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Study Design

The MuCAYA^{plus} Study—Influence of Physical Activity and Metabolic Parameters on the Structure and Function of the Cardiovascular System in Young Athletes

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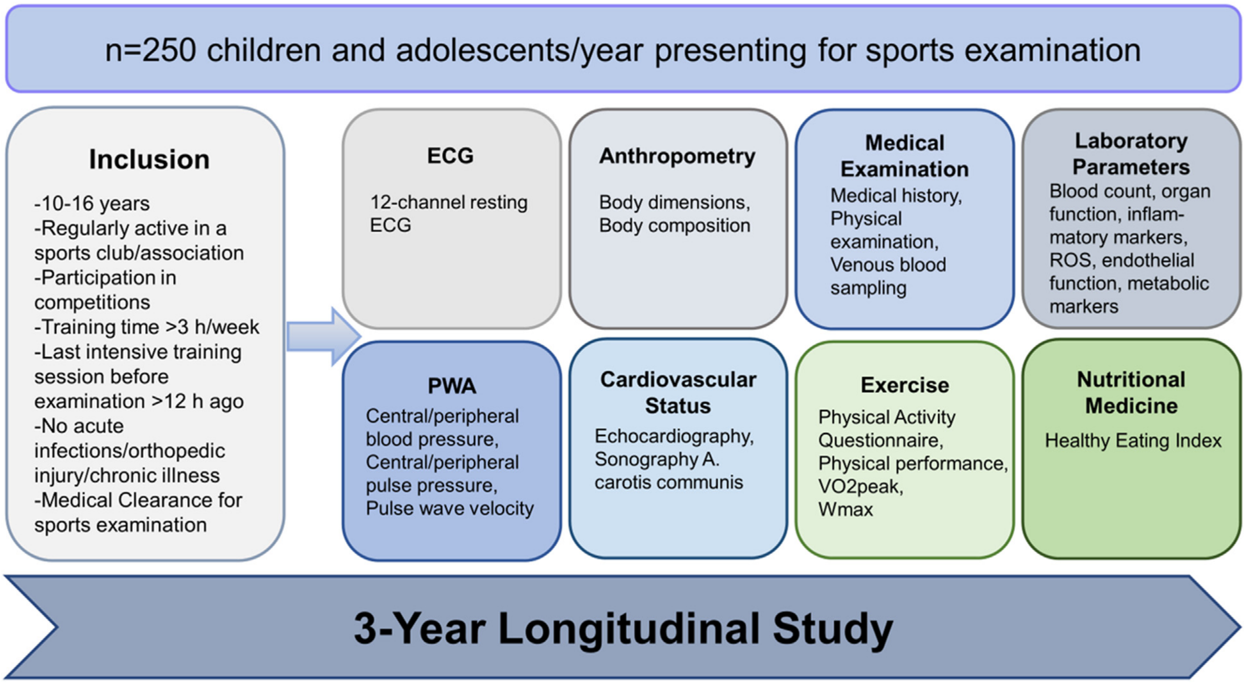

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ABSTRACT

Exercise has a significant impact on the cardiovascular (CV) health of children and adolescents, with resultant alterations in CV structure and function being evident, even at an early age. Engagement in regular, moderate physical activity (PA) is associated with long-term CV health benefits and a reduced risk of CV disease and mortality later in life. However, competitive sports often involve PA training intensities that are beyond recommended levels for young athletes, potentially leading to adverse CV outcomes. This situation emphasizes the importance of early monitoring of CV status, to prevent detrimental adaptations to intense physical exercise. The Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA^{plus}; NCT06259617) aims to investigate the as-yet-unclear adaptations to intense exercise that occur in young athletes. The study focuses on various factors, including CV health, PA, cardiopulmonary performance, body composition, eating habits, and biochemical markers.

In this longitudinal, prospective study, a sample of 250 young competitive athletes (aged 10-17 years) will undergo yearly examinations at the Institute of Preventive Pediatrics at the Technical University of Munich (TUM), over the span of 3 years. The testing protocol includes the following: anthropometric measurements; basic medical examinations; electrocardiography, with blood-pressure and pulse-wave analysis; echocardiography; sonography of the carotid artery; blood sampling for laboratory analysis; cardiopulmonary exercise testing on a bicycle ergometer; and participant completion of questionnaires regarding PA (the Motorik-Modul Longitudinal Study PA Questionnaire [MoMo-PAQ]) and nutrition.

Areas that are not yet fully understood are how exercise influences cardiac and vascular remodeling during long-term exercise, and how different biochemical and metabolic parameters, body composition, and nutrition impact such adaptations. The MuCAYA^{plus} study seeks to address these gaps in knowledge and provide comprehensive evidence on the longitudinal effects of exercise on the CV system of young athletes.

RÉSUMÉ

L'exercice physique a un impact significatif sur la santé cardiovasculaire (CV) des enfants et des adolescents, et les modifications de la structure et de la fonction CV qui en résultent sont évidentes, même à un jeune âge. La pratique régulière d'une activité physique (AP) modérée est associée à des bénéfices à long terme pour la santé CV et à une réduction du risque de maladie CV et de mortalité plus tard dans la vie. Cependant, le sport de compétition implique souvent des intensités d'entraînement qui dépassent les niveaux recommandés pour les jeunes athlètes, ce qui peut avoir des conséquences néfastes sur le plan CV. Cette situation souligne l'importance d'une surveillance précoce de l'état CV, afin de prévenir les adaptations préjudiciables en réponse à l'exercice physique intense. L'étude Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA^{plus}; NCT06259617) a pour but d'étudier les adaptations à l'exercice intense qui se produisent chez les jeunes athlètes et qui sont encore mal connues. L'étude se concentre sur différents facteurs, notamment la santé CV, l'AP, les performances cardiopulmonaires, la composition corporelle, les habitudes alimentaires et les marqueurs biochimiques.

Dans le cadre de cette étude longitudinale et prospective, un échantillon de 250 jeunes athlètes de compétition (âgés de 10 à 17 ans) sera soumis à des examens annuels à l'Institut de pédiatrie préventive de l'Université technique de Munich (TUM), sur une période de trois ans.

Le protocole de test comprend les éléments suivants : mesures anthropométriques; examens médicaux de base; électrocardiographie, avec analyse de la pression artérielle et du pouls; échocardiographie; échographie de l'artère carotide; prélèvement de sang pour analyse en laboratoire; épreuve d'effort cardiopulmonaire sur bicyclette ergométrique; et remplissage par les participants de questionnaires concernant l'AP (le Questionnaire Motorik-Modul Longitudinal Study Physical Activity [MoMo-PAQ]) et l'alimentation.

La manière dont l'exercice influence les remodelages cardiaque et vasculaire au cours d'un exercice de longue durée, et la manière dont les différents paramètres biochimiques et métaboliques, la composition corporelle et la nutrition influent sur ces adaptations ne sont pas encore parfaitement comprises. L'étude MuCAYA^{plus} vise à combler ces lacunes et à fournir des données complètes sur les effets longitudinaux de l'exercice sur le système CV des jeunes athlètes.

Engaging in regular, moderate physical activity (PA) leads to long-term health benefits, curbing overall mortality rates and reducing the risk of developing cardiovascular (CV) conditions, while decreasing the risk for several metabolic risk factors, such as obesity, diabetes mellitus, dyslipidemia, and hypertension.[1] Therefore, the World Health Organization (WHO) recommends that children and adolescents aim for an average of $\geq$ 60 minutes of moderate-to-vigorous PA, per day, for preventive purposes.[2]

In young athletes, however, the levels of PA in these recommendations are often exceeded by a significant margin. Even at a young age, competitive sports participation often requires training loads of 10-20 hours per week, with much higher intensity, frequency, and duration than recommended.[3,4] Instead of yielding health benefits, such extremely high training loads can lead to detrimental effects on the structure and function of the CV system,[5,6] potentially leading to pathophysiological events,[7] such as cardiomyopathy,[8,9], increased vascular stiffness,[10] and early atherosclerotic events.[11]

Within this context, cardiac remodelling describes the process by which the myocardium adjusts to training influenced by hemodynamic pressure—volume loads, such as heart rate, ejection fraction, and blood pressure, as well as biochemical mediators and oxidative stress.[5] In athletes, such changes manifest as ventricular enlargement and thickening of the left ventricular (LV) wall, leading to an elevated stroke volume and improved diastolic filling.[12] However, these changes also serve as risk factors for the development of dilated cardiomyopathy.[8]

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See page 1555 for disclosure information.

In cardiac remodelling that occurs due to PA, adaptations of the vascular system occur as well. Whether vascular remodelling is a consequence of cardiac adaptation, or vice versa, is still unclear. For example, an elevated cardiac output can impose an increased load on the vasculature, potentially leading to elastin fatigue and fragmentation over time. This process contributes to a loss of arterial compliance, resulting in increased arterial stiffness. Coupled with the pressure from wave reflections, this elevated level of stiffness raises the afterload, thereby promoting ventricular hypertrophy and impaired LV relaxation, which in turn leads to an enlargement of the left atrium.[13-15] Green et al.[16] describe the so-called "athlete's artery," which is characterized by an increase in vessel diameter and a decrease in wall thickness, facilitated partly by a heightened availability of vasodilatory compounds and antioxidants, along with decreased levels of inflammatory markers. Nitric oxide (NO) is the primary vasodilatory substance for endothelial relaxation. NO acts through the cyclic guanosine monophosphate (cGMP)-coupled reduction of intracellular calcium levels; it also is involved in the regulation of the primarily vasoconstrictive substance endothelin-1 (ET-1), acting as an inhibitor of ET-1 synthesis.[17] The vasoconstrictive effects of ET-1 are dependent on the binding of either 1 of its 2 receptor subtypes—ET_A—which elicits immediate and potent constriction, or ET_B, which stimulates the secretion of NO (ETA and ETB are receptor-subtypes for endothelin-1, which, upon binding of ET-1, elicit different vascular responses. ETA leads to potent constriction, ETB stimulates relaxation by stimulating NO secretion).[18] Crucial factors influencing these adaptations include exercise intensity and recovery time, as excessive intensity and inadequate recovery can provoke adverse responses.[19] Several studies have shown that endothelial function is impaired in competitive athletes, in response to highly intense exercise, and vascular stiffness is increased.[10,20,21]

Intensive PA promotes the excessive production of reactive oxygen species, through the exercise-induced contraction of active skeletal muscle fibers, an increased metabolic rate, as measured by oxygen consumption, and heightened heat production.[22-24] This excessive production of reactive oxygen species (ROS) is involved in the pathophysiology of the heart and molecular-level changes.[25] ROS contribute to contractile dysfunction associated with anomalies in intracellular Ca^{2+} homeostasis, cardiomyopathy, arrhythmia, ischemia−reperfusion damage, and mitochondrial DNA damage.[26] Additionally, ROS facilitate the oxidation of low-density lipoprotein, and thus, the development of endothelial dysfunction, atherosclerosis, and dilated cardiomyopathy.[11,27] In children and adolescents, ROS lead to age-specific changes in both oxidative and antioxidant markers.[28] Evidence indicates that lower antioxidant reserves, such as glutathione peroxidase, in children in general, as well as in children with chronically intensive training loads, predispose them to having a higher susceptibility to exercise-induced oxidative damage.[29,30] The increase in antioxidant enzymes, such as superoxide dismutase, indicates that adaptations to exercise occur even in pediatric populations.[31,32] These responses depend on factors such as training load and individual physical fitness, which have not been investigated sufficiently in relation to adaptations to oxidative stress.

Metabolic parameters, nutrition, and PA are interlinked and collectively influence the CV system. The hormone leptin and the thyroid hormone triiodothyronine (T3) affect both energy metabolism and CV health.[33,34] On one hand, leptin correlates positively with body fat mass and contributes as a vasoconstrictor to the regulation of vascular tone,[33,35] but on the other hand, it also suppresses appetite and contributes to vascular relaxation by stimulating NO synthesis.[36,37] T3 is essential for healthy growth, normal metabolism, and CV system function.[34] However, the research relating to this finding is not conclusive. Studies have shown that high levels of exercise, especially when unmatched by an increased dietary energy intake, can lead to reduced circulating concentrations of T3 levels, possibly modulated through downregulation of the hypothalamus-pituitary-adipocyte-leptin axis.[38] Low T3 levels are associated with an increased risk of CV diseases.[39] Conversely, other studies report that increased T3 levels are induced by intensive training.[40] Although an interplay occurs among leptin, thyroid function, and exercise,[41] their association with CV parameters and their changes over time in young athletes are not well understood.

The longitudinal research questions of the MuCAYA^plus study also are based on the results of the previous Influence of Vigorous Physical Activity on Structure and Function of the Cardiovascular System in Young Athletes (MuCAYA) cross-sectional study.[42] Conducted from 2017-2020, this study examined young athletes aged 7-18 years, across various performance levels, to determine the impact of PA on cardiac and vascular structure and function. Herein, adaptations in structural cardiac parameters were observed, with maximum aerobic capacity affecting the interventricular septal thickness during diastole, and training intensity influencing the LV internal diameter during diastole and systole, as well as the LV mass (LVM) indexed to body surface area (LVM/BSA).[43] In terms of vascular adaptation, young athletes have been shown to exhibit not only improved carotid arterial elasticity, and a lower level of arterial stiffness, compared to a normative reference cohort, but also a higher level of central arterial stiffness.[44] Additionally, young athletes demonstrated an increase in both carotid intima−media thickness (cIMT) and cIMT-to-carotid-diameter ratio values, with a negative association found between training load and cIMT, as well as improved central hemodynamics with a longer training duration.[44,45] However, the results of the preceding MuCAYA study did not account for the influence of biochemical factors that impact the relationship between vascular properties and exercise.

The aim of the MuCAYA^plus study is to explore how the interaction of cardiac and vascular remodelling is changed during long-term exercise in the still-developing CV system of young athletes. The study also examines the extent to which other parameters, such as biochemical markers, body composition, and nutrition, impact such adaptations. Herein, an issue of great importance to examine is what level of training load offsets the beneficial effects of exercise on the CV system and instead triggers detrimental effects on CV health, owing to disproportionate adaptations of key parameters.

Materials and Methods

Study design

All the examinations of this monocentric 3-year longitudinal prospective-cohort study have been or will be performed at the outpatient clinic at the Institute of Preventive Pediatrics of the Technical University of Munich (TUM), between December 2023 and November 2026.

Participants

Children and adolescents aged 10-16 years voluntarily enroll for sports fitness examinations, either for their competitive activities or as a requirement for their respective discipline. These include children and adolescents who match our criteria for definition as young competitive athletes,[46,47] who either have been examined in previous years or are undergoing a sports fitness examination for the first time. They are eligible to participate in the MuCAYA^{plus} study if they fulfill the following inclusion criteria for the duration of 3 years:

- being regularly active in a primary sport, and a member of a sports club and/or sports association;
- participating in athletic competitions;
- having a weekly training load of $\geq$ 3 hours;
- having a most-recent intensive training session before the study examination that was $\geq$ 12 hours earlier, to ensure sufficient recovery;
- having no acute infection and/or orthopedic injury and/or chronic illness, as confirmed by a medical examination on the day of testing;
- having clearance to undergo cardiopulmonary stress testing after a medical examination on the day of testing; and
- having participated annually (once per year) in the sport medical examination for 3 years.

The exclusion criteria are as follows:

- having an acute infection, acute orthopedic injury, or a chronic disease; and
- missing consent from the participant and/or legal guardian.

Sample-size calculation

The study investigates whether CV parameters are elevated more frequently in young athletes, compared to those in children and adolescents from a normative population.[48-50] Sample-size calculation was performed via G*Power (version 3.1.9.7)[51] with respect to LVM. A question that is examined is whether the proportion of athletes with a significantly higher LVM, compared to the norm, an indicator for hypertrophic cardiomyopathy (LVM > 95th percentile), exceeds the expected probability of 95% for the normative population. Assuming an observed probability of 10% in athletes,[49] n = 185 participants are needed to reject the null hypothesis ($P =$ 0.05), with a power of 80% (2-sided test, significance level $\alpha = 0.05$). To compensate for dropouts and missing examinations, we aim to include n = 250 athletes in the study. The sample-size calculation considers the influence of training on the left heart, represented by the LVM as a parameter. With the calculated sample size, the training effect on the heart can be demonstrated and statistically supported. Over the course of 3 years, approximately 250 young athletes are to be examined each year, totaling a final number of 750 examinations. The current recruitment and examination status is as follows: since the start of the study in December 2023, we have included and examined 170 of the desired 250 participants, as of July 2024 in the first year of the study.

Ethical considerations

The study has been approved by the TUM ethics committee (project number: 516547656). All study participants receive a document detailing study information, and they receive information about the study verbally. Depending on the age of the study participants, written consent to participate in the study is obtained from both the participants and their legal guardians.

Measurements

Medical history and examination. Participants receive a physical examination, and a personal and/or family history is taken. The medical history includes data on past and present illnesses and injuries, vaccination status, allergies, medication intake, dietary habits, use of dietary supplements, alcohol intake, smoking status, drug use, energy-drink consumption, and menarche and the menstrual cycle in female participants. Participants' training history and symptoms during exercise performance, such as dyspnea, dizziness and/or syncope, palpitations, and angina, also are documented. A family history, obtained together with the participant's parents, covers CV diseases, sudden deaths, and Marfan syndrome, among other conditions.

Venous blood sampling and analysis of laboratory parameters. Participants receive venous blood sampling after fasting, and a comprehensive blood analysis, which includes the following parameters: blood count (erythrocytes, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglogin concentration, hemoglobin, hematocrit, leukocytes, thrombocytes); specific organ function (glutamate-oxaloacetate-transaminase [GOT], glutamate-pyruvate-transaminase [GPT], gamma-glutamyltransferase [GGT], creatinine, uric acid, low-density lipoprotein, high-density lipoprotein, total cholesterol); blood glucose; inflammation (high-sensitivity C-reactive protein); enzymes of reactive oxygen species metabolism (superoxide dismutase, glutathione peroxidase); endothelial function (NO, ET-1); and metabolic function (leptin, free triiodothyronine [fT3]).

Anthropometrics. Body weight and body composition are assessed using a bioelectrical impedance analysis scale (InBody 270 Body Composition Analyzer, InBody Deutschland, Eschborn, Germany). Height, standing waist circumference, and standing hip circumference are measured with an accuracy of 0.1 cm.[52] Measurements are taken when participants are not wearing shoes and are dressed in light sports clothing.

Body mass index is calculated from height and weight. Age- and gender specific z-scores for body mass index, and waist and hip circumferences, are determined according to reference values.[53,54] Physical maturity status is evaluated based on growth in height and sitting height.

Basic CV examination

Basic CV assessment includes a 12-lead resting electrocardiogram taken while participants are in a supine position (CARDIOVIT CS-200 Office, Schiller, Baar, Switzerland). Peripheral and central systolic and diastolic blood pressure, peripheral and central pulse pressure, as well as aortic pulse-wave velocity, are evaluated from the left brachialis anticus muscle after 5 minutes of rest, using the Mobil-O-Graph, IEM, Stolberg, Germany), and are compared to reference values.[55] The Mobil-O-Graph device is noninvasive, and it has been validated across multiple studies, making it a regular choice for use in pediatric populations.[56-59] Pulse-wave velocity and central systolic blood pressure are determined using the device's proprietary algorithm.[55,60]

Sonographic examination

All sonographic examinations are performed using the Aplio i900 ultrasound imaging system (Canon Medical Systems, Neuss, Germany).

Vascular parameters. Structural vascular parameters include carotid intima−media thickness (IMT), vessel diameter and calculated IMT:diameter ratio. The IMT is measured using B-mode ultrasound, according to the method from the Association for European Paediatric and Congenital Cardiology (AEPC). Measurements are performed with participants in a supine position, at the far wall of the common carotid artery, with the participants' head tilted to the opposite side from that of the investigation. IMT measures are taken 1 cm proximal to the carotid artery bifurcation, at the end-diastolic phase, bilaterally at 2 angles on Meijer's carotid arc[61] (120°/150° right; 210°/240° left). The vascular wall function of both common carotid arteries is assessed by measuring the peak circumferential strain and the peak diastolic and systolic strain rates. These are examined in B-mode ultrasound, using speckle-tracking technology,[62,63] with participants in a supine position with their head in a neutral position and their chin elevated. Measurements are taken during a breath-hold in expiration, at a proximal and a distal location. The reference points used are the maximum transverse diameter of the ipsilateral thyroid lobe, and the carotid arterial bifurcation.

Cardiac parameters. All participants receive resting echocardiography while in a supine position, to assess their cardiac morphology and function, according to American Society of Echocardiography guidelines.

Cardiac adaptation to exercise comprises morphologic as well as functional adaptation. Morphologic parameters include m-mode measurements of end-diastolic LV diameters and wall thickness, as well as 2-dimensional LV volumetry. LV ejection fraction is calculated using the biplane Simpson method.[64] Pulse-wave Doppler measurements of mitral inflow, and myocardial Doppler tracings of the basal LV septal and lateral walls, are obtained, as a quantification of diastolic function.

Assessment of cardiopulmonary fitness

A cardiopulmonary exercise test is performed on a cycle ergometer (Corival, Lode B.V., Groningen, Netherlands) using a modified Godfrey ramp protocol.[65] All participants are instructed to cycle using maximum effort. After a 2-minute rest period, participants commence cycling with an initial load set to 50% of their body mass. Ramps were scaled to achieve participants' maximum effort level after 8-12 minutes of exercise, according to estimated individual fitness levels. Effort is considered maximal if a respiratory exchange ratio of $\geq$ 1.10 is reached.[66] Comparability of cardiopulmonary performance is ensured by normalization to body weight (relative peak oxygen uptake in mL/min/kg). Throughout the test, participants are monitored using a continuous 12-lead electrocardiogram, blood pressure measurements taken every 2 minutes, and intermittent oxygen pulse oximetry. Parameters derived from the cardiopulmonary exercise test are acquired and analyzed using the MetaMax 3B system (Cortex Biophysik, Leipzig, Germany). These include peak oxygen uptake, ventilatory thresholds, maximum heart rate, relative maximum workload, and maximum power output. After performing at their maximal exertion level, patients are monitored continuously for 5 minutes. Testing is conducted by trained sport scientists, with a cardiologist on hand.

PA questionnaire

To assess the motor performance and PA of children and adolescents, we use the Motorik-Modul-Physical Activity Questionnaire (MoMo-PAQ), which has been validated by Bös et al.[67] and Jekauc et al.[68] This questionnaire comprises data on PA load, during specific athletic training, as well as in daily life. Data on personal training history, primary competitive sporting discipline, years of experience, and current training load are collected. The numbers of metabolic equivalent of task (MET) minutes per week are calculated, for the primary sporting discipline and for daily-life PA.

Nutrition

Nutrition quality and dietary habits will be assessed via the Food Frequency Questionnaire of the German National Health Interview and Examination Survey for Children and Adolescents (KiGGS).[69] Based on the previously published Healthy Nutrition Score for Kids and Youth (HuSKY),[70] we will develop a modified and updated score considering current nutritional recommendations. The score will be calculated as the ratio of the quantity of specific food categories (eg, vegetables, fruit, dairy), as assessed by the Food Frequency Questionnaire, and the age-specific nutritional guidelines for each group. A higher score will be reflective of a healthier diet, which we define as one that is in closer agreement with the current recommendations.

Statistical analysis

The question of whether the proportion of young athletes with significantly elevated CV parameters differs from the expected proportion in the normative population is analyzed via χ^2 test (null hypothesis that this probability is 5%; 2-sided test; significance level $\alpha = 0.05$). An exact 95% confidence interval (CI; Clopper—Pearson interval) also is estimated for this probability. Additionally, mean values and standard deviations, stratified by age and gender, along with corresponding CIs for the means are presented for all parameters, including CV, cardiopulmonary, anthropometric, laboratory, PA, and nutritional parameters. To assess the relationship between training intensity and the measured parameters, linear regression models are fitted to the data. Transformations of training intensity (eg, using splines) are utilized to detect potentially nonlinear associations, such as that expected for the relationship between training intensity and LVM, and to identify a threshold at which training intensity may be considered harmful.

The ages and genders of the participants are considered in the modelling, to examine possible interaction between these parameters. For binary outcomes, a similar approach via logistic regression models is used. Mixed-effects regression models are used to explore longitudinal data, incorporating random effects for participants. This approach models the development of relevant outcomes over time, analyzes differences in level or change—for example, between genders or between groups with different training intensities. Associations of changes in parameters over time are evaluated using correlation coefficients. All secondary analyses are exploratory, and 95% CIs are estimated for relevant effect sizes.

Discussion

The MuCAYA^{plus} study aims to provide comprehensive insights into the effect of exercise on the CV system of young athletes, exploring the temporal and causal relationships associated with long-term adaptation to exercise. The study will examine various factors and their interaction, including CV health, PA levels, body composition, cardiopulmonary performance, nutrition, and biochemical markers.

The purpose of this study builds on the findings of the previous MuCAYA study,[42] in which cardiac and vascular changes were observed in young athletes. LVM, interventricular septal thickness, and relative wall thickness of the left ventricle were found to be increased significantly within 1 one year of training, with training duration and maximal aerobic capacity (peak oxygen uptake) having a significant impact. Training intensity also significantly influenced the LV internal diameter in both diastole and systole.[43] Other studies also show that cardiac remodelling occurs as early as in childhood and adolescence.[71,72] PA has been found to significantly influence the diameter and volume of the left atrium, as well as the volume, area, and diameter of the right atrium.[73-76] The evidence is mixed regarding the impact of exercise on the heart's systolic and diastolic functions. Simsek et al.[74] reported that systolic function was enhanced in adolescent strength athletes, whereas Sharma et al.[9] found no improvement in diastolic function among young athletes.

Regarding vascular changes, results of the previous MuCAYA study demonstrated that arterial elasticity was improved, and arterial stiffness was reduced in young athletes compared to those in a normative population, but the young athletes also showed a higher level of central arterial stiffness. In addition, their cIMT and cIMT-to-carotid-diameter ratio values were increased, with a negative association between training load and cIMT.[44,45] Overall, the research on vascular remodelling in young athletes is sparse. However, Demirel et al.[77] noted a decrease in carotid IMT, and an increase in diastolic wall stress, among adolescent wrestlers.

Vasoactive substances, such as the vasodilating NO or the vasoconstricting ET-1, as well as antioxidative parameters and metabolic agents, are key influencing factors in the regulation of vascular tone and vessel function.[78-81] Although evidence is limited regarding biochemical markers, particularly in the population of young, elite athletes, multiple studies have documented the positive effect of exercise on the levels of vascular active substances after different exercise interventions in children and adolescents in general, as well as in children and adolescents with preexisting conditions. These studies show that levels of dilating factors, such as NO, are elevated in response to exercise, while constricting parameters such as ET-1 are reduced.[82-85] Exercise also has been shown to boost the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, across various exercise protocols in children and adolescents,[86-88] and several studies indicate that levels of metabolic markers, such as leptin, decrease following PA.[89,90]

Limitations

The study collective is comprised of young competitive athletes who are regularly active in sports clubs and/or associations, with a required minimum of 3 hours of weekly training. We do not include a normative control group with children and adolescents who are not physically active, which limits the comparison that can be made of CV and other parameters to those in the included study population, and places focus on the longitudinal changes over the timespan of the study. The extent of adaptation differs among individuals, and individual young athletes, within a spectrum of high-level responders to low-level responders, as some children and adolescents are more predisposed genetically to muscular and CV adaptation than are others. We also do not include a detailed assessment of the physical maturation status of children and adolescents, which we assess by measuring linear growth and sitting height,[91,92] and which also influences the CV properties.

Additionally, the level of PA, as well as the quality of nutrition among participants, is assessed via written and online questionnaires. Hence, the validity of the results depends on the participants' ability to fill out the questionnaires correctly, as well as their honesty and ability in accurately remembering their physical workload and dietary habits.

Conclusion

Exercise can affect CV health through various mechanisms, starting at a young age. Exactly how exercise influences the interaction of cardiac and vascular remodelling, and how CV parameters change longitudinally in young athletes is not yet fully understood. Moreover, what influence different biochemical and metabolic parameters, as well as body composition and nutrition, have in this context remains unclear. Emphasis in research should be placed on investigating the threshold at which training load counteracts the beneficial effects of exercise on the CV system, thereby leading to adverse effects on CV health, owing to disproportionate changes in critical parameters. The

MuCAYA^{plus} study aims to close this gap in evidence within the framework of a 3-year longitudinal study.

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Ethics Statement

The study has been approved by the TUM ethics committee (project number: 516547656). All study participants receive a document detailing study information, and they receive information about the study verbally. Depending on the age of the study participants, written consent to participate in the study is obtained from both the participants and their legal guardians.

Patient Consent

The authors confirm that a patient consent form(s) has been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blai SN. Sedentary behavior, exercise, and cardiovascular health. Circ Res 2019;124:799-815.
2. World Health Organization. WHO guidelines approved by the Guidelines Review Committee. In: Global Recommendations on Physical Activity for Health. Geneva: World Health Organization, 2010:39. Section vi.
3. Sabato TM, Walch TJ, Caine DJ. The elite young athlete: strategies to ensure physical and emotional health. Open Access J Sports Med 2016;7:99-113.
4. Little CC, Howell DR, Armento AM, Sweeney EA, Walker GA. Training volume recommendations and psychosocial outcomes in adolescent athletes. Phys Sportsmed 2023;51:420-6.
5. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569-82.
6. Green DJ, Hopman MTE, Padilla J, Laughlin MH, Thijssen DHJ. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. Physiol Rev 2017;97:495-528.
7. Möhlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. Eur Heart J 2008;29:1903-10.
8. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. Ann Intern Med 1999;130:23-31.
9. Sharma S, Maron BJ, Whyte G, et al. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;40:1431-6.
10. Otsuki T, Maeda S, Iemitsu M, et al. Vascular endothelium-derived factors and arterial stiffness in strength- and endurance-trained men. Am J Physiol Heart Circ Physiol 2007;292:H786-91.
11. Wang J-S, Lee T, Chow S-E. Role of exercise intensities in oxidized low-density lipoprotein-mediated redox status of monocyte in men. J Appl Physiol (1985) 2006;101:740-4.
12. Sharma S, Merghani A, Mont L. Exercise and the heart: the good, the bad, and the ugly. Eur Heart J 2015;36:1445-53.
13. Heffernan KS. How healthy were the arteries of Phidippides? Clin Cardiol 2012;35:65-8.
14. Heffernan KS, Jae SY, Tomayko E, et al. Influence of arterial wave reflection on carotid blood pressure and intima-media thickness in older endurance trained men and women with pre-hypertension. Clin Physiol Funct Imaging 2009;29:193-200.
15. Laurent P, Marenco P, Castagna O, et al. Differences in central systolic blood pressure and aortic stiffness between aerobically trained and sedentary individuals. J Am Soc Hypertens 2011;5:85-93.
16. Green DJ, Spence A, Rowley N, Thijssen DHJ, Naylor LH. Vascular adaptation in athletes: Is there an 'athlete's artery'? Exp Physiol 2012;97:295-304.
17. Maeda S, Miyauchi T, Kakiyama T, et al. Effects of exercise training of 8 weeks and detraining on plasma levels of endothelium-derived factors, endothelin-1 and nitric oxide, in healthy young humans. Life Sci 2001;69:1005-16.
18. Schneider MP, Boesen EI, Pollock DM. Contrasting actions of endothelin ET(A) and ET(B) receptors in cardiovascular disease. Annu Rev Pharmacol Toxicol 2007;47:731-59.
19. La Gerche A, Heidbuchel H. Can intensive exercise harm the heart? You can get too much of a good thing. Circulation 2014;130:992-1002.
20. Kim Y-J, Ahn JK, Shin K-A, et al. Correlation of cardiac markers and biomarkers with blood pressure of middle-aged marathon runners. J Clin Hypertens (Greenwich) 2015;17:868-73.
21. van de Sande DAJP, Barneveld PC, Hoogsteen J, Doevendans PA, Kemps HMC. Coronary microvascular function in athletes with abnormal exercise test results. Neth Heart J 2019;27:621-8.
22. Schippinger G, Wonisch W, Abuja PM, et al. Lipid peroxidation and antioxidant status in professional American football players during competition. Eur J Clin Invest 2002;32:686-92.
23. Li G. The positive and negative aspects of reactive oxygen species in sports performance. In: Hamlin M, Draper N, Kathiravel Y, eds. Current Issues in Sports and Exercise Medicine. Rijeka, Croatia: IntechOpen, 2013. Chapter 6.
24. Powers SK, Deminice R, Ozdemir M, et al. Exercise-induced oxidative stress: friend or foe? J Sport Health Sci 2020;9:415-25.
25. Therade-Matharan S, Laemmel E, Carpentier S, et al. Reactive oxygen species production by mitochondria in endothelial cells exposed to reoxygenation after hypoxia and glucose depletion is mediated by ceramide. Am J Physiol Regul Integr Comp Physiol 2005;289:R1756-62.

26. Emami A, Tofighi A, Asri-Rezaei, Bazargani-Gilani B. The effect of short-term coenzyme Q10 supplementation and pre-cooling strategy on cardiac damage markers in elite swimmers. Br J Nutr 2018;119:381-90.

27. Doerries C, Grote K, Hilfiker-Kleiner D, et al. Critical role of the NAD(P)H oxidase subunit p47phox for left ventricular remodeling/dysfunction and survival after myocardial infarction. Circ Res 2007;100:894-903.

28. Avloniti A, Chatzinikolaou A, Deli CK, et al. Exercise-induced oxidative stress responses in the pediatric population. Antioxidants (Basel) 2017;6:6.

29. Gougoura S, Nikolaidis MG, Kostaropoulus IA, et al. Increased oxidative stress indices in the blood of child swimmers. Eur J Appl Physiol 2007;100:235-9.

30. Santos-Silva A, Rebelo MI, Castro EM, et al. Leukocyte activation, erythrocyte damage, lipid profile and oxidative stress imposed by high competition physical exercise in adolescents. Clin Chim Acta 2001;306:119-26.

31. Zalavras A, Fatorous IG, Deli CK, et al. Age-related responses in circulating markers of redox status in healthy adolescents and adults during the course of a training macrocycle. Oxid Med Cell Longev 2015;2015:283921.

32. Tong TK, Kong Z, Lin H, et al. Serum oxidant and antioxidant status following an all-out 21-km run in adolescent runners undergoing professional training—a one-year prospective trial. Int J Mol Sci 2013;14:15167-78.

33. Katsiki N, Mikhailidis DP, Banach M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. Acta Pharmacol Sin 2018;39:1176-88.

34. Mendoza A, Hollenberg AN. New insights into thyroid hormone action. Pharmacol Ther 2017;173:135-45.

35. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334:292-5.

36. Mechanick JI, Zhao S, Garvey WT. Leptin, an adipokine with central importance in the global obesity problem. Glob Heart 2018;13:113-27.

37. Rodríguez A, Fortuño A, Gómez-Ambrosi J, et al. The inhibitory effect of leptin on angiotensin II-induced vasoconstriction in vascular smooth muscle cells is mediated via a nitric oxide-dependent mechanism. Endocrinology 2007;148:324-31.

38. Steinacker JM, Brkic M, Simsch C, et al. Thyroid hormones, cytokines, physical training and metabolic control. Horm Metab Res 2005;37:538-44.

39. Jabbar A, Pingitore A, Pearce SHS, et al. Thyroid hormones and cardiovascular disease. Nat Rev Cardiol 2017;14:39-55.

40. Hackney AC, Saeidi A. The thyroid axis, prolactin, and exercise in humans. Curr Opin Endocr Metab Res 2019;9:45-50.

41. Perseghin G, Lattuda G, Ragogna F, et al. Free leptin index and thyroid function in male highly trained athletes. Eur J Endocrinol 2009;161:871-6.

42. Baumgartner L, Schulz T, Oberhoffer R, Webberuß H. Influence of vigorous physical activity on structure and function of the cardiovascular system in young athletes—the MuCAYA-Study. Front Cardiovasc Med 2019;6:148.

43. Weberruß H, Baumgartner L, Mühlbauer F, Shehu N, Oberhoffer-Fritz R. Training intensity influences left ventricular dimensions in young competitive athletes. Front Cardiovasc Med 2022;9:961979.

44. Baumgartner L, Weberruß H, Appel A, et al. Improved carotid elasticity but altered central hemodynamics and carotid structure in young athletes. Front Sports Act Living 2021;3:633873.

45. Baumgartner L, Weberruß H, Engl T, Schulz T, Oberhoffer-Fritz R. Exercise training duration and intensity are associated with thicker carotid intima-media thickness but improved arterial elasticity in active children and adolescents. Front Cardiovasc Med 2021;8:618294.

46. Fagard R. Athlete's heart. Heart 2003;89:1455-61.

47. Araújo CGS, Scharhag J. Athlete: a working definition for medical and health sciences research. Scand J Med Sci Sports 2016;26:4-7.

48. Weberruß H, Pirzer R, Böhm B, et al. Increased intima-media thickness is not associated with stiffer arteries in children. Atherosclerosis 2015;242:48-55.

49. Krysztofiak H, Młyńczak M, Folga A, Braksator W, Malek LA. Normal values for left ventricular mass in relation to lean body mass in child and adolescent athletes. Pediatr Cardiol 2019;40:204-8.

50. Foster BJ, Khoury PR, Kimball TR, Mackie AS, Mitsnefes M. New reference centiles for left ventricular mass relative to lean body mass in children. J Am Soc Echocardiogr 2016;29:441-447.e2.

51. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-91.

52. World Health Organization. Waist circumference and waist-hip ratio. Report of a WHO expert consultation, December 8-11, 2008 Geneva. Available at: https://www.who.int/publications/i/item/9789241501491. Accessed November 4, 2024.

53. Kromeyer-Hauschild K, Wabitsch M, Kunze D, et al. Perzentile für den body mass index für das kindes—und jugendalter unter heranziehung verschiedener deutscher stichproben. Monatszeitschrift Kinderheilkunde 2001;149:807-18 [in German].

54. Neuhauser H, Schienkiewitz A, Rosario AS, Dortschy R, Bärbel-Maria K. Referenzperzentile für Anthropometrische Maßzahlen und Blutdruck aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS). Berlin: Robert Koch-Institut, 2013:32-58 [in German].

55. Elmenhorst J, Hulpke-Wette M, Barta C, et al. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. Atherosclerosis 2015;238:9-16.

56. Hametner B, Wassertheurer S, Kropf J, et al. Oscillometric estimation of aortic pulse wave velocity: comparison with intra-aortic catheter measurements. Blood Press Monit 2013;18:173-6.

57. Weiss W, Gohlisch C, Harsch-Gladisch C, et al. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. Blood Press Monit 2012;17:128-31.

58. Sharman JE, Avolio AP, Baulmann J, et al. Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. Eur Heart J 2017;38:2805-12.

59. Shiraishi M, Murakami T, Higashi K. The accuracy of central blood pressure obtained by oscillometric noninvasive method using Mobil-O-Graph in children and adolescents. J Hypertens 2020;38:813-20.

60. Salvi P, Scalise F, Rovina M, et al. Noninvasive estimation of aortic stiffness through different approaches. Hypertension 2019;74:117-29.

61. Dogan S, Duivenvoorden R, Grobbee DE, et al. Ultrasound protocols to measure carotid intima-media thickness in trials; comparison of reproducibility, rate of progression, and effect of intervention in subjects with

familial hypercholesterolemia and subjects with mixed dyslipidemia. Ann Med 2010;42:447-64.

62. Saito M, Okayama H, Inoue K, et al. Carotid arterial circumferential strain by two-dimensional speckle tracking: a novel parameter of arterial elasticity. Hypertens Res 2012;35:897-902.

63. Iino H, Okano T, Daimon M, et al. Usefulness of carotid arterial strain values for evaluating the arteriosclerosis. J Atheroscler Thromb 2019;26: 476-87.

64. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

65. Godfrey S. Exercise Testing in Children: Applications in Health and Disease. Philadelphia: WB Saunders, 1974:1-168.

66. Takken T, Bongers BC, van Brussel M, Haapala EA, Hulzebos EHJ. Cardiopulmonary exercise testing in pediatrics. Ann Am Thorac Soc 2017;14(Suppl 1):S123-8.

67. Bös K, et al. *Motorik-Modul: Motorische Leistungsfähigkeit und körperlich-sportliche Aktivität von Kindern und Jugendlichen in Deutschland*. Foss Newsletter 2007;7:1-2 [in German]. Opper E, Worth A, Wagner M, Bös K. [The module "Motorik" in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Motor fitness and physical activity of children and young people]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2007;50:879-88 [in German].

68. Jekauc D, Voelkle M, Wagner MO, Mewes N, Woll A. Reliability, validity, and measurement invariance of the German version of the physical activity enjoyment scale. J Pediatr Psychol 2013;38:104-15.

69. Mensink GBM, Burger M. [What do you eat? Food frequency questionnaire for children and adolescents]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2004;47:219-26 [in German].

70. Kleiser C, Mensink GB, Scheidt-Nave C, Kurth BM. HuSKY: a healthy nutrition score based on food intake of children and adolescents in Germany. Br J Nutr 2009;102:610-8.

71. Makan J, Sharma S, Firoozi S, et al. Physiological upper limits of ventricular cavity size in highly trained adolescent athletes. Heart 2005;91: 495-9.

72. Ayabakan C, Akalin F, Mengütay S, et al. Athlete's heart in prepubertal male swimmers. Cardiol Young 2006;16:61-6.

73. Rundqvist L, Engvall J, Faresjö M, Carlsson E, Blomstrand P. Regular endurance training in adolescents impacts atrial and ventricular size and function. Eur Heart J Cardiovasc Imaging 2017;18:681-7.

74. Simsek Z, Tas MH, Degirmenci H, et al. Speckle tracking echocardiographic analysis of left ventricular systolic and diastolic functions of young elite athletes with eccentric and concentric type of cardiac remodeling. Echocardiography 2013;30:1202-8.

75. D'Ascenzi F, Solari M, Anselmi F, et al. Atrial chamber remodelling in healthy pre-adolescent athletes engaged in endurance sports: a study with a longitudinal design. The CHILD study. Int J Cardiol 2016;223: 325-30.

76. Zdravkovic M, Perunicic J, Krotin M, et al. Echocardiographic study of early left ventricular remodeling in highly trained preadolescent footballers. J Sci Med Sport 2010;13:602-6.

77. Demirel A, Baykara M, Koca TT, Berk E, Gençay ÖA. Comparison of vascular arterial stiffness parameters of adolescent wrestlers with healthy subjects: Is heavy training harmful for wrestlers? J Back Musculoskelet Rehabil 2019;32:155-60.

78. Thijssen DH, Carter SE, Green DJ. Arterial structure and function in vascular ageing: Are you as old as your arteries? J Physiol 2016;594: 2275-84.

79. Song Y, Jia H, Hua Y, et al. The molecular mechanism of aerobic exercise improving vascular remodeling in hypertension. Front Physiol 2022;13: 792292.

80. Hellsten Y, Jensen L, Thaning P, Nyberg M, Mortensen S. Impaired formation of vasodilators in peripheral tissue in essential hypertension is normalized by exercise training: role of adenosine and prostacyclin. J Hypertens 2012;30:2007-14.

81. Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. Circulation 2008;117:3238-49.

82. Souza LV, De Meneck F, Oliveira V, et al. Beneficial impact of moderate to vigorous physical activity program on circulating number and functional capacity of endothelial progenitor cells in children: the crucial role of nitric oxide and VEGF-A. Pediatr Exerc Sci 2019;31:322-9.

83. Hamurcu Z, Saritas N, Baskol G, Akpinar N. Effect of wrestling exercise on oxidative DNA damage, nitric oxide level and paraoxonase activity in adolescent boys. Pediatr Exerc Sci 2010;22:60-8.

84. Vasconcellos F, Seabra A, Cunha F, et al. Health markers in obese adolescents improved by a 12-week recreational soccer program: a randomised controlled trial. J Sports Sci 2016;34:564-75.

85. Gunay O, Onur E, Yilmaz O, et al. Effects of physical exercise on lung injury and oxidant stress in children with asthma. Allergol Immunopathol (Madr) 2012;40:20-4.

86. Woo J, Yeo NH, Shin KO, et al. Antioxidant enzyme activities and DNA damage in children with type 1 diabetes mellitus after 12 weeks of exercise. Acta Paediatr 2010;99:1263-8.

87. Gonenc S, Acikgoz O, Semin I, Ozgonul H. The effect of moderate swimming exercise on antioxidant enzymes and lipid peroxidation levels in children. Indian J Physiol Pharmacol 2000;44:340-4.

88. Alshammari E, Shafi S, Nurmi-Lawton J, et al. Altered antioxidant and trace-element status in adolescent female gymnasts. Int J Sport Nutr Exerc Metab 2010;20:291-8.

89. Jürimäe J, Võsoberg K, Tamm A-L, et al. Body composition and inflammatory markers in pubertal girls: comparison between athletes and non-athletic controls. Eur J Sport Sci 2017;17:867-73.

90. Güllü E, Güllü A, Düzova H, et al. The relationship between serum leptin and VO2max levels in pre-puberty swimmer girls: effect of acute exercise. J Nutr Intern Med 2020;22:177-84.

91. Malina RM, Rogol AD, Cumming SP, Coelho e, Silva MJ, Figueiredo AJ. Biological maturation of youth athletes: assessment and implications. Br J Sports Med 2015;49:852-9.

92. Mirwald RL, Baxter-Jones ADG, Bailey DA, Beunen GP. An assessment of maturity from anthropometric measurements. Med Sci Sports Exerc 2002;34:689-94.