.22)	112.03 (11.51)	118.02 (12.76)	< .05
DBP in mmHg, mean (SD)	63.26 (7.83)	61.02 (6.68)	64.55 (8.00)	68.48 (7.89)	70.32 (8.49)	< .05
HDL cholesterol in mg/dL, mean (SD)	47.14 (13.63)	59.58 (11.39)	56.36 (13.33)	52.37 (13.92)	47.14 (15.83)	< .05
BMI in kg/m^2, mean (SD)	24.09 (5.17)	16.59 (2.23)	17.69 (3.21)	20.11 (4.34)	24.10 (5.17)	< .05
Passive tobacco smoking, No. (%)	941 (23.34)	0 (0.00)	619 (44.95)	238 (55.61)	85 (78.70)	< .05
Parental education[a]: Low, No. (%)	495 (12.27)	181 (8.55)	203 (14.78)	86 (20.19)	24 (22.22)	< .05
Medium, No. (%)	2,296 (56.96)	1,172 (55.29)	803 (58.38)	251 (58.67)	70 (64.81)	
High, No. (%)	1,240 (30.77)	766 (36.15)	369 (26.85)	90 (21.14)	14 (12.96)	
At follow-up						
Age, mean (SD)	19.52 (3.98)	19.13 (3.86)	19.83 (4.08)	20.05 (4.11)	21.13 (3.73)	< .05
CIMT in mm, mean (SD)	0.54 (0.05)	0.53 (0.05)	0.54 (0.05)	0.55 (0.06)	0.55 (0.07)	< .05
DC in 10^{-3} kPa, mean (SD)	47.77 (12.03)	48.68 (12.56)	47.10 (11.31)	46.14 (11.58)	44.20 (9.95)	< .05
SBP in mmHg, mean (SD)	120.58 (11.07)	119.24 (10.45)	121.09 (11.12)	124.16 (12.12)	126.67 (12.86)	< .05
DBP in mmHg, mean (SD)	71.07 (7.23)	70.36 (6.82)	71.51 (7.32)	72.34 (7.95)	74.32 (8.72)	< .05
HDL cholesterol in mg/dL, mean (SD)	54.46 (12.24)	55.22 (11.78)	54.28 (12.57)	52.44 (12.75)	49.96 (13.08)	< .05
BMI in kg/m^2, mean (SD)	22.98 (4.18)	22.03 (3.29)	23.20 (4.14)	25.37 (5.05)	29.13 (6.54)	< .05
Current tobacco smoking (%)	25.11	21.22	28.22	31.26	38.00	< .05

BMI, body mass index; CIMT, Intima-media thickness of the commune carotid artery; DC, Distensibility coefficient of the commune carotid artery; DBP, diastolic blood pressure; HDL-cholesterol, high-density lipoprotein cholesterol; KiGGS, German Health Interview and Examination Survey for Children and Adolescents; SBP, systolic blood pressure; SD, standard deviation. For categorical indicators, a Chi-Square Goodness of Fit Test was performed to determine whether the proportion was equal between the groups. To test for statistically significant differences between the groups in continuous indicators, the F-test was used (significant, if $p \leq .05$).

[a] Level of education and vocational training according to simplified CASMIN [40].

[b] Risk factors are those included in the cardiovascular risk score (CV-R): overweight/obesity, elevated blood pressure/hypertension, dyslipidemia, passive smoking.

in the younger subgroup because the distribution of cardiovascular risk factors, that is, low prevalence of children exposed to two or ≥ three risk factors, did not allow the model to converge.

Discussion

This study analyzed whether childhood exposure to multiple cardiovascular risk factors predicts carotid properties in healthy adolescents and young adults. There was an association between every cardiovascular risk factor and elevated CIMT. SBP, DBP, BMI, and high-density lipoprotein–cholesterol were associated with reduced DC indicating increased carotid stiffness. The risk of elevated CIMT or reduced DC one decade after cardiovascular risk assessment was 66% higher in subjects with multifactorial cardiovascular risk compared to subjects without cardiovascular risk exposure.

This study closes an important gap between cross-sectional studies in children [10–13] and longitudinal studies, which associated childhood cardiovascular risk with subclinical atherosclerosis in middle-aged adults [20,21,32]. It clearly demonstrates that stiffening and wall thickening of the carotid arteries are accelerated in children and adolescents exposed to multiple cardiovascular risk factors. This is a relevant observation, because adolescence is a period, during which increased exposure to risk factors translates directly into elevated atherosclerotic risk in adulthood [32]. On the other hand, susceptibility of children, adolescents, and young adults to improved cardiovascular risk over the life course has been shown in the "Bogalusa Heart study" [20]. However, many adolescents get lost to regular medical monitoring during this period in life [33]. Thus, the results of this study together with evidence from the "Cardiovascular risk in young Fins study" [32], the "Muscatine study" [21], and the "Bogalusa Heart study" [20], all part of the i3C consortium [34], emphasize the importance to promote the optimization of cardiovascular risk factors via education and implementation of a healthy lifestyle in all adolescents.

For pediatric populations, individual clinical implications of elevated CIMT are very difficult to appraise because only very few studies have investigated the link between CIMT at a young age and follow-up cardiovascular events. Although cardiovascular events are rare at young ages, such studies need large cohorts and long follow-up periods. The USE-Intima-media-thickness research collaboration, a global meta-analysis project using individual participant data from several prospective population-based cohort studies, analyzed data from more than 3,000 individuals aged less than 45 years free of cardiovascular disease at baseline [35]. Although only 55 cardiovascular disease events occurred during a follow-up time of 16 years, an association of CIMT at age < 45 years with incident myocardial infarctions or strokes could be shown. These data were too scarce to investigate the prognostic value of CIMT elevation above a specific absolute threshold with regard to hard outcomes. Therefore, in studies such as ours, CIMT elevations above, for example, the 90th percentile can be used to define a group with increased cardiovascular risk. We demonstrate that subclinical vascular

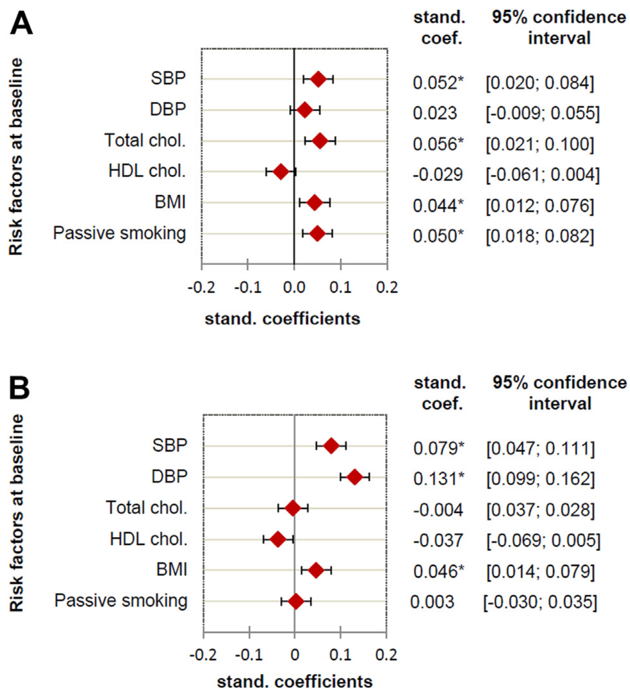

Figure 2. Multivariate linear regression of the associations of single z-standardized cardiovascular risk factors with CIMT (2a) and DC (2b). The standardized effect estimates per change of one standard deviation of the risk factor and 95% confidence intervals, allow to compare the strengths of these associations. Passive smoking is a dichotomous variable. Outcomes: Increased CIMT $\geq$ 90th centile and decreased DC $\leq$ 10th centile according to sex-specific, age-specific, and height-specific reference centiles [8,9,30]. * indicates significance at $p \leq .05$.

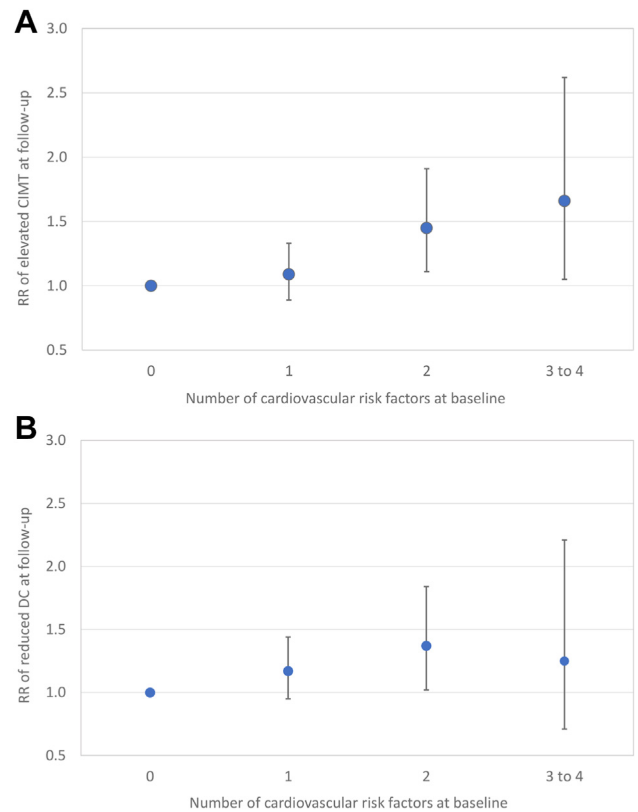

Figure 3. Relative risks (RR) of increased CIMT (A) and decreased DC (B) stratified by CV-R. RR and 95% confidence intervals from log-binomial regression. Exposure: Number of cardiovascular risk factors (zero, one, two, and three or four). Outcomes: Increased CIMT $\geq$ 90th centile and decreased DC $\leq$ 10th centile according to sex-specific, age-specific, and height-specific reference centiles [8,9,30]. * indicates significance at $p \leq .05$. Due to the asymmetrical nature of the risk scale, point estimates are not in the center of the confidence interval.

remodeling is already present in adolescents and young adults exposed to multiple cardiovascular risk factors. Although individual prediction is weak and does not support targeted interventions based on single-day measurements of risk profiles like in our study, at the population level the signal-to-noise ratio is more favorable and significant associations can be shown. This is an important observation suggesting that preventive efforts on a population level should aim for an optimal cardiovascular risk profile even in the healthy population. Together with the results of the "Cardiovascular risk in young Fins study" [32] and of the EVA-Tyrol study [36], our study emphasizes the early implementation and promotion of a healthy lifestyle as well as education about lifelong healthy living in children and adolescents.

However, there remains the need of longitudinal studies that repeatedly measure not only risk factors but also CIMT, DC, and other biomarkers of vascular aging from early childhood until late adulthood and link these to incident cardiovascular events over subsequent longer follow-up periods. Only this kind of studies will be able to demonstrate how the early life exposure to cardiovascular risk factors translates into vascular aging and finally leads to cardiovascular disease and how population-wide preventive efforts truly modify this process.

The strengths of this study include the large sample based on a cohort derived from a representative nationwide population registry, the third-generation state-of-the-art ultrasound measurement of carotid biomarkers [6], and state-of-the art statistical percentile modelling [23]. Some potential limitations need to be discussed. CIMT and DC were measured in the common but not the internal carotid artery or the carotid bulb, because visibility, completeness, procedural standardization, and precision of the measurement are highest in the common carotid artery [9,37,38]. The carotid tree was not screened for atherosclerotic plaques because the prevalence is extremely low in adolescents and young adults [39]. Health behaviors, such as those in the Life's Essential 8 [3], were not included in cardiovascular risk assessment due to incomplete data and age-dependent changes in questionnaires.

Statistical models were not adjusted for maturation status, as there is currently little evidence supporting a relevant effect on CIMT and DC in models accounting for the strongest confounders (age, sex, height, carotid lumen diameter, and blood pressure) [40,41]. Analyses were also not adjusted for the ethnic background of participants because more than 95% were Caucasians and the relevance of ethnicity for CIMT-related atherosclerotic risk assessment appears to be low [42]. The availability of only two time points for risk factor measurements and assessment of carotid properties does not allow to build trajectories demonstrating the effects of risk factor modification on CIMT progression. Repeated measurements of carotid properties and cardiovascular risk factors in further waves of this or other epidemiological studies [36] are necessary to close this gap of evidence.

Conclusion

In summary, this study demonstrates a higher risk of increased stiffness and thickness of the carotid arterial walls in adolescents and young adults exposed to multifactorial cardiovascular risk during childhood. Thereby, it closes a relevant gap in the literature, which has demonstrated accelerated vascular aging in adults aged more than 30 years in association with childhood exposure to cardiovascular risk factors but not as early as in adolescents and young adults [20,21,32]. The measurement of CIMT and DC in the general young and healthy population may be useful for a better understanding of the effects of cardiovascular risk factors on subclinical vascular remodeling. Considering the gap of medical monitoring during the teenage years [33], preventive measures targeting the determinants of cardiovascular risk factors need to be implemented already in childhood and adolescents. These measures should comprise the education and implementation of a healthy lifestyle within the entire population including the healthy individuals.

Data availability statement

KiGGS raw data for scientific use are available upon application (https://www.rki.de/DE/Content/Forsch/FDZ/Zugang/SUF.html).

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Author Contributions: K.K. made substantial contributions to the conception of the analysis, the analysis plan and interpretation of the data, and drafted and revised the manuscript. J.B. participated in the design of the analysis, conducted the data analysis, contributed to the manuscript draft, and critically revised the manuscript. H.N. designed the CIMT module of the KiGGS study, made substantial contributions to the conception of the study, analysis plan and interpretation, and critically revised the manuscript. A.S.T. made substantial contributions to the planning and implementation of the CIMT module of the KiGGS study, to the conception of the study, analysis plan and interpretation, and critically revised the manuscript. All authors gave final approval to the manuscript.

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Supplementary Data

Supplementary data related to this article can be found at http://doi.org/10.1016/j.jadohealth.2023.08.019.

References

[1] Song P, Zhang Y, Yu J, et al. Global prevalence of hypertension in children: A systematic review and meta-analysis. JAMA Pediatr 2019;173:1154–63.
[2] Ward ZJ, Long MW, Resch SC, et al. Simulation of Growth trajectories of childhood obesity into adulthood. N Engl J Med 2017;377:2145–53.
[3] Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's Essential 8: Updating and Enhancing the American heart Association's Construct of cardiovascular health: A presidential advisory from the American heart association. Circulation 2022;146:e18–43.
[4] Kruger R, Litwin M, Climie RE. Editorial: Determinants and Impact of early vascular aging in children and adolescents. Front Pediatr 2022;10:871524.
[5] Jacobs DR Jr, Woo JG, Sinaiko AR, et al. Childhood cardiovascular risk factors and adult cardiovascular events. N Engl J Med 2022;386:1877–88.
[6] Konigstein K, von Schenck U, Buschges JC, et al. Carotid IMT and stiffness in the KiGGS 2 national survey: Third-generation measurement, quality algorithms and determinants of completeness. Ultrasound Med Biol 2021; 47:296–308.
[7] Buschges J, Schaffrath Rosario A, Schienkiewitz A, et al. Vascular aging in the young: New carotid stiffness centiles and association with general and abdominal obesity - the KIGGS cohort. Atherosclerosis 2022;355:60–7.
[8] Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation 2007;115:459–67.
[9] Yang EY, Chambless L, Sharrett AR, et al. Carotid arterial wall characteristics are associated with incident ischemic stroke but not coronary heart disease in the atherosclerosis risk in communities (ARIC) study. Stroke 2012;43: 103–8.
[10] Chiesa ST, Charakida M, Georgiopoulos G, et al. Determinants of intima-media thickness in the young: The ALSPAC study. JACC Cardiovasc Imaging 2021;14:468–78.
[11] Jarvisalo MJ, Jartti L, Nanto-Salonen K, et al. Increased aortic intima-media thickness: A marker of preclinical atherosclerosis in high-risk children. Circulation 2001;104:2943–7.
[12] Gooty VD, Sinaiko AR, Ryder JR, et al. Association between carotid intima media thickness, age, and cardiovascular risk factors in children and adolescents. Metab Syndr Relat Disord 2018;16:122–6.
[13] Lamotte C, Iliescu C, Libersa C, Gottrand F. Increased intima-media thickness of the carotid artery in childhood: A systematic review of observational studies. Eur J Pediatr 2011;170:719–29.
[14] Buscot MJ, Thomson RJ, Juonala M, et al. Distinct child-to-adult body mass index trajectories are associated with different levels of adult cardiometabolic risk. Eur Heart J 2018;39:2263–2270a.
[15] Juonala M, Viikari JS, Ronnemaa T, et al. Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood: The cardiovascular risk in young Finns study. Arterioscler Thromb Vasc Biol 2006;26:1883–8.
[16] Pauciullo P, Iannuzzi A, Sartorio R, et al. Increased intima-media thickness of the common carotid artery in hypercholesterolemic children. Arterioscler Thromb 1994;14:1075–9.
[17] Yang L, Magnussen CG, Yang L, et al. Elevated blood pressure in childhood or adolescence and cardiovascular outcomes in adulthood: A systematic review. Hypertension 2020;75:948–55.
[18] West HW, Juonala M, Gall SL, et al. Exposure to parental smoking in childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood: The cardiovascular risk in young Finns study. Circulation 2015;131:1239–46.
[19] Juonala M, Viikari JS, Kahonen M, et al. Life-time risk factors and progression of carotid atherosclerosis in young adults: The cardiovascular risk in young Finns study. Research support, Non-U.S. Gov't. Eur Heart J 2010; 31:1745–51.
[20] Pollock BD, Stuchlik P, Harville EW, et al. Life course trajectories of cardiovascular risk: Impact on atherosclerotic and metabolic indicators. Atherosclerosis 2019;280:21–7.
[21] Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation 2001;104:2815–9.
[22] Kurth BM, Kamtsiuris P, Holling H, et al. The challenge of comprehensively mapping children's health in a nation-wide health survey: Design of the German KiGGS-study. BMC Publ Health 2008;8:196.
[23] Mauz E, Lange M, Houben R, et al. Cohort profile: KiGGS cohort longitudinal study on the health of children, adolescents and young adults in Germany. Int J Epidemiol 2019;49:375.
[24] Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis 2012;34:290–6.
[25] Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American society of echocardiography carotid intima-media thickness task force. Endorsed by the Society for vascular medicine. J Am Soc Echocardiogr 2008;21:93–111.
[26] Neuhauser H, Thamm M. [Blood pressure measurement in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Methodology and initial results]. Bundesgesundheitsblatt -

Gesundheitsforsch - Gesundheitsschutz 2007;50:728–35. Blutdruckmessung im Kinder- und Jugendgesundheitssurvey (KiGGS). Methodik und erste Ergebnisse.
[27] Dortschy R, Rosario AS, Scheidt-Nave C, et al. Population-based distribution of selected laboratory parameters from the German health interview and examination survey for children and adolescents (KiGGS). Berlin, Germany: RKI; 2009. ISBN: 978-3-89606-193-5.
[28] Neuhauser HK, Schienkiewitz A, Rosario AS, et al. Reference percentiles for anthropometric measures and blood pressure from the German health interview and examination survey for children and adolescents (KiGGS). Berlin, Germany: RKI; 2013. ISBN: 978-3-89606-218-5.
[29] Neuhauser HK, Thamm M, Ellert U, et al. Blood pressure percentiles by age and height from nonoverweight children and adolescents in Germany. Pediatrics 2011;127:e978–88.
[30] Neuhauser HK, Buschges J, Schaffrath Rosario A, et al. Carotid intima-media thickness percentiles in adolescence and young adulthood and their association with obesity and hypertensive blood pressure in a population cohort. Hypertension 2022;79:1167–76.
[31] McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003;157:940–3.
[32] Raitakari OT, Juonala M, Kahonen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: The cardiovascular risk in young Finns study. JAMA 2003;290:2277–83.
[33] Burns ME, Leininger LJ. Understanding the gap in primary care access and use between teens and younger children. Med Care Res Rev 2012;69:581–601.
[34] Juonala M, Magnussen CG, Venn A, et al. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: The cardiovascular risk in young Finns study, the childhood determinants of adult health study, the Bogalusa heart study, and the Muscatine study for the International childhood cardiovascular cohort (i3C) consortium. Circulation 2010;122:2514–20.
[35] Eikendal AL, Groenewegen KA, Anderson TJ, et al. Common carotid intima-media thickness relates to cardiovascular events in adults aged <45 years. Hypertension 2015;65:707–13.
[36] Kiechl SJ, Staudt A, Stock K, et al. Predictors of carotid intima-media thickness progression in adolescents-the EVA-Tyrol study. J Am Heart Assoc 2021;10:e020233.
[37] Foerch C, Buehler A, von Kegler S, Sitzer M. Intima-media thickness side differences are limited to the common carotid artery. Hypertension 2003;42:e17.
[38] Teynor A, Caviezel S, Dratva J, et al. An automated, interactive analysis system for ultrasound sequences of the common carotid artery. Ultrasound Med Biol 2012;38:1440–50.
[39] Homma S, Hirose N, Ishida H, et al. Carotid plaque and intima-media thickness assessed by b-mode ultrasonography in subjects ranging from young adults to centenarians. Stroke 2001;32:830–5.
[40] Pena AS, Maftei O, Harrington J, et al. Lack of evidence for progression of atherosclerosis during puberty in type 1 diabetes. Pediatr Diabetes 2016;17:199–205.
[41] Zanini JLSS, Rodrigues TMB, Barra CB, et al. Intima-media thickness of the carotid arteries is affected by pubertal maturation in healthy adolescents. Revista Paulista De Pediatria 2019;37:428–34.
[42] Liao X, Norata GD, Polak JF, et al. Normative values for carotid intima media thickness and its progression: Are they transferrable outside of their cohort of origin? Eur J Prev Cardiol 2016;23:1165–73.