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High cardiorespiratory fitness predicts lower risk of progression and higher chance of regression of arteriopathy during a lifestyle intervention

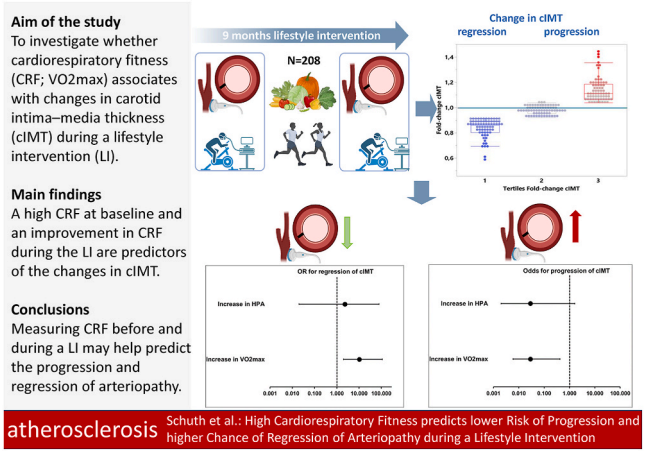
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HIGHLIGHTS

- Lifestyle intervention is recommended to prevent atherosclerosis in people who are at risk for type 2 diabetes.
- However, it is unknown what determines the effectiveness of such an intervention.
- Is cardiorespiratory fitness (CRF), associated with regression or progression of arteriopathy during a lifestyle intervention?
- High CRF at baseline and an improvement in CRF are independent predictors of the regression of the carotid intima–media thickness.
- Measuring CRF before and during a lifestyle intervention may help predict the progression and regression of subclinical arteriopathy.

GRAPHICAL ABSTRACT



Abbreviations: cIMT, carotid intima–media thickness; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HPA, habitual physical activity; OGTT, oral glucose tolerance test; TULIP, Tübingen Lifestyle Intervention Program; VO_{2max}, maximal aerobic capacity.

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ABSTRACT

Background and aims: High carotid intima–media thickness (cIMT) is a marker of arterial injury, and cIMT can be used to track the regression, arrest, or progression of arteriopathy. Because high cardiorespiratory fitness (CRF) protects from cardiovascular disease and closely associates with mitochondrial function, we determined whether baseline CRF and change in CRF predict change in cIMT during a lifestyle intervention.
Methods: A total of 208 subjects at risk for type 2 diabetes who participated in the Tübingen Lifestyle Intervention Program underwent measurements of CRF, cIMT, glucose, and lipid metabolism, body fat mass and distribution, and liver fat content at baseline and after 9 months.
Results: During the intervention, almost all cardiometabolic risk parameters improved. However, there was a large variability in the change in cIMT. In a multivariable linear regression model, CRF at baseline (std.-β −0.19, $p = 0.02$) and change in CRF (std.-β −0.18, $p = 0.01$) were associated with change in cIMT. Subjects in the upper tertile of change in cIMT had a mean (SD) increase in cIMT of 14 (9)%, while subjects in the lower tertile had a mean decrease in cIMT of 16 (7)%. Larger increase in CRF was associated with lower odds of progression of cIMT (OR per SD increase 0.05 [95% CI 0.006−0.42], $p = 0.004$) and with higher chance of regression of cIMT (OR per SD increase 13 [95% CI 2−111], $p = 0.01$).
Conclusions: We provide novel findings that measuring CRF before and during a lifestyle intervention may help predict the progression and regression of arteriopathy.

1. Introduction

Despite major improvements in treatment regimens, cardiovascular diseases (CVDs) still represent the leading cause of death worldwide [1]. Therefore, the prevention of CVDs is a cornerstone in the attempt to reduce mortality. Recently, a *Lancet* Commission recommended a larger focus on early atherosclerosis, particularly on endothelial dysfunction, intimal thickening, and plaque formation, in the prevention, diagnosis, and management of coronary artery disease [2]. Increased carotid intima-media thickness (cIMT) is a marker of arterial injury [3]. Along with other established cardiovascular risk factors, higher cIMT has been shown to predict an increased risk of future cardiovascular events [3–6]. More importantly, in a metanalysis of 119 randomized, controlled interventional studies, a reduction in cIMT and slow progression in cIMT associated with a risk reduction of developing CVDs or cardiovascular events [7]. Thus, a reduction or stabilization in increased cIMT may represent an important goal for interventions to achieve a risk reduction for cardiovascular events already at a subclinical stage of arteriopathy.

However, the specific determinants of increased cIMT and the factors influencing its change are not yet fully understood. While established cardiovascular risk factors such as smoking, hypertension, diabetes, or hyper- and dyslipidemia are associated with higher cIMT values – especially when several risk factors are present simultaneously [6,8] – other modifiable factors may also play a key role. Knowledge about these risk factors is particularly important to estimate the effects of lifestyle interventions to reduce the progression or induce the regression in cIMT.

Low physical activity is an important risk factor for CVDs and an increase in physical activity improves cardio-vascular function. An increase in physical activity also improves mitochondrial function, which can be estimated by the measurement of cardiorespiratory fitness (CRF), resulting in a reduction of oxidative stress, which is considered beneficial of overall cardio-vascular health [9].

We and others identified cardiorespiratory fitness (CRF) as a strong and independent determinant of cIMT [10–12] Furthermore, higher CRF at baseline was associated with slower progression in cIMT in middle-aged men independently of established cardiovascular risk factors [13]. In addition, the measurement of CRF was found to provide added value to cardiovascular risk classifications when combined with established cardiovascular risk factors [14,15].

However, little is known whether CRF at baseline and the change in CRF have an impact on the change in cIMT, particularly during a lifestyle intervention with the goal of reducing the cardiometabolic risk. In the present study, we aimed to close this gap by investigating the impact of CRF at baseline and the change in CRF during a lifestyle intervention on the change in cIMT in people who were overweight, insulin resistant or hyperglycemic and, therefore, have an increased risk of arteriopathy [16].

2. Methods

2.1. Participants

Data from participants of the Tübingen Lifestyle Intervention Program (TULIP) were analyzed. TULIP is a prospective uncontrolled diet and exercise intervention study (supported by the German Research Foundation). The study was performed at the University Hospital of Tübingen, Germany. The study started in 2003, and the lifestyle intervention of the last patient included in the study ended in 2009. Outcomes of the study – e.g., glucose tolerance, insulin sensitivity, insulin secretion, body fat distribution, liver fat content, adipokines, hepatokines, genetic risk of type 2 diabetes, etc. – have been published [17–19]. The TULIP study was designed to identify predictors of the effectiveness of a lifestyle intervention to improve cardiometabolic risk. Individuals from the southern part of Germany were included in the study when they fulfilled at least one of the following criteria: a family history of type 2 diabetes, a BMI >27 kg/m^2, a previous diagnosis of impaired glucose tolerance or gestational diabetes. All participants were otherwise considered healthy after physical examination and routine laboratory tests. Exclusion criteria were the presence of a severe, critical mental or physical illness or alcohol consumption of more than two alcoholic drinks per day. Smoking and lipid- and blood pressure-lowering medication were assessed by questionnaires. Serum aminotransferase levels were lower than twice the upper limit of normal. Of the 413 participants, a subgroup of 208 people had measurements of CRF and cIMT at baseline and after 9 months of the lifestyle intervention. All participants gave written and informed consent. The study was approved by the Ethics Committee at the Medical Faculty of the Eberhard Karls University and at the University Hospital of Tübingen according to the Helsinki Declaration.

2.2. Lifestyle intervention

After baseline measurements, participants attended up to 10 professional dietary counselling sessions aiming at weight reduction and lowering caloric intake (goal: < 30% energy from fat, < 10% from saturated fat, > 15g fiber/1000 kcal) over a period of 9 months. Diet composition was estimated with a validated software by analyzing two representative days of a 3-day diary (DGE-PC 3.0; Deutsche Gesellschaft für Ernährung, Bonn, Germany). Furthermore, all participants completed a standardized, self-administered, and validated questionnaire to measure physical activity, and a habitual physical activity score

(HPA) was calculated [20]. Participants were generally advised to engage in at least 3 h/week of moderate physical activity (e.g., walking or swimming) and aerobic endurance exercise. Compliance was regularly monitored by staff. Height, weight, BMI, waist circumference, and blood pressure were measured/calculated using standard procedures at each visit.

2.3. Simple anthropometrics, oral glucose tolerance test, and blood pressure

BMI was calculated as weight divided by the square of height (kg/m^2). Waist circumference was measured in the upright position at the midpoint between the lateral iliac crest and the lowest rib. Subjects underwent a frequently sampled 2-h, 75-g oral glucose tolerance test (OGTT). Venous plasma samples were obtained at 0, 30, 60, 90, and 120 min for the determination of plasma glucose and insulin levels. Blood glucose was determined using a bedside glucose analyser (glucose oxidase method; YSI, Yellow Springs Instruments, Yellow Springs, Colorado, USA). Insulin was measured using the ADVIA Centaur XP Immunoassay System, and all other blood parameters were measured with an ADVIA XPT clinical chemistry system (both Siemens Healthineers, Eschborn, Germany). For the measurement of insulin, blood samples were immediately placed on ice and transferred to the laboratory for analysis. Whole-body insulin sensitivity was calculated from glucose and insulin values during the OGTT as proposed by Matsuda and DeFronzo [21]. The blood pressure measurement was performed at the dominant arm (unless there was a deformity), using a sphygmomanometer and a stethoscope to auscultate the Korotkoff sounds. Blood pressure was measured in duplicate, and the mean value of both measurements was calculated.

2.4. Total body fat mass, body fat distribution, and liver fat content

Measurements of total body adipose tissue, subcutaneous adipose tissue, visceral adipose tissue and liver fat content were performed by an axial T1-weighted fast spin echo technique using a 1.5 T whole-body scanner (Magnetom Sonata, Siemens Healthineers, Erlangen, Germany) at baseline and after 9 months [22].

2.5. cIMT

IMT of the common carotid artery was measured in the fasting state using a high-resolution ultrasound system with an integrated electrocardiography package (AU5 idea, Esaote Biomedica, Munich, Germany) at baseline and after 9 months. A trained physician measured IMT below the bulb on the left and the right common carotid artery on the transducer far wall in two different directions, each over a length of at least 1 cm, using the same 13 MHz linear array transducer. Three measurements were taken at each scan of the artery on frozen pictures, incident with the R-wave of the continuously monitored electrocardiogram (to exclude any influence on IMT by the heartcycle). IMT was defined as the distance from the leading edge of the first echogenic line of the transducer far wall (representing the lumen-intima interface) to the leading edge of the second echogenic line (beginning of the collagen-rich upper layer of tunica adventitia) [23]. Mean values of the right and left common carotid artery were used for the main analyses.

2.6. CRF

CRF was assessed as maximal aerobic capacity (VO_{2max}) using a continuous, incremental cycle ergometer test (Ergometrics 800 S; Ergoline, Bitz, Germany) until volitional exhaustion. Oxygen consumption was measured using a spiroergometer (MedGraphics System Breese Ex 3.02 A, MedGraphics, St. Paul, Minnesota, USA). VO_{2max} was expressed as VO_2 (ml/min) per kg body mass (ml/min/kg).

2.7. Statistical analysis

Continuous variables are expressed as mean ± SD for normally distributed data and as median (interquartile range) for non-normally distributed data. Normality was assessed by the Shapiro-Wilk test. Paired *t*-test or McNemar's test was applied to evaluate within-subject changes between baseline and follow-up. Between-group differences were examined using independent t-tests or Mann–Whitney U-tests. Associations between changes in cIMT and anthropometric, metabolic or fitness parameters were first assessed using univariate correlations. Variables showing significant or borderline associations ($p < 0.10$) were entered into multivariable linear regression models, adjusting for potential confounders including age, sex, and baseline values of the respective variables. Separate models were constructed for changes in HPA and CRF as independent variables and for combined models including both parameters. To assess the probability of cIMT regression or progression, tertiles of the change in cIMT were determined, and binary logistic regression analyses were performed. Odds ratios (OR) with 95% confidence intervals (CI) were calculated per 1 SD increase in HPA or CRF, adjusting for age, sex, baseline cIMT, HPA, and CRF. A p-value < 0.05 was considered statistically significant. Data were analyzed using JMP (version 4.0; SAS Institute).

3. Results

3.1. Demographics, anthropometrics, and metabolic characteristics

Characteristics of the study population at baseline and after 9 months of follow-up are shown in Table 1. At baseline the study population had a wide range of values in several parameters such as age (19-69 years), BMI (19-43 kg/m^2), total body fat (4-61 kg), visceral adipose tissue mass

Table 1
Subject characteristics at baseline and at follow-up.

Parameter	Baseline	Follow-up	p
Gender (females/males)	119/89		
Age (years)	45 [37-53]	45 [38-54]	
Weight (kg)	86.3 [74.1-97.0]	84.0 [72.2-94.2]	<0.0001
BMI (kg/m^2)	28.9 [26.0-32.0]	28.0 [25.2-31.3]	<0.0001
Waist circumference (cm)	96.7 ± 13.6	92.9 ± 12.7	<0.0001
Total body fat (kg)	24.5 [18.0-31.3]	21.8 [16.0-28.9]	<0.0001
Visceral AT (kg)	2.61 [1.48-4.24]	2.04 [1.17-3.59]	<0.0001
Liver fat (%)	3.06 [1.46-6.90]	2.09 [1.02-5.32]	<0.0001
Fasting glucose (mmol/l)	5.17 [4.83-5.60]	5.11 [4.83-5.44]	0.007
2 h glucose (mmol/l)	6.61 [5.79-7.89]	6.42 [5.61-7.72]	0.025
Insulin sensitivity	11.64 [7.23-17.39]	13.38 [8.80-19.65]	<0.0001
Total cholesterol (mg/dl)	192 [166-215]	186 [163-210]	0.005
HDL-cholesterol (mg/dl)	50 [43-60]	51 [43-60]	0.45
LDL-cholesterol (mg/dl)	120.6 ± 29.9	116.1 ± 32.9	0.002
Triglycerides (mg/dl)	100 [76-141]	93 [66-136]	0.008
Systolic BP (mmHg)	123.0 ± 15.7	120.7 ± 15.3	0.017
Diastolic BP (mmHg)	75 [68-81]	75 [70-80]	0.035
hs CRP (mg/dl)	0.11 [0.04-0.28]	0.08 [0.03-0.22]	0.003
cIMT right (mm)	0.53 [0.46-0.61]	0.52 [0.44-0.62]	0.02
cIMT left (mm)	0.56 [0.48-0.65]	0.55 [0.46-0.63]	0.007
cIMT mean (mm)	0.56 [0.47-0.62]	0.53 [0.47-0.62]	0.004
HPA score	8.13 [7.38-8.85]	8.50 [8.00-9.25]	<0.0001
VO_{2max} (ml/min/kg)	24.5 [20.1-28.7]	25.1 [21.0-30.6]	<0.0001
Smoking, n (%)*	25 (12)	21 (11)	0.257
Lipid-lowering drugs, n (%)	10 (5)	11 (5)	0.655
BP-lowering drugs, n (%)	35 (17)	35 (17)	1.000

Data are medians and interquartile ranges and n (%) for categorical data. hs-CRP, high-sensitivity C-reactive protein; BP, blood pressure; cIMT, carotid intima-media thickness; HPA, habitual physical activity; $VO2_{max}$, maximal aerobic capacity. P-value for pairwise comparisons of changes of continuous parameters using one-sided *t-test* (improvement of parameters) and McNemar's test for changes of nominal parameters. *available in 205 people at baseline and in 195 at follow-up.

(0.2-9.7 kg), insulin sensitivity (1.6-33.3), $VO2_{max}$ (9.5-54.1 ml/min/kg) and cIMT (0.28-0.98 mm). IMT measures of the right and left common carotid arteries strongly correlated with each other (Pearsson correlation coefficient r = 0.79, p < 0.0001, Supplemental Fig. 1), nevertheless, the results indicate possible measurement error and biological variability between both arteries.

3.2. Longitudinal analyses

During the 9 months of the intervention, HPA increased (Table 1), reflecting good compliance with the recommended amount of exercise. Correspondingly, there was a significant improvement in CRF measured by VO_{2max}, along with highly significant reductions in BMI, waist circumference, total body fat mass, visceral adipose tissue mass and liver fat content, as well as an improvement in insulin sensitivity (Table 1). Of particular note, despite the relatively short duration of the follow-up period, there was a small but highly significant reduction in IMT measures of the right and left common carotid arteries and the mean values of both arteries. To investigate which metabolic parameters are most strongly associated with changes in cIMT (mean values of both carotid arteries) during the intervention, first univariate correlation analyses were performed. A change in HPA was significantly associated with a change in cIMT (r = −0.16, p = 0.02). An improvement in CRF showed a similar trend, but this relationship was not statistically significant (r = −0.13, p = 0.06; Supplemental Table 1).

3.3. Predictive analyses

Subsequently, multivariable linear regression models were used to identify independent predictors of the change in cIMT. In these models, change in HPA and change in CRF were used as independent variables (Table 2). The baseline values of the respective parameter, as well as age and gender, were included as covariates. In Model 1, the change in HPA was included as the main independent variable, whereas the change in CRF was used in Model 2. In Model 3, changes in CRF and HPA were used simultaneously. When only HPA at baseline and the change in HPA were included (Model 1), no significant association with the change in cIMT was observed. However, CRF at baseline and the change in CRF (Supplemental Fig. 2) were found to be significant determinants of the change in cIMT in both Model 2 and Model 3. Additional adjustment for high-sensitivity C-reactive protein, smoking, or lipid- and blood pressure-lowering medication did not considerably affect these relationships. For sensitivity purpose and robustness testing we also investigated these relationships for the IMT of the right and left common carotid arteries separately. The respective analyses (Models 1-3) showed similar results for the IMT measures of the right and left carotid arteries (Supplemental Tables 2 and 3).

Furthermore, ORs were calculated to determine the likelihood of a significant regression or progression in cIMT per 1 SD increase in HPA and CRF during the intervention. To define regression and progression in cIMT, the change in cIMT (expressed as the ratio of cIMT at follow-up to cIMT at baseline) was divided into tertiles. Based on these tertiles, regression in cIMT (being in the lower tertile of change in cIMT) was defined as a fold cIMT < 0.92 (corresponding to a regression of > 8%) and significant progression (being in the upper tertile of change in cIMT) as a fold cIMT > 1.04 (corresponding to a progression of > 4%). Subjects in the upper tertile of change in cIMT had a mean (SD) increase in cIMT of 14 (9)%, while subjects in the lower tertile had a mean decrease in cIMT of 16 (7)% (Fig. 1). For the calculation of ORs, the same multivariable regression models as described above were applied, adjusted for gender, age, cIMT at baseline, and HPA and/or CRF at baseline. As expected, higher ORs for cIMT regression and lower ORs for cIMT progression were observed with increasing CRF (Supplemental Table 4). Specifically, a 1 SD increase in CRF was associated with a significantly lower OR of cIMT progression (OR = 0.050, p = 0.004, Fig. 2A) and a 13.4-fold higher OR of cIMT regression (Model 2, p = 0.012, Fig. 2B). These associations remained statistically significant even when HPA and CRF were both included in the model (Supplemental Table 2, Model 3).

Table 2
Determinants of change in cIMT in multivariate linear regression models.

Covariate	Estimate (SE)	Standard-Beta	p
Model 1			
Gender	−0.014 (0.01)	−0.1034	0.1170
Age at baseline	0.116 (0.04)	0.221	0.0084
cIMT at baseline	−0.343(0.05)	−0.530	<0.0001
HPA at baseline	0.020 (0.01)	0.148	0.0644
Change in HPA	−0.063 (0.09)	−0.058	0.4644
Model 2			
Gender	−0.026 (0.01)	−0.180	0.0183
Age at baseline	0.116 (0.04)	0.220	0.0089
cIMT at baseline	−0.360 (0.06)	−0.556	<0.0001
VO_{2max} at baseline	−0.101 (0.04)	−0.185	0.0199
Change in VO_{2max}	−0.154 (0.06)	−0.177	0.0098
Model 3			
Gender	−0.031 (0.01)	−0.215	0.0055
Age at baseline	0.108 (0.04)	0.206	0.0132
cIMT at baseline	−0.371(0.06)	−0.574	<0.0001
HPA at baseline	0.023 (0.01)	0.178	0.0276
Change in HPA	−0.026 (0.09)	−0.024	0.7597
VO_{2max} at baseline	−0.116 (0.04)	−0.214	0.0075
Change in VO_{2max}	−0.136 (0.06)	−0.156	0.0213

cIMT, carotid intima-media thickness; HPA, habitual physical activity; VO_{2max}, maximal aerobic capacity.

4. Discussion

High cIMT is a marker of arterial injury, and cIMT is being used to track the regression, arrest, or progression of arteriopathy [3–7]. However, it is still under investigation how cIMT compares to other vascular biomarkers regarding the detection of arteriopathy and the prediction of future cardiovascular events. In this respect, the 2010 American College of Cardiology (ACC) Foundation–American Heart Association (AHA) guidelines for assessment of cardiovascular risk in asymptomatic adults gave cIMT a level IIa recommendation for cardiovascular risk evaluation. This was the same recommendation as was given for the ankle–brachial index and coronary artery calcium scoring, and a higher recommendation compared to carotid-femoral pulse wave velocity [24]. However, the 2013 ACC/AHA guidelines on the assessment of cardiovascular risk recommend against the use of cIMT for individual risk

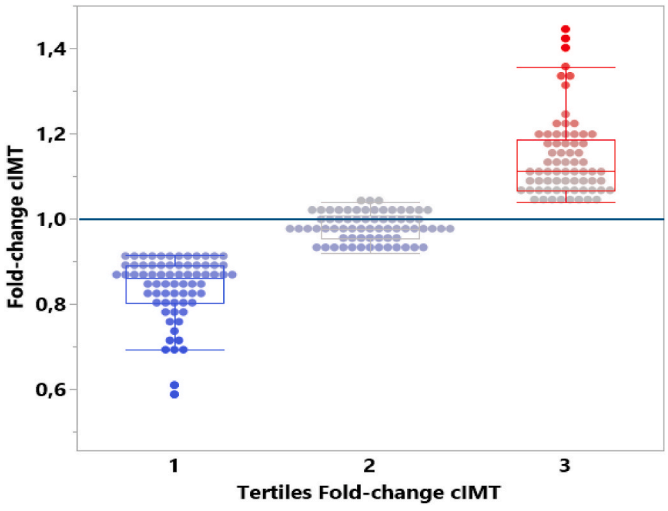
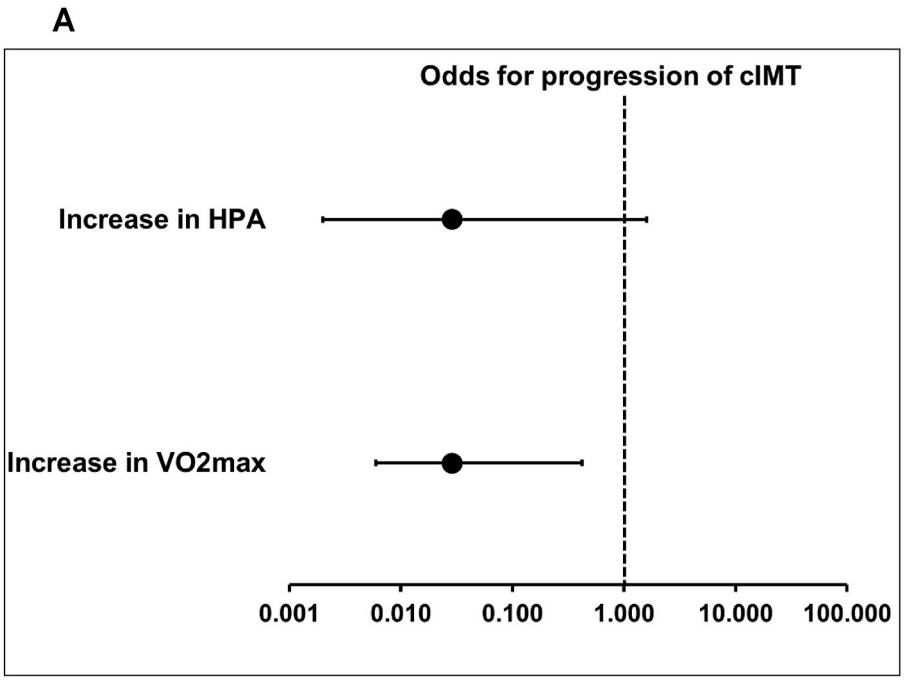


Fig. 1. Change in carotid intima-media thickness during a lifestyle intervention based on tertiles of change in cIMT. Change in carotid intima-media thickness (cIMT) between baseline and 9 month of the lifestyle intervention was divided into tertiles and their changes in cIMT was plotted.



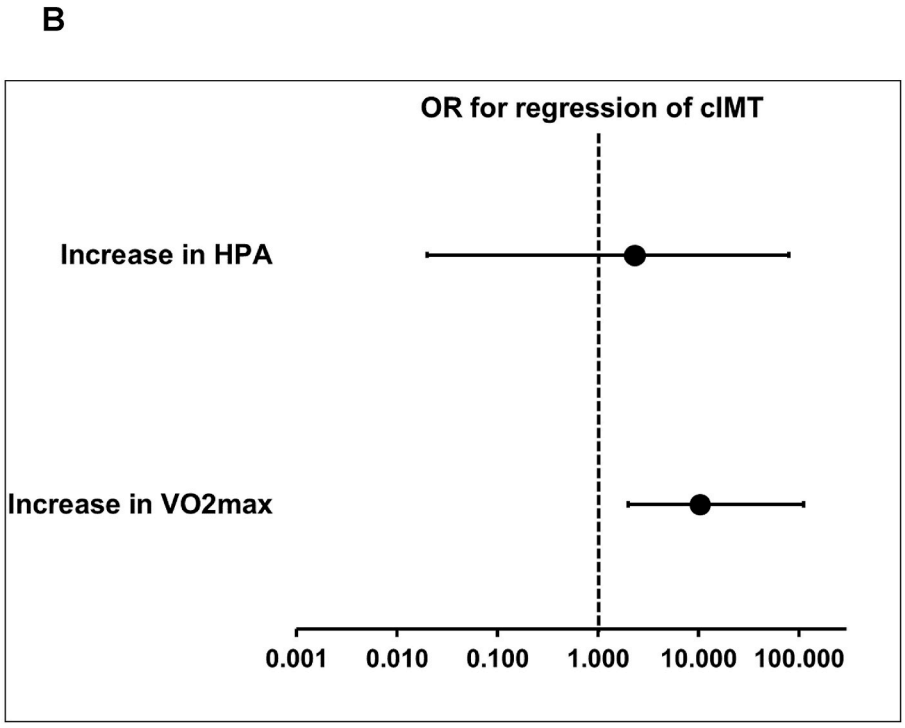


Fig. 2. Predictors of the regression and progression in carotid intima-media thickness during a lifestyle intervention. The change in carotid intima-media thickness (cIMT) (expressed as the ratio of cIMT at follow-up to cIMT at baseline) was divided into tertiles. Based on these tertiles, progression of cIMT (being in the upper tertile of change in cIMT) was defined as a fold cIMT > 1.04 (corresponding to a progression of > 4%) (A) and regression of cIMT (being in the lower tertile of change in cIMT) was defined as a fold cIMT < 0.92 (corresponding to a regression of > 8%) (B). For the calculation of odds ratios (OR), multivariable regression models were applied, adjusted for gender, age, cIMT at baseline, and HPA and/or CRF at baseline.

prediction in clinical practice [25]. In 2017, Polak et al. generated age-, sex-, and race-ethnic–specific normative values for combined measurements of both the common and internal carotid artery IMT using data from the Multi-Ethnic Study of Atherosclerosis study. They found that this IMT score significantly improved prediction of coronary events and that this improved prediction remained statistically significant when coronary artery calcium score was included in the statistical models [26]. Furthermore, in the Atherosclerosis Risk In Communities study, the addition of information about both cIMT and carotid plaque burden to traditional risk factors improved coronary heart disease risk

prediction [27]. Thus, at this time, one can continue to assume that cIMT adds value to the early detection of arteriopathy and the prediction of cardiovascular disease.

People who are overweight, insulin resistant or hyperglycemic have an increased risk of atherosclerosis [16]. The factors influencing the change in cIMT, particularly in a preventive setting, such as a lifestyle intervention to reduce the cardiometabolic risk in these people, are yet to be fully understood. For example, in the Women's Healthy Lifestyle Project (WHLP) a lifestyle intervention for 54 months with a healthy diet and an increase in physical activity lowered body weight and reduced the rise in LDL-cholesterol, triglycerides, and glucose levels compared to women in the control group [28]. However, the progression of IMT of the common carotid artery did not differ between the lifestyle intervention and the control groups [28,29].

In cross-sectional studies, higher CRF was found to associate with lower cIMT [10–12]. Furthermore, in the Kuopio Ischemic Heart Disease Risk Factor Study, a population study designed to investigate risk factors for atherosclerotic vascular diseases and related outcomes, higher CRF was associated with slower progression of cIMT, independently of cardiovascular risk factors, and low CRF was the strongest risk factor for the progression of carotid atherosclerosis in multivariable analyses [13]. However, it is unknown whether high CRF at baseline and the change in CRF associate with changes in cIMT over time, particularly during lifestyle modification, where improvements in many cardiometabolic risk factors are usually observed.

In the present study, we found that the lifestyle intervention resulted in a 4% reduction in body weight. Furthermore, significant reductions in fat mass, visceral adiposity, liver fat content, hyperglycemia, hyper- and dyslipidemia, systolic blood pressure and cIMT were observed. In addition, insulin sensitivity and CRF increased. Interestingly, the change in cIMT was not associated with improvement in the cardiometabolic risk factors total- and visceral adiposity, liver fat content, insulin resistance, hyperglycemia, hyper- and dyslipidemia or elevated blood pressure. This finding is in agreement with the findings in the WHLP [28]. In contrast, a high CRF at baseline and an improvement in CRF were independently associated with a reduction in cIMT. Furthermore, a larger adjusted increase in CRF during the lifestyle intervention was associated with lower odds for a progression in cIMT and with higher odds for a regression in cIMT. These findings indicate that the measurement of CRF prior to and during a lifestyle intervention, more so than the measurements of body fat mass and distribution, glycemia, lipidemia, and blood pressure, may help predicting the success of such an intervention to reduce arteriopathy.

With the finding that high CRF at baseline and an increase in CRF during a lifestyle intervention can positively influence arteriopathy, our study extends prior knowledge about the importance of the measurement of CRF for both short-term (10-year) and long-term (25-year) risk for CVD mortality, when added to traditional risk factors [13]. Importantly, whereas many studies have focused on slowing cIMT progression [7], our findings suggest that actual regression in increased cIMT is possible during a lifestyle intervention, even within the relatively short time frame of 9 months. Furthermore, this regression in cIMT is mainly observed in people with high CRF at baseline. However, it is important to keep in mind that cIMT typically changes slowly, and the measurement variability of cIMT results in the interpretation of data about changes in cIMT being difficult, particularly during a short period of follow-up. In adults, mean values of cIMT ranging from around 0.65 to 0.90 mm increase—on average—at a rate of 0 to 0.40 mm per year [30,31]. There is little data on the decrease in cIMT over a short period. In the Mediterranean diet and type 2 diabetes trial, a Mediterranean diet reduced the cIMT (baseline mean [SD] cIMT 0.84 [0.17] mm) by 0.032 [0.07] mm after 2 years of the intervention [32]. In a 3 months intervention study, supplementation with olive oil (baseline mean cIMT 0.96 [0.23] mm) and flaxseed oil (baseline mean cIMT 0.88 [0.24] mm) decreased the cIMT by 0.11 mm and 0.17 mm in overweight people without diabetes [33]. Furthermore, in a small study of severely obese people who underwent caloric restriction with or without physical activity for 6 months, those who lost at least 5% of their body weight had a significant mean reduction in cIMT of 0.02 mm [34]. However, in other studies, cIMT values remained unchanged after nine months, or one year, of lifestyle intervention [35,36]. In obese people who underwent bariatric surgery, a relatively large decrease in cIMT was observed (mean [95% confidence interval]: from 0.81 [0.77–0.84] mm to 0.66 [0.63–0.69] mm, as early as 1–2 months after the surgery [37].

To evaluate whether the observed change in cIMT could be attributable to measurement error, we estimated the variability expected from random measurement error alone. A review of 23 studies reported an intraobserver coefficient of variation of 2.4–10.6% (median 3.5%) [38]. Assuming a CV of 3.5% and a mean cIMT of 0.55 mm, the within-subject SD of a single measurement is 0.019 mm and the SD of a difference between two measurements is 0.027 mm. For $n = 208$, the standard error of the mean change attributable to measurement error is 0.0019 mm (95% range: ±0.0037 mm). Even assuming the upper bound of the reported CV (10.6%), this range is ±0.011 mm. The observed mean change of −0.02 mm therefore cannot be explained by random measurement error alone.

Altoghether these data and the results from our present study reporting short-term cIMT changes cannot clarify to what extent these changes are indicators of vascular remodeling or cardiovascular risk reduction. Interestingly, in a meta-analysis of eight studies reporting that with each 0.1 mm higher cIMT, the risk of myocardial infarction increased by 10%–15% and the risk of stroke by 13%–18%, the slope of the relationship between cIMT and cardiovascular events was steeper for low to average cIMT values [3]. Our observations, therefore, highlight the importance of early detection of subclinical atherosclerosis and support the implementation of timely interventions, particularly focusing on improving CRF.

The underlying mechanisms of how CRF influences cIMT are largely unknown. High CRF is closely associated with increased mitochondrial function, an important determinant of lipid oxidation [39,40]. Adequate mitochondrial function mitigates oxidative stress brought about by increased reactive oxygen species generation, which contributes to cell damage. Improved mitochondrial function can also inhibit inflammation by modulating the functions of neutrophils, macrophages, and T cells. In addition, mitochondria regulate glycolysis, fatty acid oxidation, and amino acid metabolism [41]. In a state of impaired mitochondrial function, oxidative stress, inflammation, and increased lipid peroxidation can result in thickening of the carotid artery intima-media, thereby representing an early stage of arteriopathy [42,43].

A limitation of our study is that we could only study Caucasians from Southern Germany and, therefore, cannot conclude about relationships of CRF with changes in cIMT in other ethnic groups. Furthermore, it was not possible to replicate our findings in other studies, as we are not aware of studies that investigated the relationship of CRF with changes in cIMT during an intervention that aimed at reducing the cardiometabolic risk. In addition, possibly also based on the relatively low sample size, we observed relatively large confidence intervals for the odds of regression and progression of cIMT with changes in CRF during the lifestyle intrevention, indicating limited precision. However, the fact that we found independent relationships of CRF with cIMT and with the changes in cIMT, which was also reported in other studies [11–13], supports that our findings of baseline CRF and change in CRF predicting the change in cIMT during a lifestyle intervention are valid. Another strength of our study is that we performed precise phenotyping before and after the intervention, which allowed us to account for several risk factors of increased cIMT.

5. Conclusions

A high CRF at baseline and an improvement in CRF independently associated with a reduction in cIMT during a lifestyle intervention with a healthy diet and increased physical activity. Furthermore, a larger

adjusted increase in CRF during the lifestyle intervention was associated with a lower risk of progression of cIMT and with a higher chance of regression of cIMT. Because of the relatively low sample size, the wide confidence intervals observed for several effect estimates, and the relatively short follow-up period, our findings should be considered preliminary. Nevertheless, if replicated by other studies, these findings indicate that the measurement of CRF before and during a lifestyle intervention, more so than the measurement of body fat mass and distribution, glycemia, lipidemia, and blood pressure, may help predicting the success of such an intervention to reduce arteriopathy. Furthermore, the improvement in CRF could serve as a valuable target for interventions aiming at reducing the risk of CVDs.

Author contributions and guarantor statement

S.S. and K.K.: methodology, validation, formal analysis, data curation, investigation, writing-original draft, editing, visualization; J.M. and F.S.: investigation, resources, data curation. M.B.S., K.M-S. and N. M.: editing and visualization; R.J.-v.S. and A.L.B.: editing, project administration. A.*P. and* A.F.: investigation, resources and editing. A.L-St.: methodology, investigation, validation, writing-original draft, writing-review and editing. N.S.: conceptualization, methodology, investigation, validation, data curation, formal analysis, writing-original draft, writing-review, visualization, editing and supervision. All authors approved the final version of the manuscript. N.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability

Data from the Tuebingen Lifestyle Intervention Programme (TULIP) study are not publicly available due to data protection regulations. Data analyzes of TULIP data in accordance with German Federal and State data protection regulations may be timeline unlimited initiated upon an informal enquiry addressed to the TULIP Data Use and Access Committee (projektantrag.idm@med.uni-tuebingen.de). Each request will then have to pass a formal process of application and review by the respective Principal Investigator and a scientific board.

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Declaration of competing interest

All authors declare that they have no conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2026.121945.

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