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JUTA KRAAV

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Department of Paediatrics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

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1. LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications referred to in the text by their Roman numerals (I–III):

I Kraav J, Tamme R, Remmel L, Mäestu E, Zagura M, Jürimäe J, Tillmann V. Arterial structure in 18-year-old males is dependent on physical activity at 12 years and cumulative cardiorespiratory fitness from puberty to late adolescence. Pediatric Exercise Science. 2023 25(3):144–154

II Kraav J, Zagura M, Remmel L, Mäestu E, Jürimäe J, Tillmann V. Rapid trabecular bone growth in puberty associated with stiffer arteries in adulthood – longitudinal study on healthy young males. Archives of Osteoporosis. 2023; 18(1):62.

III Kraav J, Zagura M, Viitasalo A, Soininen S, Veijalainen A, Kähönen M, Jürimäe J, Tillmann V, Haapala E, Lakka T. Associations of cardiovascular health metrics in childhood and adolescence with arterial health indicators in adolescence: The PANIC Study. Journal of the American Heart Association. 2024; 13(22):e035790.

Author's contribution:
In all papers, JK performed data analysis, interpreted the results, drafted the manuscripts and was the responsible author of the manuscripts. Additionally for paper III JK was responsible for requesting the data from PANIC study and cooperation with the co-authors.

2. ABBREVIATIONS

AHA	American Heart Association
AIx	augmentation index
AIxHR75	augmentation index standardised to heart rate of 75bpm
ALSPAC	Avon Longitudinal Study of Parents and Children
ap-PWV	aorto-popliteal pulse wave velocity
BMAD	bone mineral apparent density
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BPM	beats per minute
cf-PWV	carotid-femoral pulse wave velocity
CI	confidence intervals
cIMT	carotid intima-media thickness
CVD	cardiovascular disease
CVH	cardiovascular health
DXA	dual-energy X-ray absorptiometry
eNOS	endothelial nitric oxide synthase
ESC	European Society of Cardiology
FM	fat mass
IMT	intima-media thickness
LBM	lean body mass
LDL	low-density lipoprotein
MET	metabolic equivalent of task
MHz	megahertz
MVPA	moderate to vigorous physical activity
NHANES	National Health and Nutrition Examination Survey
NO	nitric oxide
PANIC	Physical Activity and Nutrition in Children
PWV	pulse wave velocity
ROS	reactive oxygen species
SBP	systolic blood pressure
SDS	standard deviation score
STRIP	Special Turku Coronary Risk Factor Intervention Project
VO2peak	peak oxygen consumption
VSMC	vascular smooth muscle cell
WHO	World Health Organization

3. INTRODUCTION

Cardiovascular disease (CVD), the leading cause of death and disability in Europe (European Society of Cardiology, 2025), is an umbrella term covering a number of diseases affecting the heart and vessels (World Health Organization, 2025). Coronary artery disease, cerebrovascular disease and peripheral arterial disease have a common underlying atherosclerotic mechanism, although in different vessel regions (Jebari-Benslaiman et al., 2022). Atherosclerosis starts from endothelial dysfunction and is followed by a cascade of events including fatty streaks and fibrous plaques formation, the latter being observed in children and adolescents as shown in autopsy studies (Berenson et al., 1998). Vascular disease originates early, making prevention during youth essential.

Non-invasive measures such as intima-media thickness (IMT) and pulse wave velocity (PWV) are increasingly applied to assess subclinical vascular health in youth. Together, IMT and PWV provide complementary insights into vascular health, IMT reflecting structural changes and PWV reflecting functional alterations related to arterial stiffness. The use of augmentation index (AIx) complements the above as it provides insight to the wave reflection properties. The use of these measures in paediatric research could allow for early identification of at-risk individuals and help elucidate the relationships between cardiovascular health (CVH) and modifiable lifestyle factors. Although both are widely used, questions remain about their sensitivity, reproducibility, and predictive value in paediatric populations.

The concept of primordial prevention, which targets the avoidance of risk factor development altogether, is particularly relevant during childhood, a period of rapid growth and behavioural formation (Daniels et al., 2005). Early life habits and health status not only influence short-term well-being but also set the trajectory for lifelong CVH. Rising rates of unhealthy behaviour (Ng et al., 2014) amplify the urgency to identify early vascular alterations and their determinants.

Several modifiable factors may shape arterial health early in life. Body composition, especially excess adiposity, is linked to arterial structural and functional alterations through inflammation and metabolic dysregulation (Cote et al., 2015; Dangardt et al., 2008). Yet, evidence on its effects on arterial stiffness is inconsistent, with some studies reporting associations and others showing null findings (Agbaje et al., 2021; Chiesa et al., 2021; Williams et al., 2017). Physical activity is often promoted as protective, but associations with arterial markers in youth remain mixed. Some studies report association of lower PWV or IMT with higher physical activity (Ried-Larsen et al., 2013), others, including large cohort analyses, found no direct associations between these parameters (Marshall et al., 2023; Sansum et al., 2025). Methodological heterogeneity likely contributes to these inconsistencies. Cardiorespiratory fitness appears to be a more consistent predictor, independent of activity levels, but may mediate the relationship between adiposity and arterial health (Silveira et al., 2023). Longitudinal

evidence of associations between changes in these risk factors and arterial health in paediatric cohorts remains scarce.

Beyond these traditional risk factors, bone health has emerged as a potential but underexplored correlate of arterial health. Shared biological pathways including inflammation, oxidative stress, and hormonal regulation suggest interconnections between skeletal and vascular systems (Demer & Tintut, 2008). While some adult studies report associations between low bone mineral density (BMD) and cardiovascular outcomes (Veronese et al., 2017), paediatric data are limited and inconsistent, leaving this relationship poorly understood in early life.

This thesis addresses the current lack of integrated analyses of longitudinal changes in body composition, physical activity, cardiorespiratory fitness bone health and combined CVH measures in relation to arterial structure and function in paediatric populations.

4. REVIEW OF THE LITERATURE

4.1. Arterial health

As most of the CVDs manifest within the arteries, it is appropriate to assess arterial health as a biomarker of CVD. Several of the physiological arterial function and structure changes can be explained by the interaction between blood flow–induced frictional load (wall shear stress) and the endothelium's sensitivity to this mechanical force. When wall shear stress is maintained at its physiological "set point," endothelial cells remain functionally stable. An increase in flow raises wall shear stress , prompting endothelial cells to release signals that cause the underlying vascular smooth muscle cells (VSMCs) to relax, leading to vessel dilation. This expansion lowers flow velocity and restores wall shear stress to its baseline. If elevated wall shear stress persists, the initial functional dilation is followed by structural remodelling of the vessel wall, producing long-term lumen enlargement – a process that contributes to general and regional vascular growth and the development of collateral vessels (Rodbard, 2008).

4.1.1. Arterial structure

Although structural changes in the vessel walls are part of normal, physiological reaction, they also occur during atherosclerosis progression. This includes mainly the intima layer, consisting of endothelial cells supported by a thin basement membrane. Intima is cushioned by VSMCs in combination with collagen and elastin within the media layer and with the outermost adventitia layer consisting mainly of collagen fibres (Chow et al., 2014). It is important to note that the elastin fibres provide the vessels elasticity while collagen contributes to the stiffer extracellular matrix component. Although within the context of atherosclerosis the intima layer is of interest, it is too thin to be measured with the available non-invasive methods and thus a surrogate of the intima-media thickness is in use. IMT refers to the combined thickness of the intima and media layers of the carotid arterial wall, measured via ultrasound. The measurements are usually performed in the carotid artery (cIMT) and less commonly in the aorta. The location of measurement in the carotid artery is also of importance, as it has been shown that although the common carotid artery provides robust evidence of systemic vascular health, the carotid bulb is the most sensitive marker for detecting early atherosclerotic changes. As measurements from the common carotid artery are easier to be performed and have higher reproducibility, they are more widely used both in population studies as well as for risk stratification. Due to the low reproducibility and difficulty in measurement process, the internal carotid artery is less frequently used. (Choi et al., 2025) Aortic IMT has found its focus in children and adolescents as well as in people with familial hypercholesterolaemia, type 1 diabetes and other metabolic disorders as it shows earlier evidence of athero-

sclerosis (sooner than in the carotid arteries). The main limitation of aortic measurements are the lower reproducibility and necessity for an abdominal ultrasound (Järvisalo et al., 2001; Urbina et al., 2009).

Increased IMT is interpreted as an early sign of atherosclerosis as it has been shown to correlate with traditional cardiovascular risk factors in both children and adults (Kampus et al., 2007; O'Leary et al., 1999; Raitakari et al., 2003; Willeit et al., 2020). In youth, higher IMT values have been observed in individuals with obesity, hypertension, insulin resistance, and a positive family history of CVD (Doyon et al., 2013). As such, IMT could provide information on arterial health even before clinical symptoms or overt disease manifest. The main pitfall of measuring IMT lies in the fact that media layer can be 10 times thicker than the intima and is influenced by different risk factors (Kim et al., 2016). It has been recently suggested that in healthy youth, the thickening of IMT can be caused by adaptation to physical exercise and it is related to increased lean body mass (LBM) (Agbaje et al., 2022; Baumgartner et al., 2021). At the same time adaptive intimal thickening due to macrophage foam cells may present in certain arterial sites (e.g., coronary bifurcations) (Stary et al., 1994). These are the same locations prone to mechanical stressors (low wall shear stress or turbulent flow), suggesting that it rather represents physiological remodelling. Animal studies have shown that the arterial remodelling is mainly driven by the endothelial cells , as once they are removed, the response to reduced blood flow is abolished (Langille & O'Donnell, 1986). In adults, it has been found that IMT correlates well with the current ventricular mass and systolic function (Ahmed et al., 2021; Evensen et al., 2014; Inuwa et al., 2023; Liao et al., 2021; Nakanishi et al., 2020; Poppe et al., 2011) as well as with future cardiovascular and overall mortality (Den Ruijter et al., 2012; Koc et al., 2025; Mitra et al., 2025; Murakami et al., 2005; Polak et al., 2011).

With appropriate considerations, IMT is considered a reliable and appropriate measure for assessing arterial structural changes in the context of atherosclerosis in adults as well as children and youth.

4.1.2. Arterial function

Arterial function is central to CVH, encompassing both the mechanical and biological properties of the vascular wall. Arteries are not just passive conduits for blood flow; they actively regulate hemodynamics and contribute to systemic blood pressure control, organ perfusion, and long-term cardiovascular homeostasis. Dysfunction in the arterial wall is an early marker for CVD and can be detected even before clinical symptoms appear, making arterial assessment particularly important across the lifespan (Jebari-Benslaiman et al., 2022).

Vascular endothelium produces and secretes several bioactive substances, including vasodilators (nitric oxide [NO], prostaglandin I_2, C-type natriuretic peptide, and endothelium-derived hyperpolarizing factor) and vasoconstrictors (endothelin, angiotensin II, prostaglandin H_2, and thromboxane A_2) which have exactly opposite effects (Higashi, 2024). NO is synthesized and released by the

endothelium in response to mechanosensors that detect shear stress from blood flow and to the binding of bioactive molecules to endothelial receptors (Palmer et al., 1987). NO production occurs from the essential amino acid L-arginine through the activation of endothelial nitric oxide synthase (eNOS) (Ignarro & Napoli, 2005). Once released, the gaseous NO diffuses to adjacent VSMCs, where it stimulates soluble guanylate cyclase, leading to muscle relaxation. The role of VSCMs extends beyond the contractile function as during development, following injury or in the presence of growth factors and mitogens (including inflammatory cytokines and oxidized lipids) they can proliferate and shift phenotype from contractile to synthetic, producing more extracellular matrix, forming into foam cells by taking up more lipids and secrete inflammatory cytokine and growth factors which can cause inappropriate vascular remodelling (Wilson, 2011). VSMCs are also central to vessel calcification, as they can differentiate into osteoblast-like cells and release matrix vesicles that function as nucleation sites for calcium-phosphate deposition within the arterial wall. Previously thought to be a passive phenomenon, vascular calcification is now understood as a highly regulated and complex process, involving cellular signalling pathways, circulating inhibitors of calcification, genetic predispositions, and hormonal influences (Leopold, 2015).

Alterations of arterial functions result in elevated systolic blood pressure (SBP), increased pulse pressure and early wave reflections contributing to left ventricular afterload (Chirinos et al., 2019; Nichols & Edwards, 2001).

Assessment of arterial functions can be divided into physiological tests, including endothelial function and arterial stiffness measurements, and biomarker measurements, including inflammatory, metabolic, endothelial function, oxidative stress, and lipid markers. Biomarker measurements alone do not provide a comprehensive assessment of vascular function and are typically used as complementary evaluations alongside physiological tests of vascular function (Higashi, 2024). Flow-mediated vasodilation and reactive hyperaemia index are methods for assessing blood flow and vessel diameter changes caused by postischemic reactive hyperaemia and are considered valid markers of endothelial function (Ghiadoni et al., 2015). Flow mediated vasodilation assesses the conduit arteries (brachial) and targets NO-mediated vasodilation while reactive hyperaemia index measures microvascular tone (finger arteries) and covers endothelial-dependent vasodilation (Kato, 2021). Main drawbacks in their use are related to technical variability and device dependence as well as limited availability of reference values for children and adolescents (Urbina et al., 2009).

The arterial properties that have been well studied as markers of functional change include arterial compliance, distensibility, and stiffness. Although both compliance and distensibility can be used as measures of stiffness, they individually represent different facets of arterial function. Distensibility is a measure of the elastic properties of an artery, whereas compliance is a measure of the local vessel capacity to respond to changes in blood volume. Arterial stiffness is the reciprocal of distensibility. Both distensibility and compliance can be assessed through ultrasound (Urbina et al., 2009). Arterial stiffness is defined by the

amount of vascular smooth muscle, elastic fibres (elastin), calcium deposition, and presence of atheroma. Clinically, arterial stiffness can be assessed by measures like PWV and AIx (Higashi, 2024). PWV evaluates the speed at which the blood pressure wave travels through the arterial tree. It is widely regarded as the gold standard for assessing arterial stiffness (Laurent et al., 2006). Evidence suggests that central arteries (i.e., the aorta) might be more vulnerable to atherosclerosis, thus aortic stiffness as measured by PWV between carotid to femoral arterial segments (cf-PWV) is a better measure of atherosclerosis than carotid to radial arterial segment (Vlachopoulos et al., 2010). In children and adolescents, higher PWV values have been linked to obesity, elevated blood pressure, low physical fitness, and systemic inflammation (Cruickshank et al., 2016; Reusz et al., 2010). Longitudinal studies suggest that elevated PWV in general population may predict cardiovascular outcomes (Ben-Shlomo et al., 2014). This reinforces the clinical and epidemiological relevance of PWV use. AIx is a measure of the enhancement (augmentation) of central aortic pressure by a reflected pulse wave and is calculated as the ratio of the augmentation pressure to pulse pressure expressed as a percentage (Papaioannou et al., 2019; Wilkinson et al., 2002). AIx is influenced by arterial stiffness, peripheral vascular tone, heart rate, age, and body height. Numerous studies have shown that AIx is associated with traditional cardiovascular risk factors such as aging, hypertension, dyslipidaemia, smoking, and C-reactive protein levels, and higher AIx is linked to adverse cardiovascular outcomes (Kampus et al., 2004, 2007; Shimizu & Kario, 2008).

4.2. Subclinical cardiovascular disease

Subclinical CVD represents the earliest, often silent, stage of vascular pathology, in which structural and functional alterations precede the onset of clinical events such as stroke, myocardial infarction, or claudication. Although individuals at this stage are typically asymptomatic, pathological processes including endothelial dysfunction, inflammation, dyslipidaemia, high-grade oxidative stress, and vascular remodelling are already underway (Jebari-Benslaiman et al., 2022).

4.2.1. Pathophysiology of subclinical disease

Endothelial dysfunction represents one of the earliest detectable abnormalities in subclinical CVD (Hadi et al., 2005). Multiple risk factors, such as hypertension, smoking, dyslipidaemia, and hyperglycaemia damage the endothelium and reduce NO bioavailability through enhanced oxidative stress. Reactive oxygen species (ROS) activate pro-atherogenic pathways, including nuclear factor-κB, leading to increased expression of pro-inflammatory cytokines (tumour necrosis factor-α, interleukins [IL]-1 and 6), adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1), and chemokines (monocyte chemoattractant protein-1) (Esper et al., 2006). These mechanisms not only diminish

NO availability but also impair endothelial repair mediated by circulating endothelial progenitor cells (Deanfield et al., 2007).

NO production is not the only function of endothelial cells that is disabled in the early phase of atherosclerosis. Within turbulent flow and low wall shear stress regions several atherogenic genes are upregulated in endothelial cells, including monocyte chemoattractant protein-1 which facilitates monocyte infiltration into the arterial wall, and platelet-derived growth factors that promote VSMC migration thereby contributing to atherogenesis and plaque development (Chatzizisis et al., 2007; Katoh, 2023; Medrano-Bosch et al., 2023; Sun et al., 2021). In addition to wall shear stress, high-grade oxidative-stress environment may cause VSMCs to undergo increased proliferation and hypertrophy and, under certain conditions, apoptosis, all contributing to vascular remodelling. (Schulz et al., 2004). Additionally, extracellular matrix components such as collagen accumulate, also contributing to arterial stiffening (Jebari-Benslaiman et al., 2022; Segal, 1994). Once the endothelium is damaged and permeable, low-density lipoprotein (LDL) particles infiltrate the subendothelial space, where they undergo several different modifications. LDL modification is accompanied by an inflammatory response, attraction of monocytes that transform into macrophages and ingestion of modified LDL with development into foam cells – hallmarks of early atherosclerotic lesions (Pirillo et al., 2013). The immune cells again release pro-inflammatory cytokines, amplifying the inflammatory cascade and oxidative stress. Eventually, fatty streaks are formed (Libby, 2012).

As endothelial dysfunction, inflammation, VSMC proliferation and migration together with lipid accumulation persist, the development of fibrous plaque and fibrous cap take place. The necrotic core and the fibrous cap constitute the hallmark of advanced atherosclerosis, and atheroma plaque regression is unlikely to happen in this stage, although the advancement to plaque rupture is inhibited through fibrous cap formation. It has been shown that endothelial function impairment is affected by degree of inflammation in the subclinical condition, whereas arterial stiffening is determined by level of oxidative modifications in atherosclerosis (Kals et al., 2008). Calcification of atheromatous plaques is initiated in inflammatory regions where collagen is reduced, often triggered by the death of macrophages and VSMCs which release matrix vesicles that serve as nucleation sites for calcium deposition. Calcium initially forms amorphous phosphate and eventually crystallizes. Additional contributors include reduced mineralization inhibitors and the osteogenic trans differentiation of pericytes and VSMCs, which acquire bone-like properties and produce mineralized matrix. Early microcalcifications appear in both the intima and media and can progress into larger deposits extending from necrotic cores. Transition from subclinical atherosclerosis to rupture of the plaque and following cardiovascular events depends on the location, size and stability of the plaque; thickness of the fibrous cap; continuation of the pro-inflammatory state; and continuity of hypercholesterolemia (Chen et al., 2016; Jebari-Benslaiman et al., 2022; Loftus, 2011).

4.2.2. Subclinical atherosclerosis in childhood and adolescence

The earliest indications for atherosclerotic changes to be present in young adults were found through autopsy studies in soldiers, indicating that 45–70% of young men had some evidence of atherosclerosis (Enos et al., 1953; McNamara et al., 1971). In 204 subjects within the Bogalusa Heart Study (Berenson et al., 1998), the existence of fatty streaks and fibrous plaques in the aorta and coronary arteries were examined in individuals aged 2–39 years. The prevalence of fatty streaks in the coronary arteries increased with age from approximately 50% at 2–15-years-of-age to 85% at 21–39-years-of-age, and the prevalence of raised fibrous-plaque lesions increased with age from 8% at 2–15-years-of-age to 69% at 26–39-years-of-age. In another study, fatty streaks were present in the abdominal aortas of approximately 20% and in the coronary vasculature of approximately 10% of 15- to 19-year-old subjects. Associations of risk factors with raised fatty streaks became evident in subjects in their late teens, whereas with raised lesions it was later, at age >25 years. These results show that coronary artery disease risk factors accelerate atherogenesis mainly in the second decade of life (McGill et al., 2000). In Japan, recurring autopsy studies have shown that from the 1970s to the 1990s, the prevalence of aortic atherosclerotic lesions has increased in young men (Imakita et al., 2001), illustrating the increasing prevalence of subclinical atherosclerosis occurrence at an early age. Although autopsy studies provide straightforward evidence of atherosclerotic lesions, intravascular ultrasound has also found its use. Using this method in heart transplant recipients, the prevalence of atherosclerosis in coronary arteries was found below 20% in individuals (donor hearts) below 20 years of age (Tuzcu et al., 2001).

These results collectively show that although some changes can occur already in infants, the clinically relevant atherosclerotic processes present themselves in the early puberty with prevalence of at least 8% for plaques and more than 20% for fatty streaks - this should be considered high enough for increased attention, additional research and intervention.

4.2.3. Childhood arterial health and CVD in adulthood

Although the association between altered arterial structure and function measures with future CVD and CVD events is evident mainly in patients aged above 45 years and with comorbidities (Cheong et al., 2024; Hametner et al., 2021; Øygarden, 2017; Sequí-Domínguez et al., 2020), research in children and adolescents is scarce, as it necessitates extremely long-term studies for target events to occur. 7-year mediation analysis from the Avon Longitudinal Study of Parents and Children (ALSPAC), UK birth cohort, revealed that the cf-PWV, but not IMT at mean age of 17.7 years was related to left ventricular hypertrophy indices after 7-years, showing that arterial stiffness progression temporally precedes cardiac damage in youth, with partial mediation by increased systolic blood pressure and insulin resistance (Agbaje, Justin P. Zachariah, & Tuomainen, 2023). Another analysis on ALSPAC cohort proposed that increased arterial

stiffness (measured by cf-PWV) in adolescence predicts the later development of hypertension, insulin resistance, and hyperinsulinemia in young adulthood, suggesting a causal role rather than a mere association. The findings challenge earlier beliefs that high blood pressure drives arterial stiffening, indicating instead that stiff arteries may precede hypertension. Arterial stiffness in youth linked with future obesity and metabolic dysfunction, forming a bidirectional but stronger causal path from adiposity to stiffness. Sex differences were noted, with boys showing a stronger relationship between early arterial stiffening and later hypertension. Collectively, a number of analyses, although in this same UK cohort, support arterial stiffness as an early biomarker and potential therapeutic target for preventing cardiovascular and metabolic diseases beginning in adolescence (Agbaje, 2022, 2023). Longitudinal progression of aortic and carotid stiffness from puberty to early adulthood has also shown to be related with concurrent changes in left ventricular mass. This highlights the interconnectedness of vascular function and cardiac structure, implying that early arterial stiffening could contribute to left ventricular hypertrophy and subsequent cardiovascular risk (Mikola et al., 2015).

Taken together, these longitudinal paediatric data suggest that arterial stiffening in adolescence is an upstream driver of later cardiometabolic alterations and cardiac remodelling, whereas structural thickening is a less clear contributor. Accordingly, early-life vascular phenotyping may help identify high-risk youth before fixed hypertension or overt target-organ damage develops.

4.3. Risk factors for arterial health in healthy children and adolescents

Although direct evidence linking childhood arterial health to hard cardiovascular outcomes is still limited, paediatric cardiovascular risk factors have been extensively characterized in relation to arterial structure and function measures. The AHA statement for paediatrics (Steinberger et al., 2016) highlights that achieving and maintaining ideal CVH in childhood (healthy behaviours and favourable biometrics) is associated with better cardiometabolic profiles and lower future cardiovascular risk.

4.3.1. Established risk factors for CVD and their associations with arterial health

European Society of Cardiology (ESC) and American Heart Association (AHA) state in their guidelines (Arnett et al., 2019; Visseren et al., 2021) that the major risk factors for CVD include dyslipidaemia, hypertension, smoking, diabetes, adiposity, physical inactivity and poor diet. AHA has also emphasised the importance of CVH promotion in childhood through primordial prevention and lists the same established modifiable risk factors in children as the Life's Simple 7 metrics

noting these factors often cluster and track from childhood into adulthood (Steinberger et al., 2016).

Autopsy studies in children and young adults have confirmed the importance of CVD risk factors on atherosclerosis progression. A cluster of risk factors including higher body mass index (BMI), elevated BP, and adverse lipid levels was strongly associated with greater atherosclerotic lesion burden in both the aorta and coronary arteries. Cigarette smoking further amplified disease, increasing fibrous plaque coverage in the aorta and fatty streaks in coronary vessels. There was a clear dose–response: as the number of risk factors rose from 0 to 3–4, fatty streak coverage increased from 19.1% to ~35% in the aorta, and in the coronary arteries from 1.3% to 11.0%, while fibrous plaques in coronary arteries increased from 0.6% to 7.2% (Berenson et al., 1998). In another autopsy study in persons aged 15 to 34 years, the percent intimal surface involved with raised fatty streaks increased with age in arteries and was associated with adverse cholesterol profile, hypertension, obesity and impaired glucose tolerance (McGill et al., 2000). Interestingly, the risk factors may have different effects to atherosclerosis progression in different arterial regions, as was shown in a Japanese study (Tanaka et al., 1988). There, serum cholesterol and BP were associated with atherosclerotic lesions in the carotid arteries, whereas atherosclerosis of cerebral arteries showed a significant correlation only with BP.

From autopsy assessments the research has transitioned to non-invasive surrogate markers of atherosclerosis, including arterial structure and function measures. Tobacco smoke exposure (Harbin et al., 2020; Raghuveer et al., 2016), hypertension, hypercholesterolaemia, overweight (Dawson et al., 2009; Doyon et al., 2013; Hudson et al., 2015; Zagura et al., 2012) and diabetes (Giannopoulou et al., 2019; Heilman et al., 2009; Shah et al., 2018; Urbina et al., 2019) have all shown associations with arterial stiffness and in some studies with arterial structural changes.

The associations with physical activity levels and body composition measures are more controversial and thus discussed further below.

4.3.2. Longitudinal research for risk factors and arterial measures

Data from large longitudinal studies following participants from childhood and adolescence into adulthood has shown that risk factors such as overweight hypertension, and increased lipid levels were significantly associated with increased cIMT even at adulthood. Each additional adverse risk factor increased the likelihood of having thickened adult carotid arteries. Importantly, risk factors measured before age 9 were not predictive. (Juonala et al., 2010; Koskinen et al., 2018; Vos et al., 2003). Similarly, it has been proven that youngsters with high and sustained BP have significantly higher IMT, left ventricular mass and arterial stiffness in adulthood (Chu et al., 2022; Hao et al., 2017; Wang et al., 2025; Yan et al., 2021). Pulse pressure, central blood pressure and SBP in contrast to diastolic pressure has been found to be the main driver of arterial stiffness and

thickening formation at an early age (Aatola et al., 2013; Doyon et al., 2013; Kohara, 2009; Koskinen et al., 2019; Li et al., 2004; Lona et al., 2020; Oren et al., 2003; Stergiou et al., 2010; Vos et al., 2003), as it is in adulthood (Ferreira et al., 2016; Wilson, 2011). Studies on diet quality in early childhood have shown some associations with BP and PWV in later life but no statistically significant associations were found with IMT (Buckland et al., 2024; Krijger et al., 2021; Leed et al., 2023).

4.3.3. Physical activity

Physical activity has been found to be associated with a wide range of cardiovascular benefits in youth (Heil et al., 2020). These benefits include improved lipid profiles, reduced BP, lower inflammation and enhanced endothelial function (Andersen et al., 2006). Mechanistically, physical activity increases shear stress on the vascular endothelium, promoting NO production, enhancing prostacyclin, and reducing endothelin-1, which in combination move the balance toward vasodilation and improved vessel tone. Concurrently, physical exercise elevates antioxidant-enzymes such as superoxide dismutase and glutathione peroxidase which neutralize ROS, preserving NO bioavailability and protecting against high-grade oxidative damage that can promote arterial stiffening and increase arterial wall thickness. Over repeated bouts, these molecular adaptations can translate into changes such as increased lumen diameter, slower progression of wall thickening and improved distensibility, thereby promoting more compliant and resilient arteries. In childhood and adolescence, the associations of arterial function and structure with physical activity are controversial. Longitudinal data extending from childhood into the teens and early adulthood show that greater cumulative sedentary time predicts higher cf-PWV and in some studies thicker intima media (Agbaje, A R Barker, et al., 2023; Agbaje et al., 2024) while increasing light physical activity slows the progression of endothelial dysfunction and arterial wall thickening (Pahkala et al., 2011). At the same time, others have not found associations with moderate to vigorous physical activity (MVPA), light physical activity nor sedentary time with vascular outcomes in the same study population (Sansum et al., 2025). Studies showing MVPA to controversially associate with arterial wall thickening interpret this as training-related remodelling rather than early atheroma while it is accompanied by lower arterial stiffness (Baumgartner et al., 2021; Winder et al., 2025). Finally, the intensity and consistency of physical activity matter: higher intensity may maximise shear and metabolic stimuli, resulting in stronger, long-lasting vascular benefit (Haferanke et al., 2025). Meta-analytic and interventional evidence supports intensity as a key modifier: structured exercise programs, particularly aerobic or high-intensity interval training, can improve arterial stiffness in youths (Sequi-Dominguez et al., 2023). The improvements in arterial functions are generally more apparent in subjects with impaired endothelial function and are in some studies, but not always, accompanied by evidence for structural vascular changes. Mode and intensity of exercise produce unique patterns of arterial pressure, blood

flow, and shear stress, each leading to specific vascular adaptations. The resulting vascular responses depend on which regions of the circulation are engaged; for instance, arteries supplying active skeletal muscles experience different hemodynamic stimuli and adaptations compared with those perfusing inactive tissues, reflecting the distinct flow and pressure dynamics elicited by different forms of exercise (Green & Smith, 2018; Hambrecht et al., 2003).

Taken together, the literature suggests a dose–intensity response in which MVPA, particularly vigorous physical activity, confers the clearest benefits on arterial function in childhood, with emerging longitudinal evidence that maintaining higher activity and limiting sedentary time can slow early arterial aging and may translate into lower atherosclerotic burden later in life.

4.3.4. Cardiorespiratory fitness

As results for physical activity and arterial health are complicated, more focus has recently been put to analysis of physical fitness. Cardiorespiratory fitness, typically assessed through peak oxygen uptake (VO_2peak) or submaximal endurance tests, reflects the efficiency of the cardiovascular and respiratory systems in delivering oxygen during sustained physical activity. Cardiorespiratory fitness is considered a powerful, independent predictor of CVH in both youth and adults (Kim et al., 2024; Ortega et al., 2008; Veijalainen et al., 2016). Unlike physical activity, which reflects behaviour, cardiorespiratory fitness integrates genetic predisposition and physiological adaptation. Higher cardiorespiratory fitness in children is associated with lower arterial stiffness and more favourable IMT profiles, even after adjusting for body composition and physical activity levels (Boreham et al., 2004; Ferreira et al., 2002, 2003; Veijalainen et al., 2016). It has been proposed that cardiorespiratory fitness may mediate the relationship between body fat and cardiometabolic risk (Silveira et al., 2023), as well as body fat and arterial structure (E. Laitinen et al., 2025; Pahkala, Laitinen, et al., 2013). Controversially, another longitudinal investigation found that a 1-year progression in peak oxygen uptake was associated with increases in SBP, aortic pulse wave velocity, and left ventricular mass, suggesting cardiovascular remodelling in adolescent athletes (Baumgartner et al., 2025). Controversial findings have also presented in cross-sectional studies, showing negative or mixed results for cardiorespiratory fitness and arterial health measures (Meyer et al., 2017). Results seem to be extremely dependent on the methods used for arterial health and fitness assessment.

In general, across paediatric cohorts, objectively measured cardiorespiratory fitness is often, but not always, associated with more favourable arterial phenotypes (lower aortic IMT, greater distensibility, lower PWV, better endothelial function). Effects can be vascular-bed specific (e.g., aorta vs. carotid) and partly confounded or mediated by adiposity, maturation, and physical activity intensity. Careful attention to measurement choice, pubertal status, and adiposity in analyses is necessary.

4.3.5. Body composition

Obesity, defined as BMI at or above 95th percentile for age and sex, has been confirmed as a major risk factor for CVDs and atherosclerosis development (Arnett et al., 2019). Although BMI is a widely used instrument for assessing excessive body fat, it does not actually distinguish between fat and LBM. Some earlier findings suggested that increased adiposity may initially be accompanied by reduced arterial stiffness (Charakida et al., 2012; Dangardt et al., 2008). Nevertheless, meta-analyses and large cohorts show that youth with obesity, defined through BMI, have higher cf-PWV than their normal-weight peers (Cote et al., 2015; Hudson et al., 2015). At the same time, it has been proposed that metabolic health status, rather than obesity alone, plays a crucial role in the development of arterial stiffness (Yuan et al., 2020). FM measured from childhood through adolescence predicts higher PWV at early adulthood, even after accounting for conventional risk factors. Arterial stiffness shows further aggravation by an unfavourable metabolic profile and reverting to normal FM index by adolescence shows associations with normal arterial stiffness (Dangardt et al., 2019). Excess FM is presumed to promote endothelial dysfunction and arterial stiffening via low-grade inflammation (e.g., interleukin-6, tumour necrosis factor-α), high-grade oxidative stress that reduces nitric-oxide bioavailability, insulin resistance and dyslipidaemia that accelerate extracellular matrix remodelling, as well as sympathetic and renin–angiotensin activation that raise blood pressures and smooth-muscle tone (Chait & den Hartigh, 2020; Jia et al., 2015; Kwaifa et al., 2020; Martínez-Martínez et al., 2021). The distribution of FM also appears relevant, as central or truncal fat confers greater cardiovascular risk, though the contribution of peripheral fat during adolescence remains uncertain (Mathieu et al., 2014). Higher total adiposity as well as truncal subcutaneous fat in adolescence are associated with increased arterial stiffness in adulthood (Ferreira et al., 2004).

Although FM has shown strong associations with arterial measures, longitudinal ALSPAC analyses suggest that cumulative LBM not FM drives carotid artery wall thickening from adolescence into young adulthood, consistent with physiologic outward remodelling under higher flow and shear (Agbaje, Alan R. Barker, et al., 2023). Recent mediation work in adolescents further shows that LBM partially explains seemingly paradoxical findings e.g., higher MVPA linked to increased cIMT, by indicating that training-related increases in lean tissue mass may thicken the carotid artery wall without the maladaptive matrix changes seen in adiposity-driven atherogenesis (Agbaje, Samuel Barmi, Sansum, et al., 2023). As is discussed above, it is well-established is that childhood obesity elevates arterial stiffness, a potential precursor of later cardiovascular risk; what remains controversial is the direction and meaning of IMT differences in physically active or highly trained youth, where lean-mass driven adaptive remodelling may increase wall thickness yet coincide with better pulse wave velocity. Overall, separating FM (metabolically more adverse) from LBM (hemodynamically

adaptive) usually clarifies why studies diverge on the results for arterial structure and function.

4.3.6. Bone mineral content and growth

While body composition, physical activity and cardiorespiratory fitness are more commonly studied as potential associates with arterial health, emerging research points to a link between skeletal and CVH, though this relationship remains less well-defined in children.

Bone growth, which is expressed through bone mineral content (BMC), is a dynamic process governed by endocrine, nutritional, and mechanical factors that together establish peak bone mass in early adulthood. Linear growth occurs through endochondral ossification at the epiphyseal plates, while increasing BMC reflects ongoing mineral deposition under the influence of growth hormone , insulin-like growth factor-1, and sex hormones during puberty (Rauch & Schoenau, 2001). Shared pathways such as inflammation, high-grade oxidative stress, renal damage and endocrine function suggest that bone and vascular health may be interconnected (Demer & Tintut, 2008; Paapstel et al., 2016). Mechanical loading from greater body and muscle mass stimulates osteogenesis via mechanotransduction pathways (Robling & Turner, 2009), similarly as they contribute to arterial measures. Notably, the skeletal and vascular systems share developmental and regulatory pathways, particularly bone morphogenetic proteins, matrix Gla protein, and the osteoprotegerin /RANKL axis which coordinate both bone mineralization and vascular calcification (Demer & Tintut, 2008). In health, these mechanisms support adaptive arterial remodelling as the vasculature becomes functionally more compliant to meet the metabolic and hemodynamic demands of growth (Jebari-Benslaiman et al., 2022). However, metabolic disturbances such as obesity, insulin resistance, alterations in vitamin D levels or inflammation can disrupt this coupling, leading to premature arterial stiffening as well as reduced bone accrual. Increased inflammation and obesity may shift vascular smooth muscle cells toward osteogenic phenotypes, enhancing arterial wall calcification and atherosclerotic susceptibility (Sage et al., 2010; Zagura et al., 2011). In adult osteoarthritis patients, it has been shown that cf-PWV is increased, suggesting vascular alteration involvement in osteoarthritis pathogenesis (Tootsi et al., 2016). Research has found that higher total body and hip BMD are positively associated with increased cIMT in premenopausal women and their adolescent offsprings, suggesting a link between bone density and early markers of atherosclerosis. Controversially, higher femoral neck BMD was found associated with arterial distensibility, suggestive of reduced stiffness. The authors propose that these associations may reflect shared pathways in vascular and skeletal development rather than a direct causal relationship (Frysz et al., 2016). Some studies have reported associations between BMD and CVD outcomes (Veronese et al., 2017), but findings are inconsistent, and the directionality of the relationship remains unclear. Although prior research has demonstrated regulatory effects of bone metabolism on organs such as the pancreas, liver, and adipose

tissue (Mizokami et al., 2013; Nilsson et al., 2005), the relationship between bone and vascular tissues remains less clearly understood. Investigating these associations independent of common risk factors in paediatric populations may provide insights into systemic processes that affect both skeletal and vascular systems at an early age.

4.3.7. Composite risk assessment

Several studies in youth have utilised composite cardiometabolic risk scores or risk-factor clustering approaches and examined their associations with early vascular structure and function measures (Krefman et al., 2021; Liu et al., 2019). It is found that in childhood and adolescence composite CVH score that includes 7 components (BMI, BP, lipids, glycaemic status, smoking, physical activity and diet) is associated with more favourable outcomes in adulthood including hypertension, metabolic syndrome, incident cardiovascular events, fatal cardiovascular events, markers of coronary artery disease and retinal microvasculature. Optimal CVH in adulthood has even shown protective effects for dementia (Peloso et al., 2020) and combined cancer incidence, even when smoking was not used as a health metric (Rasmussen-Torvik et al., 2013). Deterioration in CVH often begins early, with adverse exposures in childhood leading to measurable arterial changes such as increased cIMT and arterial stiffness during adolescence and early adulthood (Allen et al., 2020; Jacobs et al., 2022; Pedamallu et al., 2023). The prevalence of ideal CVH depends much on the region, age and methods of assessment, but it has been shown that in 4–7-year-olds the prevalence was only 6.9% with reduced MVPA and poor diet being the main drivers of loss in ideal CVH (Perng et al., 2021). Another study showed 16% of ideal CVH for young adults (Gooding et al., 2016), but it did not account for diet. Interestingly, research shows that there are two critical timepoints where the deterioration of CVH accelerates – in late adolescence and early middle age. Childhood health motivation and socioeconomic status are shown to carry over to adulthood and influence future CVH (Gall et al., 2019; Pahkala, Hietalampi, et al., 2013). While all components of the CVH are important, it has been shown that keeping optimal BMI and nonsmoking status are associated with lower risk for future CVH decline, probably due to their associations with adequate diet, physical activity and higher awareness of health (Gooding et al., 2015, 2016). The composite scores most commonly include the same 7 variables listed above, while recent guidelines have recommended extending it to 8 components by adding sleep time as an important variable (Lloyd-Jones et al., 2022).

Overall, these data suggest that composite risk or pattern scores can help summarise multi-factor exposure in youth and are meaningfully associated with arterial structure and function as well as CVD in future.

4.3.8. The effect of risk factor exposure reduction on CVD risk

There is increasing evidence from interventional trials that reducing exposures to CVD risk-factors through diet and physical exercise can favourably impact arterial structure and vascular function. For adults with obesity, it has been shown that both diet as well as diet and physical exercise combined provide beneficial results for arterial stiffness measures (Nordstrand et al., 2013). Similar results for obesity are available from a randomised study in children aged 9–12 years showing that after six weeks both diet and diet combined with physical exercise improved endothelial function. Furthermore, at one year the diet with exercise group had significantly less carotid intima-media thickening compared to those who withdrew (Woo et al., 2004). The beneficial effect of this intervention on arterial structure measures has been confirmed in children and adolescents by a meta-analysis (García-Hermoso et al., 2017).

Intensive lifestyle interventions have also been useful in hypertensive adult patients. 6-month intervention by dietitian counselling focused on anti-inflammatory diet with physical exercise lowered BP, improved arterial stiffness and endothelial function compared to standard care (Vamvakis et al., 2020). BP reduction in children and adolescents through weight reduction and increased physical activity has been shown to concurrently improve arterial structure and function measures (Farpour-Lambert et al., 2009). Moreover, BP control through pharmacological therapy alone has also shown the same benefit in arterial structure and function measures (Litwin et al., 2010; Soffer et al., 2000).

In sedentary, healthy middle-aged/older adults, aerobic training improved flow-mediated vasodilation (Landers-Ramos et al., 2016; Tanaka et al., 2000). Dietary improvement alone was found to lower BP and improve flow-mediated vasodilation(Davis et al., 2017). Among smokers without established coronary disease, a randomized smoking-cessation trial demonstrated significant recovery of endothelial function at one year, and more recent prospective data confirm improvements in flow-mediated vasodilation within ~20 weeks of cessation treatment (Johnson et al., 2010; Okuyama et al., 2024).

In youth, infancy-onset low–saturated-fat dietary counselling led to better endothelial function at age 11 compared to unrestricted diet group (Raitakari et al., 2005). A meta-analysis also found that interventions which improved vascular function included physical activity and dietary programmes. It was also suggested that endothelial function could be the first variable of vascular functions to change as a response to intervention (Edwards et al., 2023).

Taken together, these studies show that targeted lifestyle interventions (including dietary, physical activity and smoking cessation) in both youth and adult populations can improve vascular measures (IMT, PWV, flow mediated vasodilation) in both healthy as well as obese/overweigh or hypertensive subjects. Although the magnitude of effect and duration are more robust in adults, the paediatric data still support that vascular changes are modifiable, and early intervention is beneficial.

4.3.9. Summary of the Literature

As discussed above, subclinical CVD refers to early, asymptomatic alterations in vascular structure and function that precede overt clinical events. The pathophysiology of subclinical disease begins with endothelial dysfunction, inflammation, and vascular remodelling driven by cumulative exposure to metabolic, hemodynamic, and lifestyle risk factors. Evidence from paediatric autopsy studies and non-invasive imaging shows that atherosclerotic lesions are present in the aorta as well as in carotid arteries in childhood and adolescence, indicating that vascular changes begin decades before clinical CVD.

During childhood and adolescence, measures of arterial structure and function provide valuable insights into early vascular health. IMT quantifies arterial wall thickening. PWV provides information about arterial stiffness, and AIx serves as a marker of arterial wave reflection. However, methodological heterogeneity and the lack of standardized paediatric reference values still limit comparability across studies. Both IMT and PWV in adolescence have been shown to track with adult values, supporting their relevance as early indicators of lifetime cardiovascular risk.

Accumulating evidence links childhood cardiovascular risk factors, including BP, obesity, glucose regulation, diet, smoking exposure, and low physical activity, to adverse arterial and cardiovascular phenotypes. More recent research highlights the importance of physical activity and cardiorespiratory fitness, which are expected to provide beneficial effects to arterial health. Emerging work also suggests a link between specific body composition measures and bone metabolism with the development of optimal cardiovascular profile.

Current research on paediatric vascular health is constrained by significant gaps. Long-term studies tracking inflammatory and oxidative biomarkers alongside vascular structure and function from childhood to adulthood are scarce, limiting understanding of causal pathways. The influence of growth, puberty, and body composition on vascular remodelling remains insufficiently defined, and normative reference data across ethnicities and developmental stages are lacking. Methodological inconsistencies such as heterogeneous assessment protocols, variable definitions of pathological arterial changes and incoherent adjustment to risk factors impede comparability across studies. In addition, inconsistent assessment of physical activity and cardiorespiratory fitness, together with reliance on BMI rather than detailed body composition or fat distribution measures, restricts assessment of the independence of associations. Finally, few longitudinal or interventional studies have established the predictive or reversible value of early vascular changes, leaving causal evidence for the long-term benefits of lifestyle modification incomplete.

This thesis focuses on several of these shortcomings with the focus on holistic approaches to these complex systems.

5. AIMS OF THE THESIS

The general aim of the thesis was to map the potential associations of arterial structural and functional changes in healthy children and adolescents with objectively measured longitudinal cardiovascular health factors. The focus was on finding the associations which are independent from the already established cardiovascular risk factors to provide a better risk assessment at an early age and support earlier intervention in cardiovascular disease risk development.

Specific aims:

1. To define associations between arterial structure and function with longitudinally assessed physical activity, cardiorespiratory fitness and body composition in healthy children and adolescents (Paper I and Paper III).
2. To assess associations between arterial structure and function with longitudinally assessed measures of bone mineral content and bone growth in healthy children and adolescents (Paper II).
3. To define the associations between arterial structure and function with American Heart Association cardiovascular health metrics and assess the independence of these measures from already established risk factors (Paper III).

6. SUBJECTS AND METHODS

6.1. Study design and protocol

This thesis integrates data from two cohorts. Papers I and II originate from a longitudinal cohort of generally healthy adolescent boys recruited in and around Tartu, Estonia (Tartu study) in the years 2009–2018. Boys were invited to the study at approximately 9–12 years of age (T0) and followed prospectively from early puberty through late adolescence (at 1-, 2-, 3- and 7-year follow-ups, respectively T1, T2, T3, T4). The number of participants in the initial study cohort is shown on Figure 1. The overall participation rate was 74 % (Mäestu et al., 2013). Paper III is based on an independent community sample of healthy children from Kuopio, Finland recruited at the age of 6–9 years (baseline) followed up at 2- and 8-years (Physical Activity and Nutrition in Children [PANIC] study). A total of 736 children aged 6 to 9 years who started the first grade in 16 primary schools of the city of Kuopio in 2007 to 2009 were invited to participate in the study (Figure 2). Altogether, 512 (70%) children (248 girls, 264 boys) accepted the invitation and participated in the baseline examinations. Although not the focus of this analysis, the study was interventional in nature, consisting of physical activity and diet intervention and a control group. Because arterial health was assessed in detail only at 8 years and the intervention had no effect on the outcomes based on the primary statistical review, control and intervention groups were pooled and are not discussed further.

Physical activity, cardiorespiratory fitness, body composition (Paper I and Paper III), BMC/BMD (Paper II) and AHA CVH components (Paper III) were measured at the relevant study visits and arterial structure/function at the final follow-up. Both studies conformed to the Declaration of Helsinki. Written informed consent was obtained from participants and, where applicable, guardians. Study protocols were approved by the Research Ethics Committee of the University of Tartu in 2020 (Statement 327-T20) and the Research Ethics Committee of the Hospital District of Northern Savo in 2006 (Statement 69/2006).

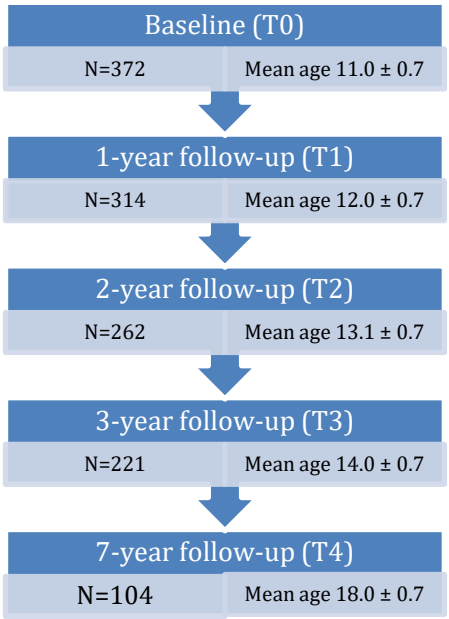

Figure 1. Flow chart of Tartu study.

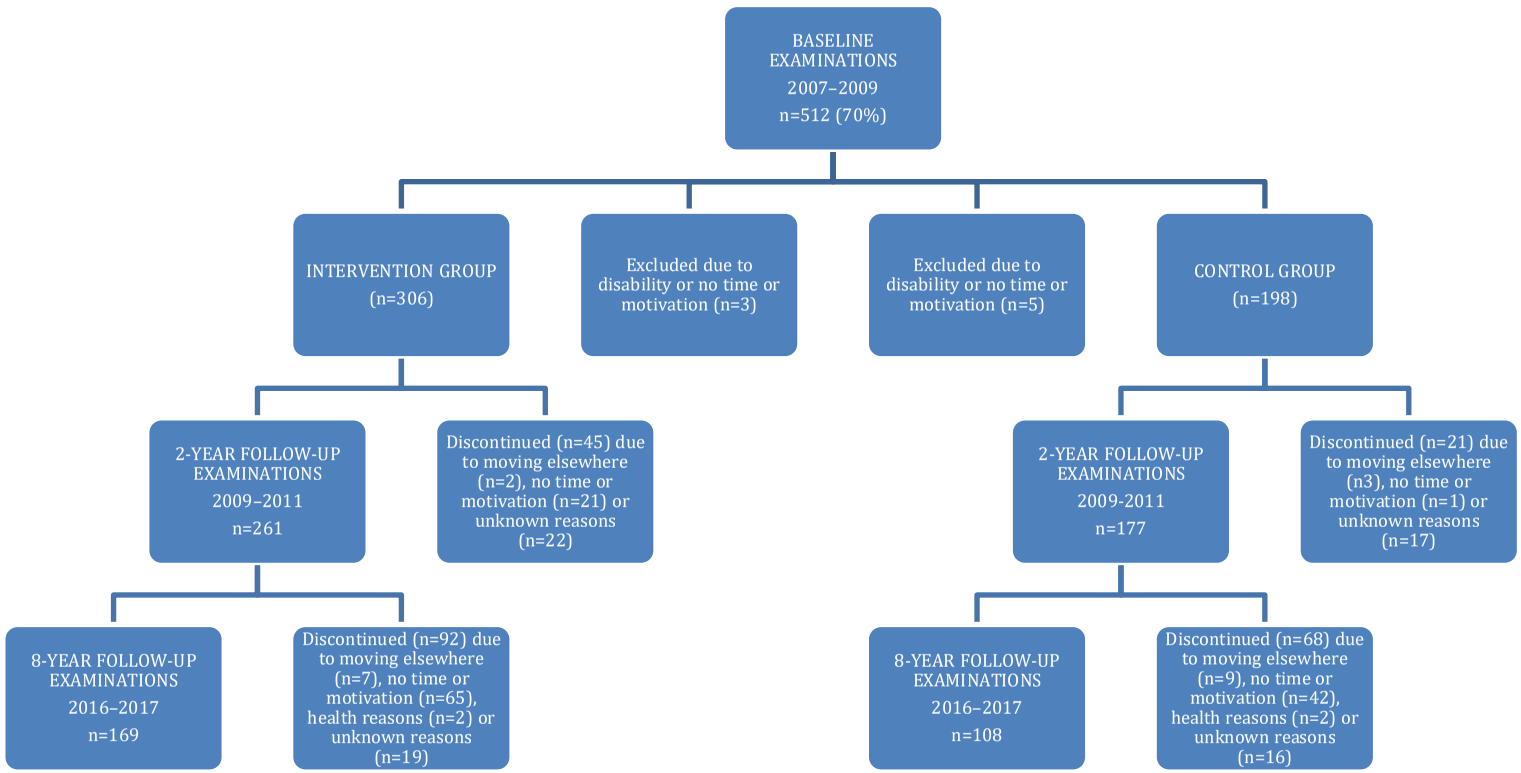

Figure 2. Flow chart of the PANIC study

6.2. Subjects

For the present analyses, we included those who completed the longitudinal protocol, had outcome measurements at late adolescence, and were considered generally healthy according to questionnaires filled by them regarding health status and used medications. In the arterial outcome subsamples a total of 379 participants (in Paper I/II n=102 and Paper III n=277) who attended the follow-up examinations are described in this thesis. The participants included in the final analyses did not differ from the original study population regarding the mean age, anthropometry, body composition, cardiorespiratory fitness, physical activity, and arterial parameters and can thus be considered representative to the initial cohorts.

Baseline characteristics of the study populations for Paper I, II (Tartu study cohort) and III (PANIC study cohort) are presented in Table 1 and arterial health parameters in Table 2. T1 was used as Baseline for Paper I as physical activity information was not measured at the first study visit. Bone parameters in all timepoints for Paper II are presented in Table 3.

Table 1. Basic characteristics of the participants at different timepoints in two sets of cohorts.

General characteristics	Baseline				2-year follow-up				Final follow-up			
	Tartu study	PANIC study			Tartu study	PANIC study			Tartu study	PANIC study		
	Boys N=102	Total N=504	Girls N=243	Boys N=261	Boys N=102	Total N=437	Girls N=214	Boys N=223	Boys N=102	Total N=277	Girls N=126	Boys N=151
Age, years	12.0 (0.7)	7.6 (0.4)	7.6 (0.4)	7.7 (0.4)	13.1 (0.7)	9.8 (0.4)	9.7 (0.4)	9.8 (0.4)	18.0 (0.7)	15.8 (0.4)	15.8 (0.4)	15.8 (0.5)
Height, cm	154.7 (8.3)	128.8 (5.7)	127.8 (5.6)	129.7 (5.6)	163.1 (9.3)	140.5 (6.3)	139.7 (6.5)	141.2 (6.0)	181.3 (6.4)	171.7 (8.6)	165.7 (5.8)	176.6 (7.4)
Weight, kg	47.2 (12.9)	26.9 (5.0)	26.5 (5.1)	27.3 (5.0)	54.0 (14.6)	34.3 (7.3)	33.6 (7.2)	35.0 (7.3)	73.5 (12.1)	62.2 (13.3)	57.9 (9.1)	65.8 (15.1)
Smoking status												
Non-smoker	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	79 (79.0%)	222 (89.0%)	106 (91.4%)	116 (86.6%)
Previous/ occasional smoker	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12 (12.0%)	18 (7.2%)	6 (5.2%)	12 (9.0%)
Current/ daily smoker	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9 (9.0%)	10 (4.0%)	4 (3.4%)	6 (4.5%)
BMI, kg/m2	19.5 (4.0)	16.1 (2.1)	16.1 (2.2)	16.1 (2.1)	20.1 (4.2)	17.3 (2.7)	17.1 (2.6)	17.4 (2.8)	22.3 (3.3)	21.0 (3.6)	21.1 (3.1)	21.0 (4.0)
MVPA, min/d	66.4 (26.9)	115.0 (64.3)	95.7 (54.4)	134.3 (67.6)	62.0 (23.8)	99.9 (56.4)	79.9 (38.6)	119.1 (56.2)	55.4 (24.1)	45.0 (35.8)	41.7 (20.2)	47.9 (29.5)
Pubertal stage by Tanner												
1	1 (1%)	490 (98%)	233 (96.3%)	257 (98.8%)	0 (0%)	322 (77%)	142 (66.7%)	180 (87.0%)	N/A	0 (0%)	0 (0%)	0 (0%)
2	37 (36%)	12 (2.4%)	9 (3.7%)	3 (1.2%)	10 (9.8%)	98 (23%)	71 (33.3%)	27 (13.0%)	N/A	0 (0%)	0 (0%)	0 (0%)
3	53 (52%)	0 (0%)	0 (0%)	0 (0%)	48 (47%)	0 (0%)	0 (0%)	0 (0%)	N/A	21 (8.7%)	4 (3.5%)	17 (13.4%)
4	11 (11%)	0 (0%)	0 (0%)	0 (0%)	35 (34%)	0 (0%)	0 (0%)	0 (0%)	N/A	139 (58%)	61 (53.5%)	78 (61.4%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (8.8%)	0 (0%)	0 (0%)	0 (0%)	N/A	81 (34%)	49 (43.0%)	32 (25.2%)

General characteristics	Baseline				2-year follow-up				Final follow-up			
	Tartu study	PANIC study			Tartu study	PANIC study			Tartu study	PANIC study		
	Boys N=102	Total N=504	Girls N=243	Boys N=261	Boys N=102	Total N=437	Girls N=214	Boys N=223	Boys N=102	Total N=277	Girls N=126	Boys N=151
Fat mass, kg	11.1 (8.3)	5.7 (3.6)	6.4 (3.5)	5.2 (3.5)	12.1 (9.0)	8.7 (5.2)	9.1 (5.0)	8.3 (5.4)	13.3 (5.9)	14.5 (8.8)	17.1 (6.9)	12.2 (9.7)
Lean mass, kg	33.5 (6.3)	20.6 (2.4)	19.5 (2.1)	21.7 (2.2)	39.6 (8.2)	24.7 (3.1)	23.5 (2.9)	25.9 (2.9)	55.6 (7.2)	45.2 (8.7)	38.2 (4.0)	51.5 (6.9)
VO2 peak/LBM, ml/kg/min	69.2 (7.0)	N/A	N/A	N/A	64.6 (8.7)	67.5 (6.4)	65.9 (6.0)	69.0 (6.3)	59.2 (10.0)	61.8 (6.3)	61.0 (5.6)	62.4 (6.7)
AHA score (0–14)	N/A	11.3 (1.3)	11.3 (1.5)	11.6 (1.2)	N/A	11.2 (1.3)	11.2 (1.4)	11.1 (1.3)	N/A	11.1 (1.5)	11.3 (1.4)	11.0 (1.5)
Diet score, (0–4)	N/A	1.2 (0.9)	1.5 (1.0)	1.3 (1.0)	N/A	1.3 (0.9)	1.4 (0.9)	1.3 (0.9)	N/A	1.5 (1.0)	1.7 (1.0)	1.3 (0.9)
Cholesterol mmol/l	4.3 (0.6)	4.3 (0.6)	4.3 (0.6)	4.2 (0.6)	4.0 (0.7)	4.3 (0.7)	4.3 (0.7)	4.3 (0.6)	3.8 (0.6)	3.8 (0.6)	4.0 (0.7)	3.7 (0.6)
Glucose, mmol/l	5.1 (0.4)	4.8 (0.4)	4.8 (0.4)	4.9 (0.4)	5.0 (0.4)	5.0 (0.4)	4.9 (0.4)	5.1 (0.4)	4.6 (0.6)	5.2 (0.4)	5.1 (0.3)	5.3 (0.4)

Abbreviations: AHA, American Heart Association; BMI, body mass index; MVPA, moderate to vigorous physical activity; and VO2 peak, peak oxygen consumption. Values reported represent mean (standard deviation) or N (percentage).

Table 2. Arterial structural and functional parameters at final follow-up in two sets of cohorts

Arterial variables	Final follow-up			
	Tartu study	PANIC study		
	Boys N=102	Total N=277	Girls N=126	Boys N=151
Age, years	18.0 (0.7)	15.8 (0.4)	15.8 (0.4)	15.8 (0.5)
Peripheral systolic BP, mm Hg	122.6 (9.2)	113.3 (10.5)	110.4 (9.1)	115.7 (10.9)
Peripheral diastolic BP, mm Hg	67.1 (7.0)	67.4 (9.7)	66.7 (9.9)	68.0 (9.5)
cIMT max, mm	0.6 (0.1)	0.4 (0.1)	0.4 (0.1)	0.5 (0.1)
PWV, m/s	5.6 (0.9)	5.8 (0.6)	5.9 (0.6)	5.8 (0.6)
AIxHR75, %	−2.6 (12.6)			

Abbreviations: AIxHR75, augmentation index adjusted to heart rate of 75×/min; BP, blood pressure; PWV, pulse wave velocity; cIMT, carotid intima media thickness. Mean (standard deviation) reported.

Table 3. Bone characteristics at different time points in Tartu study cohort.

Characteristic	T0, N=102	T1, N=101	T2, N=99	T3, N=102	T4, N=101
Age, years	11.0 (0.7)	12.0 (0.7)	13.1 (0.7)	14.0 (0.6)	18.0 (0.7)
Total body BMC, g	1518.1 (285.4)	1728.5 (372.8)	2022.1 (471.2)	2325.8 (517.8)	2875.3 (398.3)
Femoral neck BMC, g	3.8 (0.6)	4.1 (0.7)	4.6 (0.9)	5.1 (1.0)	5.7 (0.8)
Lumbar spine BMC, g	23.9 (4.9)	27.6 (7.1)	33.2 (9.5)	40.3 (11.4)	58.3 (9.3)
Total body BMD, g/cm2	0.96 (0.06)	0.98 (0.07)	1.03 (0.09)	1.07 (0.10)	1.23 (0.09)
Femoral neck BMD, g/cm2	0.89 (0.09)	0.91 (0.10)	0.96 (0.12)	1.01 (0.14)	0.99 (0.12)
Lumbar spine BMD, g/cm2	0.80 (0.08)	0.84 (0.10)	0.91 (0.13)	0.99 (0.15)	1.06 (0.11)
Total body, BMAD g/cm3	0.091 (0.006)	0.088 (0.006)	0.087 (0.005)	0.085 (0.005)	0.095 (0.005)
Femoral neck BMAD, g/cm3	0.206 (0.023)	0.204 (0.024)	0.205 (0.026)	0.204 (0.027)	0.171 (0.025)
Lumbar spine BMAD, g/cm3	0.146 (0.013)	0.148 (0.014)	0.151 (0.015)	0.158 (0.017)	0.144 (0.014)
BMC/height	1018 (152)	1109 (187)	1230 (227)	1362 (251)	1584 (196)

Abbreviations: BMC, bone mineral content; BMAD, bone mineral apparent density; BMD, bone mineral density.
Mean (standard deviation) reported.

6.3. Methods

6.3.1. Measurement of arterial structure and function

In both cohorts, cIMT was obtained under standardized, resting conditions, targeting the far wall of the common carotid artery ~10 mm proximal to the bifurcation, with multiple measurements aggregated to enhance precision.

Papers I and II employed SonoSite M-Turbo portable ultrasound device (SonoSite, Bothell, WA, USA) with a 5–10 MHz high-resolution linear transducer to image both common carotid arteries over a 10-mm segment at ~1 cm from the bifurcation, acquiring far-wall views in lateral, anterior, and posterior projections (6 measurements/participant). Quantification used SonoCalc (SonoSite, Bothell, WA, USA) to compute arithmetic mean and maximum cIMT, with within-observer coefficient of variation 2.2% and between-observer variation of 5.9%.

Paper III used the Sequoia 512 ultrasound scanner (Acuson, Mountain View, CA, USA) with a 14.0-MHz linear array transducer. A 5-s cine loop, which included the beginning of the left carotid artery bifurcation and the left common carotid artery, was recorded and manually analysed by the sonographer using the callipers of the ultrasound scanner. For the assessment of cIMT, the best quality end-diastolic frames, incident with the R-wave on a continuously recorded electrocardiogram, were selected from the video clip. Three measurements were taken from the far wall of the left common carotid artery ≈10 mm proximal to the carotid bifurcation to derive the maximal cIMT. The diameter of the common carotid artery was measured twice both at end-diastole and at end-systole. The means of the measurements were used as the end-diastolic and end-systolic diameters. Coefficient of variation between visits was 6.4% (n = 60 re-examined ≈ 3 months later) and between observers 5.2% (n = 113 rescored).

Thus, both protocols share supine positioning, far-wall, near-bifurcation acquisition, and multi-measure aggregation, while Paper I emphasises bilateral, multi-angle acquisition and Paper III emphasises left-side cine-loop capture.

Arterial function was assessed for both cohorts under standardized supine conditions using validated waveform–based methods, but with different measurement paths and instruments. In Papers I and II, we recorded radial artery pressure waveforms from the left wrist with a high-fidelity applanation tonometer (SPT-301B, Millar, Houston, TX, USA); after 20 sequential beats, the integral software (SphygmoCor Px version 7.0, AtCor Medical, Sydney, Australia) generated the central (ascending aortic) waveform via a prospectively validated generalized transfer function (Sharman et al., 2006). AIx was computed as the difference between the second and first systolic peaks divided by central pulse pressure, expressed as a percentage, and standardized to 75 bpm (AIxHR75) using the SphygmoCor algorithm (Wilkinson et al., 1998). Carotid–femoral PWV (cf-PWV) was then obtained by the foot-to-foot method: electrocardiogram -gated carotid and femoral waveforms were recorded sequentially, transit time was referenced to the electrocardiogram R-wave, and path length measured as the

distance from the suprasternal notch to the common femoral artery minus the distance from the suprasternal notch to the common carotid artery (Wilkinson et al., 1998). In Paper III, arterial stiffness was quantified as aorto-popliteal PWV (ap-PWV) using impedance cardiography device CircMon B202 (JR Medical Ltd, Saku Vald, Estonia) after 15 min of supine rest: the software estimates the foot of the impedance cardiography signal that coincides with pulse transmission in the aortic arch. The distal impedance plethysmogram was recorded from a popliteal artery at knee joint level and is comparable to the cf-PWV (Wilenius et al., 2016). PWV was computed as $L/\Delta t$, where Δt is the pulse transit time between the two sites and L the measured surface distance (Kööbi et al., 2003). Thus, both protocols rely on foot-to-foot transit timing after supine rest to derive PWV, while Papers I/II measure carotid femoral PWV with electrocardiogram-gated applanation tonometry and Paper III ap-PWV with impedance cardiography.

6.3.2. Measurement of physical activity

Both cohorts quantified physical activity objectively over multiple days and derived MVPA, but they used different devices, wear protocols, epochs, and intensity classifications tailored to age and setting. In Papers I/II, hip-worn accelerometers GT1M at T1, T2 and T3; GT3X at T4 (ActiGraph LLC, Pensacola, FL, USA) were used during waking hours for seven consecutive days, initialized at 15-s epochs. Data cleaning excluded 00:00–06:00 and ≥10 min of consecutive zero counts; inclusion required ≥2 weekdays and ≥1 weekend day with ≥10 h/day of wear. Intensities followed Evenson (Evenson et al., 2008) cut-points (sedentary ≤100 counts·min^{-1}; light 101–2295; moderate 2296–4011; vigorous ≥4012). Physical activity categories were calculated according to WHO guideline (≥60 vs <60 min·day^{-1}) (World Health Organization, 2020).

In Paper III, chest-worn (Actiheart, CamNtech, Papworth, UK) monitors (combined accelerometer and heart rate [HR]) were attached with electrocardiogram electrodes, sampled in 60-s epochs, and worn continuously including sleep (Brage et al., 2005). Wear criteria were ≥4 days (≥2 weekdays and ≥2 weekend days) at baseline and 2-year follow-up, and 7 days at 8-year follow-up. Median (range) wear times for baseline, 2- and 8-year follow-up were 104 h (52–212), 101 h (48–171), and 170 h (65–425), respectively. Intensities were MET-based with 1 MET = 71.2 J·min^{-1}·kg^{-1}: sedentary ≤1.5 METs (sleep excluded from sedentary), light >1.5–≤4.0, moderate >4.0–≤7.0, and vigorous >7.0 (Collings et al., 2014; Janssen & LeBlanc, 2010).

6.3.3. Measurement of cardiorespiratory fitness

Both cohorts assessed cardiorespiratory fitness with maximal, graded cycle-ergometer tests using breath-by-breath gas analysis, but they differed in ergometer protocols and analysers.

In Papers I/II, testing was performed on an electronically braked ergometer (Corival V3 Lode, Groningen, Netherlands) with a stepwise protocol: 60 W start,

25 W increments every 3 min, cadence 60–70 rpm, and volitional exhaustion under strong verbal encouragement. Participants breathed through a face mask; oxygen consumption (VO2), carbon dioxide output and minute ventilation were measured continuously with a spirometry (MetaMax I Cortex, Leipzig, Germany) system (calibrated with known gases), stored in 10-s intervals, and processed with integral software (MetaMaxAnalysis v3.21, Cortex, Leipzig, Germany). A test was acceptable if any maximality criterion was met (respiratory exchange ratio ≥ 0.99, VO_2 plateau, heart rate > 200 beats per minute, or clear clinical signs of intense effort). Because body size strongly influences paediatric fitness (Loftin et al., 2016; Welsman & Armstrong, 2019) and this was present for the current case, VO_2peak was allometrically scaled to LBM using a log-linear model (exponent b = 0.82; 95% CI 0.78–0.86), which eliminated the VO_2peak–LBM association (r = 0.01, p = .815); thus, cardiorespiratory fitness was expressed as $VO_2peak \cdot LBM^{-0.82}$ ($mL \cdot min^{-1} \cdot kg\ LBM^{-0.82}$).

In Paper III, VO_2peak ($mL \cdot min^{-1}$) was obtained at 8-year follow-up on an electromagnetically braked ergometer with an Oxycon Pro (Jaeger Medical GmbH, Hoechberg, Germany) analyser using a continuous ramp after standardized staging: 2.5-min anticipatory sit, 3-min warm-up at 5 W, 1-min at 20 W with incremental 1 W every 6 s until volitional fatigue. Maximality required objective/subjective criteria (e.g., heart rate > 85% predicted age-appropriate maximum, sweating, flushing, inability to continue despite encouragement). In this cohort, LBM and VO_2peak were not associated (r = 0.02, P = 0.75), so allometric scaling was not applied; VO_2peak relative to LBM was used instead.

6.3.4. Measurement of body composition

Both cohorts obtained standardized anthropometry and dual-energy x-ray absorptiometry (DXA) derived body composition. Specifically, in Papers I/II, stature was measured to 0.1 cm with a Martin metal anthropometer (GPM Anthropological Instruments, Switzerland) and body mass to 0.05 kg on a medical electronic scale (A&D Instruments, Tokyo, Japan) with light clothing. Body FM and LBM were assessed by DXA, using Lunar aDPX-IQ (Lunar Corporation, Madison, WI, USA) at earlier time points and Discovery scanner (Hologic QDR Series, Waltham, MA, USA) at T4; participants laid supine in minimal clothing, and medium scan mode was used. In Paper III, height was measured three times with a wall-mounted stadiometer (0.1 cm; Frankfurt plane, no shoes) and mean of the two closest values was used. Weight was measured to 0.1kg twice with a BIA scale (InBody 720, Seoul, South Korea) after a 12-h fast, bladder emptied, light underwear, mean value was used. DXA body composition was measured with a DXA device (Lunar Prodigy Advance; GE Medical Systems, Madison, WI, USA) at baseline, 2-year, and 8-year visits; participants were nonfasted, bladder emptied, in light clothing with all metal removed.

BMI was computed as $kg \cdot m^{-2}$, with BMI-SDS derived from WHO (Paper I/II) (de Onis et al., 2007; World Health Organization, 2013) or Finnish (Paper III) (Saari et al., 2011) references. According to BMI for age, subjects were divided

into weight categories as normal (BMI below 85th percentile; z-score <1.04) or overweight/obese (BMI above 85th percentile; z-score >=1.04) in Paper II (Barlow & Expert Committee, 2007).

6.3.5. Measurement of bone mineral content and growth

BMC in grams and areal BMD as $g \cdot cm^{-2}$ at total body, lumbar spine, and femoral neck by DXA scanner aDPX-IQ at T0–T3 (Lunar Corporation, Madison, WI, USA) and scanner Hologic Discovery at T4 (Hologic QDR Series, Waltham, MA, USA) were measured in supine position, medium scan mode with standard subject positioning. To reduce body-size dependence of areal BMD, we derived bone mineral apparent density (BMAD, $g \cdot cm^{-3}$) using established formulas:

- Total body BMAD = total body BMC / (total body bone area^2 / height)
- Lumbar spine BMAD = lumbar spine BMC / (lumbar spine bone area$^{1.5}$) (Estrada et al., 2014)
- Femoral neck BMAD = femoral neck BMC / (femoral neck bone area^2) (Katzman et al., 1991)

We also expressed total body BMC relative to height (BMC/height). A single qualified observer analysed scans to minimize operator variability; precision coefficient of variation < 2% for bone mineral outcomes. Longitudinal growth speeds (annualized change, e.g., $\Delta BMD \cdot y^{-1}$, $\Delta BMAD \cdot y^{-1}$) were computed from T0–T3 to capture pubertal accrual. BMC and BMD increased across T0–T3; the T4 levels reflect a different DXA platform and are therefore used primarily for cross-sectional associations at 18 years rather than direct longitudinal deltas.

6.3.6. Other arterial health contributors

Both cohorts collected standardized covariates to contextualize vascular and growth outcomes, with overlap in BP, pubertal status, and smoking, and a key difference in diet assessment (measured only for Paper III).

BP was measured supine on the left arm using an automated oscillometric device (OMRON M4-I, Omron Healthcare Europe, Hoofddorp, Netherlands) for Papers I/II. In Paper III, BP was measured on the right arm using a Heine Gamma G7 (Heine Optotechnik, Herrsching, Germany) aneroid sphygmomanometer (auscultatory method, 2-mmHg precision). All measurements were performed after 5 min of sitting, with three readings at 2-min intervals using appropriately sized cuff. Age, sex and height-based percentiles were computed for all studies (Lo et al., 2013; Martin et al., 2022).

Pubertal development was assessed by self-report (Papers I/II) or by a research physician (Paper III) according to Tanner staging (Marshall & Tanner, 1969, 1970). Puberty was not re-assessed at T4 in the Tartu study, as T3 indicated that most participants had reached Tanner stages 4–5.

Smoking was obtained by questionnaires at the late-adolescent follow-up in both cohorts.

Diet in the PANIC study was captured with 4-day weighed/household-measure food records (2 weekdays and 2 weekend days) through instructed, checked, and completed diaries (Eloranta et al., 2016) and analysed with Micro Nutrica v2.5 (Finnish food composition database; continuously updated) (Rastas et al., 1997). A healthy diet score was derived per AHA criteria (fruits/vegetables, fish, sodium, sugar-sweetened beverages, whole grains), energy-scaled to each participant (Laitinen et al., 2012).

Blood sampling used for Paper III was collected by a research nurse in the morning after at least 12 h of overnight fasting and following 10 min of seated rest. Plasma glucose was analysed using the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). The within-day and between-day coefficients of variation for glucose were 0.7%–0.9% (5.1–11.9 mmol/L) and 1.5%–1.8% (3.4–14.1 mmol/L), respectively. Plasma total cholesterol was measured on a clinical chemistry analyser (Hitachi High Technology Co, Tokyo, Japan) using a colorimetric enzymatic assay (Roche Diagnostics GmbH, Mannheim, Germany).

6.3.7. AHA cardiovascular health score

The AHA CVH score was derived from modified AHA metrics, the "Life's Simple 7" (Lloyd-Jones et al., 2010), assigning 0 points for poor CVH, 1 point for intermediate health, and 2 points for ideal health for each component (Table 4). The smoking metric was adapted to three categories (current smoker = 0 points, former smoker = 1 point, non-smoker = 2 points). The total AHA CVH score was obtained by summing the points across components. A long-term (8-year) average score was computed as the mean of the scores at baseline, 2-year follow-up, and 8-year follow-up.

Table 4. Definitions for poor, intermediate, and ideal cardiovascular health in children and adolescents: "Life's Simple 7"

Metric	Poor (0 points)	Intermediate (1 point)	Ideal (2 points)	Modifications to original metric
Smoking status	Tried prior 30 days		Never tried; never smoked whole cigarette	Modified to categories: Current smoker/Previous smoker/non-smoker
BMI	>95th percentile	85th-95th percentile	<85th percentile	-
Physical activity	None	0–59 min/d MVPA every day	≥60min/d MVPA every day	-
Healthy diet score	0–1 components	2–3 components	4–5 components	-
Total plasma cholesterol	≥200 mg/dl (≥5.2 mmol/l)	170–199 mg/dl (4.4–5.2 mmol/l)	<170 mg/dl (< 4.4mmol/l)	-
Blood pressure	>95th percentile	90–95th percentile	<90th percentile	Systolic or diastolic at least 95th percentile for poor; both systolic and diastolic less than 90th percentile for ideal.
Fasting plasma glucose	≥126 mg/dl (≥7 mmol/l)	100–125 mg/dl (6–7 mmol/l)	<100 mg/dl (<6 mmol/l)	-

The healthy diet score is based on adherence to the following dietary recommendations: fruits and vegetables, ≥4.5 cups per day (≥450 g/d); fish, ≥2 servings of 3.5-oz (99.2 g) per week; sodium, ≤1500 mg/d; sugar-sweetened beverages, ≤450 kcal (36 oz; 1020.6 g) per week; and whole grains, ≥3 servings a day scaled to a 2000 kcal/d diet (*Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction | Circulation*, n.d.).

6.3.8. Statistical analysis

Across all three studies, analyses were conducted in R (version 1.3.1093 and v4.1.2) for iOS (R Core Team, 2020) with the primary analysis being multivariable linear regression with standardised summaries and covariate control. Continuous variables were described as mean and standard deviation (SD) when normally distributed (otherwise medians with interquartile ranges), categorical variables as counts and percentages. α=0.05 defined significance. Body size has shown to be a major contributor of IMT (Doyon et al., 2013; Drole Torkar et al., 2020), thus cIMT was standardized to height (IMT-SDS) in Papers I and II and in Paper III adjusted by height.

Paper I modelled both cross-sectional (at around 12 and 18 years) and longitudinal effects (cumulative sums across four time points at T1, T2, T3 and T4) of the proposed risk factors (BMI z score, fat percentage, FM, LBM, sedentary time, vigorous physical activity, MVPA (min/day and WHO category where appropriate), cardiorespiratory fitness ($mL \cdot min^{-1} \cdot kg\ LBM^{-0.82}$), and smoking years) with arterial outcomes (IMT-SDS, cf-PWV and AIxHR75) measured at final follow-up. Adjustment was performed for late-adolescent smoking, SBP, Tanner stage, cardiorespiratory fitness, MVPA category, and where not collinear LBM (LBM was omitted when body composition was the exposure). physical activity–cardiorespiratory fitness correlations were below prespecified thresholds ($r<0.25$), allowing joint adjustment. Missing values for independent variables were imputed using 20 datasets for the multiple imputation method. Complete case data existed for 51 subjects.

Paper II evaluated separate models for each skeletal parameter (total body, femoral neck, lumbar spine BMD/BMC/BMAD; total body BMC/height) with IMT-SDS, AIxHR75, and cf-PWV as outcomes at T4, complemented by models using pubertal gains (annualized Δ from T0–T3) to test longitudinal bone growth–artery relations. Model 1 was unadjusted, and Model 2 adjusted for T4 weight category, LBM, physical activity category, smoking, $VO_2peak \cdot LBM^{-0.82}$ and Tanner stage at T3. Finally, combined models to assess independence of cross-sectional bone status and growth speed were developed. For these analyses Model A included only the exposure variable, Model B was adjusted for relevant longitudinal bone parameter as factorial variable and Model C was additionally adjusted for statistically significant risk factors (stepwise removal with $p<0.05$). Complete-case T4 data existed for 76 participants, and multiple imputation with 20 datasets addressed remaining missingness (Buuren & Groothuis-Oudshoorn, 2011).

Paper III compared baseline characteristics by sex using Fisher/Mann–Whitney tests and χ^2 for categorical variables. cIMT and PWV at 8-year follow-up as outcomes were modelled with the AHA CVH score (baseline, follow-up, and 8-year average), its individual metrics (smoking, BMI-SDS, MVPA, healthy diet score, total cholesterol, BP percentiles, fasting glucose), and cardiorespiratory fitness, LBM, and fat percentage, reporting standardized β with 95% confidence intervals (CI). Adjustments included age, sex, height, and pubertal status, with additional SBP adjustment for PWV models and, when cardiorespiratory fitness /lean/fat were exposures, further adjustment for the AHA score. Intervention status was tested and excluded from analyses due to no confounding effect. Complete cases were used per model.

7. RESULTS

7.1. Associations of arterial structure with longitudinal measures of physical activity, cardiorespiratory fitness and body composition in childhood and adolescence (Papers I and III)

Paper I results (Table 5) indicated that higher BMI, FM, and body fat percentage were consistently associated with increased intima-media thickness standard deviation score (IMT-SDS) from early adolescence to late adolescence, even after adjusting for confounders. However, LBM showed no significant relationships with arterial structure nor function at any time point. Vigorous physical activity and MVPA at early adolescence were initially correlated with better arterial structure and function, but these associations disappeared after adjusting for co-factors. Notably, meeting the MVPA guideline of 60 min per day at early adolescence was linked to a smaller IMT-SDS, independent of later MVPA levels. Cardiorespiratory fitness (VO2peak per $LBM^{0.82}$) in late adolescence and cumulatively from puberty was inversely associated with IMT-SDS, suggesting a protective effect on arterial structure that remained significant even after adjustment for key risk factors. Notably, no associations were found for arterial function parameters when models were adjusted to confounders.

Controversially, Paper III showed that higher cardiorespiratory fitness and greater LBM at the 8-year follow-up were linked to increased cIMT at the same time point, independent of the AHA CVH score (Table 6). Greater MVPA at the same time point was also associated with higher cIMT but lower PWV. A higher BMI-SDS at the 8-year follow-up was linked to increased cIMT and PWV (Table 7). No other significant associations were observed.

Table 5. Associations of risk factors at different time points with arterial structure at final follow-up (Tartu study).

	Baseline			Final follow-up			Cumulative		
IMT-SDS	β	SE	p	β	SE	p	β	SE	p
BMI z-score	0.392	0.167	0.021	0.342	0.225	0.131	0.106	0.047	0.028
Fat %	0.052	0.020	0.012	0.070	0.049	0.158	0.018	0.006	0.006
Fat mass (kg)	0.066	0.025	0.010	0.055	0.039	0.159	0.020	0.007	0.007
Lean mass (kg)	0.009	0.037	0.815	0.013	0.030	0.673	0.001	0.009	0.930
Sedentary time (min/day)	0.002	0.004	0.555	-0.003	0.003	0.280	0.000	0.001	0.778
Vigorous activity (min/day)	-0.031	0.016	0.063	0.005	0.018	0.790	-0.008	0.006	0.232
MVPA (min/day)	-0.016	0.008	0.067	0.006	0.015	0.698	-0.005	0.004	0.141
MVPA>60min/day (vs <60)	-1.091	0.475	0.026	-0.639	0.755	0.413	N/A	N/A	N/A
VO_2peak (ml/ $kg^{0.82}$/min)	-0.025	0.017	0.152	-0.031	0.012	0.010	-0.011	0.005	0.036

Abbreviations: BMI, body mass index; MVPA, moderate to vigorous physical activity; IMT-SDS – intima media thickness standard score adjusted to height.
Adjusted to cofactors: late adolescence smoking, systolic blood pressure, Tanner stage, CRF, MVPA category (>60 or <60 min/d), and LBM depending on the predictor variable.

Table 6. Associations of cardiorespiratory fitness, lean mass, and fat percentage at 8-year follow-up with arterial structure and function at 8-year follow-up (PANIC study).

Variable	N	β	95% CI	p-value
Carotid intima media thickness				
VO2peak/lean mass	98	0.29	0.08 – 0.51	0.008
Lean mass	105	0.51	0.03 – 0.98	0.036
Fat percentage	105	0.07	-0.18 – 0.33	0.579
Aorto-popliteal pulse wave velocity				
VO2peak/lean mass	89	0.02	-0.18 – 0.21	0.870
Lean mass	95	0.32	-0.11 – 0.75	0.141
Fat percentage	95	0.07	-0.15 – 0.28	0.534

Abbreviations: VO2peak, peak oxygen consumption; CI, confidence interval.
Adjusted to cofactors: age, sex, height, and pubertal status. The associations dealing with ap-PWV were additionally adjusted for systolic blood pressure.

Table 7. Associations of AHA cardiovascular health metrics at 8-year follow-up with arterial structure and function at 8-year follow-up (PANIC study).

Variable	N	β	95% CI	p-value
Carotid intima media thickness				
Previous smoking	240	0.01	-0.77 – 0.79	0.984
Current smoking	240	0.26	-0.37 – 0.90	0.414
Body mass index standard deviation score	241	0.18	0.05 – 0.31	0.009
Moderate to vigorous physical activity	130	0.25	0.07 – 0.43	0.008
Healthy diet score	210	0.10	-0.04 – 0.24	0.158
Plasma total cholesterol	229	-0.06	-0.19 – 0.08	0.398
Systolic blood pressure percentile	240	0.13	0.00 – 0.25	0.049
Diastolic blood pressure percentile	234	0.04	-0.09 – 0.17	0.515
Fasting plasma glucose	230	0.11	-0.03 – 0.24	0.111
Aorto-popliteal pulse wave velocity				
Previous smoking	210	-0.23	-1.10 – 0.64	0.610
Current smoking	210	-0.09	-0.83 – 0.64	0.806
Body mass index standard deviation score	211	0.20	0.07 – 0.34	0.003
Moderate to vigorous physical activity	117	-0.25	-0.44 – -0.06	0.010
Healthy diet score	186	-0.01	-0.14 – 0.13	0.924
Plasma total cholesterol	200	0.02	-0.11 – 0.15	0.729
Systolic blood pressure percentile	211	0.13	0.00 – 0.26	0.049
Diastolic blood pressure percentile	205	0.12	-0.01 – 0.25	0.071
Fasting plasma glucose	201	0.03	-0.09 – 0.16	0.599

Abbreviations: CI, confidence interval.
Adjusted to cofactors: age, sex, height, and pubertal status. The associations dealing with ap-PWV were additionally adjusted for systolic blood pressure.

7.2. Associations of arterial function with longitudinal BMC and bone growth in different body regions in childhood and adolescence (Paper II)

Analysis of cross-sectional results at final follow-up indicated that lumbar spine BMD (ß=-2.679. p=0.016) and BMC (ß=- 0.029, p=0.023) were associated with cf-PWV, even after adjustment to cofactors (Table 8). Inverse relationship with lumbar spine BMC with AIxHR75 was initially present but diminished after adjustment. Consistent with the cross-sectional findings, longitudinally measured (change from baseline to puberty) lumbar spine BMAD was associated with AIxHR75 (β = 700.40, p = 0.033), with additional associations observed for femoral neck BMD (β = 134.289, p = 0.003) and BMAD (β = 672.50, p < 0.001). These associations remained significant after adjusting for physical activity, body composition measures, smoking, pubertal stage, and cardiorespiratory fitness (Table 9). A combined analysis examining lumbar spine BMC at age 18 and femoral neck BMD growth speed quartiles alongside key risk factors (smoking and adherence to daily physical activity recommendations) demonstrated that cross-sectional lumbar spine BMC associations with AIxHR75 were independent of bone growth speed quartiles and other risk factors (lumbar spine BMC β = -0.29, p = 0.023). Model A included only the exposure variable, Model B adjusted for femoral neck bone growth speed quartiles (Q4 vs. Q1), and Model C incorporated additional significant risk factors identified through stepwise removal (p < 0.05), including smoking and physical activity adherence.

Associations with IMT-SDS were not present in any of the studied bone regions cross-sectionally nor longitudinally. cf-PWV revealed no significant associations with longitudinally measured bone parameters.

Table 8. Associations of bone parameters and cf-PWV at 18-year timepoint (Tartu study), cofactor adjusted (Model 2).

cf-PWV	ß	95% CI	P Value
Total body BMC (g)	-0.001	-0.002 – 0.000	0.116
Femoral neck BMC (g)	-0.126	-0.448 – 0.197	0.44
Lumbar spine BMC (g)	-0.029	-0.053 – -0.004	0.023
Total body BMD (g/cm2)	-1.750	-4.529 – 1.029	0.214
Femoral neck BMD (g/cm2)	-0.086	-2.054 – 1.882	0.931
Lumbar spine BMD (g/cm2)	-2.679	-4.837 – -0.522	0.016
Total body BMAD (g/cm3)	-20.858	-62.065 – 20.350	0.315
Femoral neck BMAD (g/cm3)	1.582	-7.592 – 10.756	0.729
Lumbar spine BMAD (g/cm3)	-14.869	-30.646 – 0.908	0.064
BMC/height	-0.001	-0.003 – 0.001	0.283

Abbreviations: BMC, bone mineral content; BMAD, bone mineral apparent density; BMD, bone mineral density; CI, confidence interval; cf-PWV, carotid-femoral pulse wave velocity.

Adjusted to cofactors: weight category (normal vs overweight/ obese), lean mass, physical activity category (>60min/day or <60min/day), self-assessed Tanner stage, smoking and VO2peakLBM$^{0.82}$

Table 9. Associations between longitudinal bone parameters and 18-year AIxHR75, cofactor adjusted.

AIxHR75	Beta	95% CI	P Value
Δ Total body BMC (g/y)	0.017	-0.017 – 0.052	0.325
Δ Femoral neck BMC (g/y)	8.64	-5.313 – 22.592	0.222
Δ Lumbar spine BMC (g/y)	0.532	-0.723 – 1.787	0.402
Δ Total body BMD (g/cm2/y)	105.282	-51.637 – 262.202	0.186
Δ Femoral neck BMD (g/cm2/y)	134.289	46.55 – 222.03	0.003
Δ Lumbar spine BMD (g/cm2/y)	77.428	-9.997 – 164.853	0.082
Δ Total body BMAD (g/cm3/y)	702.047	-857.591 – 2261.686	0.373
Δ Femoral neck BMAD (g/cm3/y)	672.5	348.07 – 996.93	< .001
Δ Lumbar spine BMAD (g/cm3/y)	700.4	57.384 – 1343.423	0.033
Δ BMC/height/year	0.038	-0.034 – 0.111	0.299

Abbreviations: AIxHR75, augmentation index adjusted for heart rate of 75bpm, BMC, bone mineral content; BMAD, bone mineral apparent density; BMD, bone mineral density; CI, confidence interval.
Adjusted to cofactors: weight category (normal vs overweight/ obese), lean mass, physical activity category (>60min/day or <60min/day), self-assessed Tanner stage, smoking and VO2peakLBM$^{0.82}$

Table 10. Associations between cross-sectional and longitudinal bone characteristics with augmentation index

Exposure	Model A	p-value	Model B	p-value	Model C	p-value
Outcome: AIxHR75	R^2=0.045, adj. R^2=0.035		R^2=0.174, adj. R^2=0.139		R^2=0.412, adj. R^2=0.351	
Lumbar spine BMC (g)	-0.29 [-0.55 – -0.02]	0.034	-0.40 [-0.66 – -0.13]	0.004	-0.29 [-0.54 – -0.04]	0.023
Δ Femoral neck BMAD (g/cm3/y) Q4 (compared to Q1)			11.94 [5.31 – 18.57]	0.001	10.33 [3.91 – 16.75]	0.002
Smoking weekly (compared to non-smoking)					8.69 [1.64 – 15.74]	0.016
Smoking daily (compared to non-smoking)					11.32 [3.36 – 19.29]	0.006
Fulfilling physical activity recommendations					-7.74 [-12.57 – -2.93]	0.002

Abbreviations: AIxHR75, augmentation index adjusted for heart rate of 75bpm, BMC, bone mineral content; BMAD, bone mineral apparent density; BMD, bone mineral density; CI, confidence interval.
ß and [95% CI] reported

7.3. Associations of arterial function and structure with CVH score in childhood and adolescence (Paper III)

The AHA CVH score declined over the 8-year follow-up, although more than 75% of participants attaining at least 10 points from the maximum of 14 by the final assessment (Figure 3). The prevalence of ideal CVH over the 8-year follow-up varied depending on the specific metric (Figure 4). The proportion of participants meeting ideal MVPA criteria declined from 78.9% to 26.9% and from 91.0% to 81.6% for BP over an 8-year period. No clear trend was observed for BMI or fasting plasma glucose levels. In contrast, the percentage of participants with ideal or intermediate diet quality increased from 34.7% to 48.3% and for ideal fasting plasma total cholesterol from 58.0% to 82.1%. By the 8-year follow-up, most ideal CVH metrics were higher than those reported in the AHA strategic impact goal paper (Lloyd-Jones et al., 2010) based on NHANES 2005–2006 data (Table 11). The only exceptions were physical activity (27% in PANIC vs. 44% in NHANES) and BP (82% in both PANIC and NHANES).

A higher baseline AHA CVH score was linked to lower PWV at the 8-year follow-up (Table 12). Although the inverse relationship between the average AHA CVH score over the 8-year period and PWV was even stronger, it did not reach statistical significance. No statistically significant results were present for cIMT

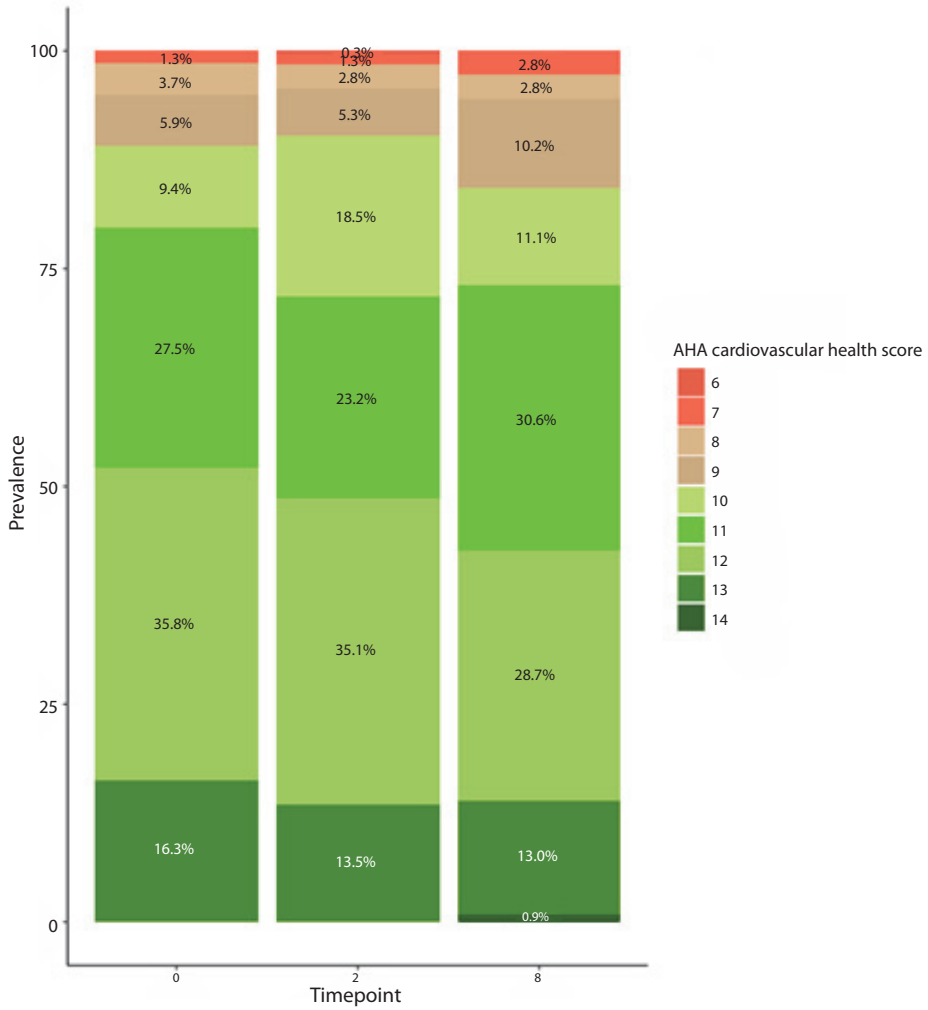

Figure 3. American Heart Association (AHA) cardiovascular health score at baseline, 2-year follow-up, and 8-year follow-up. [1]

[1] Figure has been updated from the originally published version to correct for the fact that smoking behavious was not accounted for in the Baseline and 2-year follow-up. No other analyses were affected.

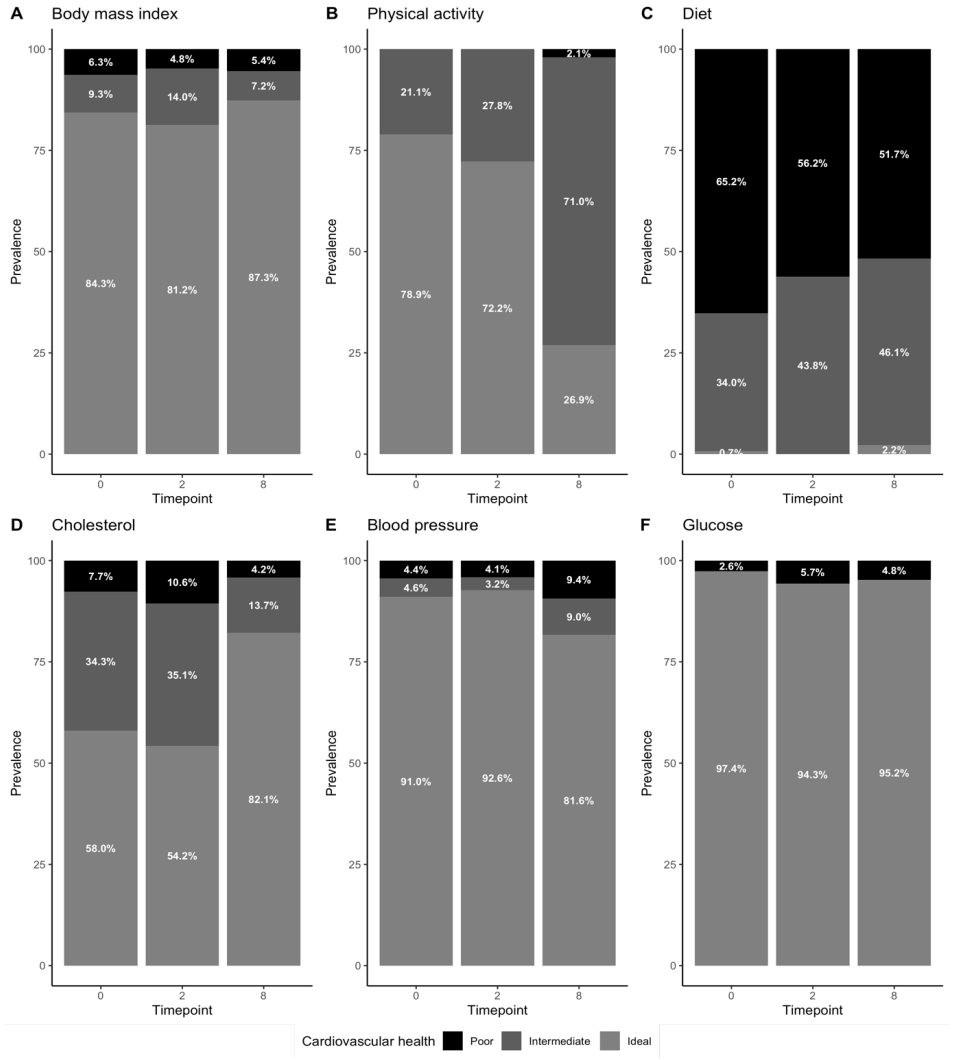

Figure 4. AHA cardiovascular health metrics at baseline, 2-year follow-up, and 8-year follow-up. Panels A, B, C, D, E and F correspond to body mass index, physical activity, diet, cholesterol, blood pressure, and glucose prevalence of ideal, intermediate, and poor category at different timepoints.

Table 11. Prevalence of ideal cardiovascular health metrics based on NHANES 2005–2006 cohort, AHA strategic impact goals through 2020 and beyond, and PANIC 8-year follow-up results.

	NHANES 2005–2006 (%)	AHA 2020 goal (%)	PANIC 8-year follow-up (%)
Smoking	83,0	99,6	88,8
Body mass index	69,0	82,8	87,3
Physical activity	44,0	52,8	26,9
Healthy diet score	0,5	0,6	2,2
Plasma total cholesterol	67,0	80,4	82,1
Blood pressure	82,0	98,4	81,6
Fasting plasma glucose	81,0	97,2	95,2

Data presented in the AHA Strategic Impact Goals Through 2020 and Beyond (Lloyd-Jones et al., 2010) for the prevalence (NHANES 2005–2006) as well as future goals (AHA 2020 goal).

Table 12. Associations of baseline, 8-year follow-up and 8-year average AHA cardiovascular health score with arterial structure and function at 8-year follow-up.

Variable	N	β	95% CI	p-value
Carotid intima media thickness				
Baseline AHA cardiovascular health score	187	-0.15	-0.31 – 0.00	0.053
8-year follow-up AHA cardiovascular health score	95	0.04	-0.19 – 0.28	0.711
Average AHA cardiovascular health score	67	-0.06	-0.19 – 0.08	0.432
Aorto-popliteal pulse wave velocity				
Baseline AHA cardiovascular health score	160	-0.19	-0.34 – -0.05	0.011
8-year follow-up AHA cardiovascular health score	105	-0.15	-0.38 – 0.07	0.187
Average AHA cardiovascular health score	58	-0.28	-0.59 – 0.04	0.084

Abbreviations: CI, confidence interval.
Adjusted to cofactors: age, sex, height, and pubertal status. The associations dealing with ap-PWV were additionally adjusted for systolic blood pressure.

8. DISCUSSION

8.1. Arterial structure, body composition, physical activity, and cardiorespiratory fitness (Papers I and III)

In both studied cohorts (Papers I and III), indicators of adiposity emerged as consistent determinants of arterial morphology. In the longitudinal study of Tartu boys, higher FM and body fat percentage both at 12 years and as cumulative exposure were independently associated with greater carotid IMT-SDS by 18 years, supporting earlier findings from the Bogalusa Heart Study that the life course burden of adiposity contributes to arterial wall thickening from early life onward (Fan et al., 2022). These results together with other (Agbaje et al., 2021; Chiesa et al., 2021) suggest that the commonly observed associations between BMI and arterial structure are primarily driven by FM, reinforcing the need to distinguish between the metabolic consequences of different body composition components. In the PANIC study population (Paper III) higher BMI-SDS and SBP were associated with increased cIMT and ap-PWV, further indicating that excess body mass in addition to increased BP exerts a lasting detrimental effect on both arterial structure and function.

The relationship between physical activity, cardiorespiratory fitness, and arterial health was more complex. In the Estonian cohort, fulfilling the WHO physical activity recommendation of at least 60 min per day at 12 years predicted better arterial structure six years later, independent of later physical activity levels (Paper I), suggesting that early adolescence may represent a critical window during which activity promotes vascular resilience. Cumulative and late-adolescent cardiorespiratory fitness was inversely related to IMT-SDS, independent of LBM and physical activity. These results highlight the protective structural effects of sustained high cardiorespiratory fitness consistent with previous research (Ascenso et al., 2016; Ortega et al., 2008; Weberruß et al., 2017). Conversely, in the PANIC cohort, higher MVPA, LBM, and cardiorespiratory fitness in adolescence were associated with higher cIMT, while greater MVPA was simultaneously related to lower ap-PWV. Similar observations have been reported in other adolescent studies, where training intensity and duration as well as higher LBM led to thicker but more compliant arteries (Baumgartner et al., 2021; Chiesa et al., 2021). This structural adaptation reflects physiological, rather than pathological, arterial remodelling as a response to increased hemodynamic load from regular activity and muscle mass accrual during growth. Functional adaptation of the arteries has been suggested to occur before structural adaptation, evaluated in exercise training programs as temporal relationships. The consequent up-regulation of functional pathways can contribute to arterial remodelling, which, once expressed, allows function to return toward baseline levels. This interrelationship may act to homeostatically regulate wall shear stress, as suggested in some early experiments (Green & Smith, 2018). The apparent discrepancy between cohorts in our analyses as well as other studies may therefore arise from

differences in maturational timing, measurement periods, distinction between functional versus structural markers of arterial health and finally the methods used for adjusting the analyses. It has been clearly shown that both IMT and PWV are dependent not only on the age, but also body size, namely height and LBM (Baier et al., 2018; Chiesa et al., 2021; Reusz et al., 2010), thus inclusion or exclusion of these factors from the analyses could significantly alter the results. It is important to note that the age of assessment as well as location of arterial thickness measurement can change the found associations, as for example lipid levels seem to correlate with aortic IMT earlier than for carotid IMT (Dawson et al., 2009). This supports the hypothesis that aortic structural change occurs earlier than carotid (Davis et al., 2010; Dawson et al., 2009; T. T. Laitinen et al., 2025; Nasir et al., 2025).

Our study found that from the "Life's Simple 7" factors, blood pressure, MVPA and BMI were related to arterial function, and structure, but the other factors, namely smoking habits, blood cholesterol and sugar levels did not relate to arterial health. Collectively, these findings indicate that while cIMT thickening in active or fit youth may represent adaptive remodelling, increased PWV in central arterial segments remains a more sensitive indicator of early arterial health and adverse cardiovascular risk.

8.2. Arterial function and bone growth (Paper II)

Arteriosclerosis is characterized by reduced arterial compliance, increased fibrosis, loss of elasticity, and vascular calcification, typically affecting large and medium-sized arteries (Ferreira & Twisk, 2017). The shared biological mechanisms underlying arteriosclerosis and osteoporosis include parallel changes in collagen and elastin architecture, calcium dependence, and overlapping genetic determinants (Cassidy-Bushrow et al., 2011). Our findings demonstrated that greater BMC and BMD are linked to lower arterial stiffness in healthy adolescent males independent of confounders such as pubertal stage, LBM, cardiorespiratory fitness, physical activity, smoking, and pubertal development. These results confirm some associations previously reported in the literature, specifically, it has been found that low BMD is associated with higher pulse wave velocity in a large cohort of clinically healthy adults (Wang et al., 2015). However, our association was limited to specific skeletal sites, corresponding to trabecular bone regions. While cortical bone constitutes approximately 80% of total bone mass and primarily serves structural and mechanical functions, trabecular bone that is located predominantly in the lumbar spine and femoral neck is more metabolically active (Stagi et al., 2013). Across multiple cohorts, shared systemic factors appear to underlie the association between regional bone mineral density and both arterial wall thickness and stiffness. In postmenopausal Moroccan women (mean age ~59 years) without major overt cardiovascular disease, BMD at the lumbar spine and femoral sites was examined alongside carotid and femoral artery IMT. Carotid IMT, but not femoral IMT, correlated inversely and independently with femoral

total, femoral neck, Ward's triangle and trochanter BMD, whereas no association was seen with lumbar spine BMD (Hmamouchi et al., 2009). Similar inverse associations between cIMT and DXA-derived T-scores at the lumbar spine and femoral neck have been reported in smaller sample of postmenopausal women referred for osteoporosis screening, again linking low regional BMD with intima-media thickening in older, oestrogen-deficient women (Mohammadi et al., 2014). In contrast, a large family-based study of 1,679 Korean adults (men, premenopausal and postmenopausal women) found that lumbar spine BMD was positively associated with composite carotid IMT, particularly common carotid IMT in premenopausal women and in men with higher BMI, but not in postmenopausal women, highlighting that the direction and strength of the BMD and thickness association depend on age, sex, adiposity and menopausal status (Shin et al., 2017). When arterial stiffness is considered, similar risk-factor constellations emerge. In a general Macedonian community sample (n=558 adults), femoral neck and lumbar spine BMD were inversely related to cf-PWV, and both lower femoral neck BMD and higher PWV independently predicted cardiovascular mortality over 36 months, again implicating site-specific BMD (particularly at the femoral neck) and central arterial stiffness as co-phenotypes of an adverse cardiometabolic milieu in middle-aged and older adults (Avramovski et al., 2016).

From a developmental perspective, rapid bone growth in males occurs during puberty, typically between 11 and 14 years of age, with peak bone mass achieved near the beginning of the third decade of life (Weaver, 2002). Bone formation results from the dynamic balance between osteoclastic resorption and osteoblastic formation, with the latter dominating during childhood and adolescence at the time of maximal mineralization velocity. Bone resorption increases later in life, contributing to osteopenia and osteoporosis (Florencio-Silva et al., 2015). The associations of lumbar spine BMC and arterial stiffness at 18 years persisted when modelled together with femoral neck bone growth velocity, showing that both bone growth velocity as well as current bone mineral content have independent associations with arterial health. Interestingly, the direction of association differed between bone growth velocity and final mineral content, suggesting complex physiological interactions. During the pubertal growth spurt, cycles of chondrocyte proliferation and differentiation, extracellular matrix secretion, calcification, vascular invasion, and osteoblast differentiation occur repeatedly within the growth plate. Numerous bioactive molecules including fibroblast growth factor 23, insulin-like growth factor I, and vascular endothelial growth factor are secreted during this period (Nilsson et al., 2005), many of which are also known to influence vascular remodelling (Girerd et al., 2022; Zachariah et al., 2012). More extreme clinical models, such as osteoporotic outpatients, underscore biological pathways that can simultaneously demineralise bone and stiffen or thicken arterial walls. In a pilot study of older osteoporotic outpatients (predominantly women) compared with age- and risk-factor–matched controls, DXA-derived lumbar spine and femoral neck BMD was substantially lower in the osteoporosis group, who also exhibited higher cf-PWV, cIMT and AIx.

Within the osteoporotic group, femoral neck BMD was inversely associated with cf-PWV even after adjustment for age, blood pressure and sex, indicating that regional BMD differences at the hip track with large-artery stiffening over and above shared classical risk factors (Gaudio et al., 2020). Systematic review and meta-analytic data pooling 25 observational studies (over 10,000 participants, predominantly older adults and postmenopausal women) further show that decreased BMD is an independent predictor of a broad spectrum of atherosclerotic vascular abnormalities (including increased IMT, arterial calcification and clinical coronary artery disease), with risk gradients that worsen as BMD falls from normal to osteopenic to osteoporotic ranges (Ye et al., 2016). Contemporary narrative reviews of the "bone–vascular axis" propose shared mechanisms like age-related sex hormone deficiency, chronic low-grade inflammation and high-grade oxidative stress, impaired glucose and lipid metabolism, and disturbances in calcium–phosphate–vitamin D–FGF-23–Klotho signalling that may concurrently accelerate trabecular-rich lumbar vertebral bone loss, cortical–trabecular demineralisation at the femoral neck, and medial arterial remodelling with increased wall thickness and stiffness (Ajamu et al., 2021; Cretoiu et al., 2021; Tap et al., 2020). Experimental and translational data on osteogenic trans differentiation of vascular smooth muscle cells, RANKL/osteoprotegerin signalling, Wnt/β-catenin pathways, and modulators such as sclerostin collectively support the idea that molecules governing skeletal turnover can also regulate vascular calcification and stiffness, further cementing a mechanistic bridge between regional BMD at the lumbar spine and femoral neck and the structural and functional properties of large arteries (De Maré et al., 2022; Herzog et al., 2025). Some studies suggest that in younger populations, associations between bone and vascular parameters may primarily reflect concurrent processes of growth and maturation rather than pathological mechanisms (Frysz et al., 2016). Indeed, cIMT increases with age and somatic growth in both children and adults, whereas arterial functional indices appear more independent of anthropometric and maturational factors. Our results were independent of these and several other potential confounders linking arterial and bone metabolism, suggesting an independent association between the two. Further research is needed to elucidate the shared biological determinants of bone growth and arterial stiffness underlying the relationships observed in our study.

8.3. Cardiovascular health score and arterial measures (Paper III)

Pahkala et al. Reported in the STRIP (Special Turku Coronary Risk Factor Intervention Project) study, that serum total cholesterol increased, and smoking became more common from ages 15 to 19, while other components of the AHA CVH score remained stable (Pahkala, Hietalampi, et al., 2013). In the present cohort, MVPA similarly declined over eight years from the age of 8 to 16, whereas BMI and fasting plasma glucose levels remained stable. In contrast, diet

quality improved with the concurrent decrease of plasma cholesterol, although blood pressure percentiles increased. Paper III analyses along with other evidence (Corder et al., 2019; Husøy et al., 2024), indicate a consistent decline in physical activity from childhood to adulthood and its associations with increased arterial stiffness and cIMT, emphasizing the need for interventions that promote sustained activity in order to retain cardiovascular and arterial health. Nevertheless, comprehensive assessment of CVH requires evaluating integrated health indices rather than single risk factors. It is also important to emphasise that in children and adolescents' ap-PWV is better related with cardiovascular risk profile than cIMT.

Higher mid-childhood AHA CVH score, irrespective of the future CVH score, in our study predicted lower ap-PWV in adolescence, reflecting reduced arterial stiffness. The large prospective i3C (International Childhood Cardiovascular Cohort) study (Jacobs et al., 2022) and a nationwide Japanese epidemiological analysis (Kaneko et al., 2020) both showed that childhood cardiovascular risk profiles predict future cardiovascular events, underscoring the long-term impact of early-life health behaviours. Cumulatively, this supports hypothesis that favourable early-life behaviours and risk factor profiles modulate the trajectory of vascular aging beginning in childhood. Because PWV reflects arterial wall stiffness and is sensitive to blood pressure, metabolic milieu, and physical fitness, the association likely represents attenuation of adverse hemodynamic load and inflammatory signalling across development (Jacobs et al., 2022). The absence of a cross-sectional relationship at adolescence in our cohort further suggests that cumulative favourable exposure (earlier and sustained CVH) rather than a single time-point CVH status is required to manifest differences in arterial function. Prior findings by Raitakari et al. showed that higher childhood cardiovascular risk factors predict greater cIMT in adulthood (Raitakari et al., 2003). Importantly, this cohort was at the age of 24 to 39 years when the arterial measurements took place. Our longitudinal results revealed associations between the AHA score and ap-PWV, but not with cIMT suggesting that ap-PWV is a better measure of cardiovascular health than cIMT in children and adolescents. The discordance between ap-PWV and cIMT associations in our study is consistent with prior reports and can be explained by differences in population age, risk factor profile and etiologic processes. PWV commonly detects early changes in the arterial stiffness, whereas cIMT captures longer-term structural remodelling that may require larger cumulative exposure or older age to appear. Measurement variability and the smaller dynamic range of cIMT in otherwise healthy paediatric populations also reduce power to detect associations in adolescence. Population health status modulates which arterial markers change earliest. In diseased or high-risk paediatric populations (e.g., familial hypercholesterolemia, paediatric hypertension, obesity), studies commonly find elevated arterial stiffness compared with controls, indicating accelerated functional pathology (Reiner et al., 2019). Thus, discrepancies across studies may reflect baseline risk, age at follow-up, and severity or duration of exposure. Because our largely healthy cohort had very few participants with major cardiometabolic risk factors (e.g., regular

tobacco use, diabetes, hypercholesterolaemia), the level of pathological exposure was probably inadequate to provoke the structural arterial remodelling that cIMT captures, even though functional alterations reflected by PWV may still occur. Thus, PWV in central regions may be a sensitive marker of adverse exposures in childhood, while cIMT better reflects chronic atherogenic processes measurable later in life. This theory is supported by the results gained from Paper I, for which the population was a few years older than in Paper III, had a higher prevalence of tobacco use and already thicker intima-media.

8.4. Strengths and limitations

Until recently, there was a lack of longitudinal evidence linking pre-pubertal and pubertal exposures such as physical activity, cardiorespiratory fitness, body composition, and metabolic status to validated measures of arterial structure and function. Most paediatric vascular studies were cross-sectional and focused on individual risk factors like BMI or BP, with little integration of comprehensive CVH metrics or consideration of cumulative exposures over time. Similarly, evidence on the independent and combined effects of physical activity and cardiorespiratory fitness remained limited, and the relative importance of fitness versus activity independent of adiposity was unclear. Moreover, interactions between bone and vascular systems during growth had been scarcely explored. Most existing data were derived from clinical or high-risk groups, leaving little known about subclinical vascular adaptations in a healthy population of children and adolescents.

Our series of longitudinal studies (Papers I, II, III) directly addressed many of these evidence gaps by integrating behavioural, metabolic, skeletal, and vascular measures across key developmental stages. Together, these studies represent comprehensive longitudinal efforts to connect childhood lifestyle, fitness, growth, and composite CVH to vascular outcomes in adolescence and early adulthood. By combining structural and functional vascular measures within population-based cohorts and by examining normal physiological development rather than clinical pathology, this research is novel and provides critical insight into how modifiable behaviours and growth trajectories shape early vascular remodelling. Collectively, the work advances the field from isolated, cross-sectional risk-factor analyses toward an integrative, longitudinal, and mechanistic model of vascular development, demonstrating that early-life behaviours and growth patterns leave lasting, measurable imprints on the arterial system well before the onset of disease.

While these longitudinal studies advance the understanding of early vascular development, several limitations should be acknowledged. First, the cohorts were homogeneous Northern European populations, limiting ethnic and environmental diversity and constraining the generalizability of findings to other populations with differing growth, lifestyle, and cardiometabolic profiles. Second, two of the studies used male-only cohort, which precludes assessment of sex-specific developmental and hormonal influences on vascular structure and function.

Third, although the designs were prospective, the sample sizes were modest and attrition across follow-up periods may introduce selection bias toward healthier participants, potentially underestimating true effect sizes. In addition, vascular outcomes were limited to macrovascular indices – primarily carotid intima–media thickness and pulse wave velocity – without corresponding measures of microvascular function, which may capture various aspects of early vascular aging. It is important to emphasise that the population age and methods for measuring PWV were different for the two cohorts used for the current thesis, this being an important factor when considering the results side-by-side. Importantly, these studies are observational and cannot fully establish causality; confounding by unmeasured lifestyle, genetic, or pubertal maturation factors remains possible. Finally, the follow-up periods, although longer than most paediatric studies, do not extend into adulthood, and thus the long-term clinical relevance of the observed subclinical vascular changes remains to be determined.

8.5. Remaining evidence gaps

Despite these advances, important gaps remain in our understanding of early vascular health trajectories. Long-term follow-ups extending from childhood into mid-adulthood for arterial measures are still scarce, leaving the predictive validity of paediatric arterial measures for later clinical cardiovascular outcomes largely untested. While recent work has focused on healthy cohorts, there is still limited representation of females, ethnically diverse populations, and lower-income settings, restricting generalizability. The mechanistic pathways linking pubertal growth, bone metabolism, and vascular remodelling remain incompletely defined, and require integration of hormonal, inflammatory, and molecular biomarkers alongside imaging outcomes. Standardized reference values and methodological harmonization for paediatric arterial stiffness and intima–media thickness are also lacking, impeding cross-study comparability. Moreover, few intervention studies have demonstrated whether early modification of lifestyle, fitness, or body composition can reverse or slow vascular stiffening and thickening. Future research should therefore emphasise multi-system, multi-ethnic, and mechanistic longitudinal designs that combine behavioural, metabolic, and biological data to clarify causal pathways and to identify the most effective developmental windows for cardiovascular risk prevention.

9. CONCLUSIONS

1. Childhood and adolescence higher body mass index, fat mass, and body fat percentage were consistently associated with increased cIMT in adolescence. The associations of cardiorespiratory fitness, physical activity and lean mass with cIMT suggest that all three factors contribute to arterial remodelling, but the size and direction of associations is dependent on the studied population. It is important to note that in adolescence increases in cIMT do not purely reflect pathological changes but also functional adaptation to higher physical activity, cardiorespiratory fitness and increased lean mass. This is supported by the finding that higher physical activity was associated with decreased ap-PWV in adolescence. These results were independent of cardiovascular risk factors and other cofactors studied, supporting their individual associations to arterial structure and function.
2. Higher bone mineral content and density in trabecular bone regions like lumbar spine and femoral neck were related to cf-PWV in healthy adolescent males. Controversial pubertal rapid bone growth in these same regions was related to increased arterial wave reflection in late adolescence. As the results are independent of other cardiovascular risk factors, they indicate that skeletal growth patterns and mineral content are independently associated with arterial stiffness rather than bone and arteries just having common traits of growth and maturation.
3. Body mass index, physical activity and systolic blood pressure from American Heart Association's cardiovascular health metrics had the highest independent associations with cIMT and ap-PWV in adolescence. Combined cardiovascular health score at early childhood independent of adolescence score was related to decreased ap-PWV in the future, but not intima-media thickening. This provides evidence that the composite score in childhood predicts later vascular function, and that ap-PWV is a more sensitive marker of early vascular damage than cIMT, calling for caution when interpreting these markers of arterial health.

9.1. Practical implications

1. Although fat mass and percentage are more specific indicators of body composition that contribute negatively to arterial health, body mass index remains a valid and practical proxy measure for assessing arterial health in children and adolescents.
2. When interpreting cIMT in children and adolescents, it should be acknowledged that it does not solely reflect pathological arterial remodelling but may also capture physiological adaptations related to higher cardiorespiratory fitness, greater lean mass, and higher levels of physical activity. This consideration is particularly important in young athletes and physically active youth.

3. Among lifestyle factors, particular emphasis in childhood and adolescence should be placed on the prevention of obesity, adequate blood pressure control, and the promotion of a physically active lifestyle to preserve arterial health.
4. The American Heart Association's "Life's Simple 7" construct represents a practical tool for screening children and adolescents for elevated cardiovascular risk, as it predicts future impairments in arterial function.
5. In children and adolescents, ap-PWV appears to be a more sensitive marker of arterial health than cIMT, as it shows stronger associations with established cardiovascular risk factors.

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11. SUMMARY IN ESTONIAN

Arterite struktuuri ja funktsiooniga seonduvad tegurid tervetel lastel ja noorukitel

Kardiovaskulaarsed haigused (CVD), sealhulgas ateroskleroотilised haigused on jätkuvalt üks olulisemaid surma ja töövõime kaotuse põhjuseid kogu maailmas. Ateroskleroos on aeglaselt arenev protsess, mis saab alguse endoteeli düsfunktsioonist ja oksüdatiivsest stressist. Nende muutuste tagajärjel käivituvad põletikulised reaktsioonid, toimub lipiidide ladustamine ning veresoonte seinad paksenevad ja kaotavad oma elastsuse. Uuringud näitavad, et esimesed märgid nendest protsessidest võivad olla nähtavad juba lapse- ja noorukieas. Seetõttu on varajane ennetus ning riskitegurite tundmine äärmiselt oluline.

Ateroskleroosi varasest tekkest annavad märku rasvladestused ja sidekoelised naastud, mida on lahkamisuuringutes leitud isegi laste ja noorte täiskasvanute veresoonte seintest. Ateroskleroosi patogeneesis on olulisel kohal veel endoteelirakkude kahjustus, põletikuliste tsütokiinide vabanemine, silelihasrakkude liigkasv ja arterite seina kaltsifikatsioon. Varajased ateroskleroотilised muutused võivad olla pöörduvad, seega on õigeaegne sekkumine olulise tähtsusega.

Laste ja noorukite arterite seisundit saab hinnata mitteinvasiivsete meetodite abil, näiteks unearteri intima-meedia paksuse (cIMT) või pulsilaine levikukiiruse (PWV) mõõtmisega. Need annavad väärtuslikku teavet arterite struktuuri ja funktsiooni kohta, kuigi nende tundlikkus ja standardiseeritus noorema elanikkonna puhul vajavad veel täiendavat uurimist. Arterite jäikus ja seina paksenemine on haiguslikest seisunditest seotud kõrgema vererõhu, rasvumise ja insuliiniresistentsusega.

CVD peamised riskitegurid on kõrge vererõhk, düslipideemia, suitsetamine, diabeet, rasvumine ja vähene liikumine. Lapse- ja noorukieas väljakujunenud riskitegurid on otseselt seotud veresoonte seina paksenemise ja jäikusega täiskasvanueas. Longitudinaalsed uuringud on näidanud, et varajane vererõhu, lipiidide ja kehamassi tõus kiirendab ateroskleroosi arengut ning arterite jäikus noorukieas võib olla varane märk tulevasest hüpertensioonist ja ainevahetushäiretest.

Regulaarne kehaline aktiivsus ja hea kardiorespiratoorne võimekus aitavad säilitada arterite elastsust, parandada endoteeli talitlust ja vähendada põletikku. Kui liigne rasvamass seostub pigem arterite jäigastumise ja põletikuga, siis suurem lihasmass võib viia füsioloogilise, mittepatoloogilise arteriseina paksenemiseni. Huvitavalt on hiljutised uuringud toonud esile ka luutiheduse ja veresoonte tervise vahelised seosed – põletiku, oksüdatiivse stressi ja hormonaalse regulatsiooni ühised mehhanismid võivad juba varases eas siduda skeleti ja veresoonkonna arengut.

Kokkuvõttes näitab senine teadus selgelt, et veresoonte funktsiooni ja struktuuri muutused algavad tunduvalt varem, kui haigused ise välja kujunevad. Subkliiniliste markerite kasutamine võimaldab tuvastada riskirühmi ja hinnata

elustiilitegurite mõju juba enne haiguste avaldumist. Samas on endiselt vaja standardiseeritud mõõtemetoodikaid, pikaaegseid seireuuringuid ja terviklikke analüüse, mis ühendaksid kehalise koostise, füüsilise aktiivsuse, kardiorespiratoorse võimekuse ja luutervise andmed arterite tervise näitajatega. Käesolev doktoritöö uuribki nende tegurite vastastikmõju, et mõista, kuidas varajased elustiili mõjutused kujundavad arterite struktuuri ja funktsiooni lapse- ja noorukieas.

Uurimuse eesmärgid

Antud doktoritöö üldiseks eesmärgiks oli uurida arterite struktuuri ja funktsiooni tervetel lastel ja noorukitel ning kaardistada nende seoseid longitudinaalselt mõõdetud teguritega. Olulisel kohal oli uuritavate tegurite sõltumatus juba teadaolevatest kardiovaskulaarsetest riskiteguritest ning uute potentsiaalsete riskihindamise tegurite kaardistamine, et toetada südame-veresoonkonna haiguste riski varasemat ennetust.

Uuringu täpsemad eesmärgid

1. Uurida arterite struktuuri ja funktsiooni seoseid longitudinaalsete kehalise aktiivsuse, kardiorespiratoorse võimekuse ja keha koostise näitajatega tervetel lastel ja noorukitel.
2. Uurida arterite struktuuri ja funktsiooni seoseid longitudinaalse luu mineraalsisalduse ja luu kasvukiirusega tervetel lastel ja noorukitel.
3. Hinnata arterite struktuuri ja funktsiooni seoseid Ameerika Südameassotsiatsiooni (AHA) südame-veresoonkonna tervise näitajatega ning nende sõltumatust juba teadaolevatest riskiteguritest.

Uuritavad ja uuringu meetodid

Antud teadustöö ühendab kahe longitudinaalse kohortuuringu andmed: Tartu laste uuringus jälgiti 9–12-aastaseid terveid poisse alates puberteedist kuni hilise noorukieani ning Soomes läbiviidud PANIC-uuringus 6–9-aastaseid tüdrukuid ja poisse 8 aasta jooksul. Mõlemas uuringus mõõdeti kehalist aktiivsust, kardiorespiratoorset võimekust ja kehalist koostist. Tartu uuringus hinnati täiendavalt ka luu näitajaid. Arterite struktuuri ja funktsiooni hinnati 8-aasta jälgimisvisiidi ajal nii Tartu kui PANIC uuringus cIMT ja PWV põhjal, kasutades standardiseeritud ultraheli ja tonomeetria (Tartu uuring)/ impedants kardiograafia (PANIC uuring) meetodeid. Tartu uuringus arvutati ka 75 südame löögisagedusele kohandatud augmentatsiooni indeksit (AIxHR75). Kehalist aktiivsust määrati objektiivselt aktseleromeetri või südame löögisageduse ja liikumise kombineeritud anduritega, kardiorespiratoorset võimekust koormustestidega ning kehalist koostist ja luutihedus luudensitomeetriaga. PANIC uuritavatel arvutati AHA kardiovaskulaarse tervise kombineeritud skoor kasutades AHA programmi "*Life's Simple 7*" näitajaid (vererõhk, kolesterooli ja veresuhkru tase, kehaline aktiivsus, toitumine, kehakaal, tubaka tarvitamine). Andmeid analüüsiti mitmemuutuja

regressioonmudelite abil kohandades tulemusi vanusele, soole, keha koostisele ja teistele riskiteguritele.

Tulemused ja järeldused

1. Lapsepõlves ja puberteedieas mõõdetud kehamassiindeks, rasva mass ja keha rasvaprotsent olid järjepidevalt seotud suurenenud cIMT-iga puberteedieas. Kardiorespiratoorse võimekuse, kehalise aktiivsuse ja rasvavaba massi seosed cIMT-iga olid populatsiooniti erinevad, kuid viitasid, et kõik kolm tegurit on seotud arterite remodelleerimisega, mis on ilmselt füsioloogiline arvestades kehalise aktiivsuse ja arterite elastsuse seoseid. Tulemused olid sõltumatud teistest uuritavatest teguritest. Lapse- ja noorukieas ei pruugi seega cIMT väljendada vaid arterite tervist, vaid ka funktsionaalset adaptatsiooni regulaarsele füüsilisele aktiivsusele, paremale kehalisele võimekusele ning kõrgemale rasvavabale massile.
2. Luutiheduse ja -mineraalsisalduse suurenemine trabekulaarse luukoe piirkondades, nagu nimmelülid ja reieluukael, oli seotud väiksema PWV-ga tervetel noorukieas poistel. Samade piirkondade kiire luukasv puberteedieas oli aga seotud suurenenud AIxHR75-ga hilises noorukieas. Kuna tulemused olid sõltumatud teistest kardiovaskulaarsetest riskiteguritest, võivad need viidata sellele, et luustiku kasvumustrid ja mineraalsisaldus on arteriaalse jäikusega otseses seoses, mitte vaid läbi ühiste riskifaktorite.
3. Kehamassiindeks, mõõduka kuni tugeva intensiivsusega kehaline aktiivsus ja süstoolne vererõhk Ameerika südameassotsiatsiooni kardiovaskulaartervise näitajatest omasid suurimat sõltumatut seost cIMT ja PWV-ga. Kardiovaskulaarse tervise kombineeritud skoor varases lapseeas, sõltumata noorukiea tulemustest, oli seotud tulevase arteriaalse jäikusega. See viitab, et lapsepõlve üldine südame-veresoonkonna tervis seostub hilisema veresoonte funktsiooniga ning et PWV on tundlikum varajase veresoonkonna muutuste marker kui cIMT.

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13. PUBLICATIONS

14. CURRICULUM VITAE

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Education:

2020–2026	University of Tartu, Faculty of Medicine, PhD
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Professional employment:

2022–…	Visiting lecturer, University of Tartu, Institute of Family Medicine and Public Health
2021–…	Clinical assessor, State Agency of Medicines
2023–2024	Junior research fellow, University of Tartu, Institute of Clinical Medicine, Department of Paediatrics
2017–2021	Lead specialist, State Agency of Medicines
2016–2021	Manager of clinical trials department, OÜ Quretec
2014–2016	Clinical trials manager (data/project), OÜ Quretec

Membership in scientific organizations:
Estonian Society of Cardiology
Estonian Medical Association

Scientific work:
My scientific work focuses on the associations between arterial health and physical activity and fitness, body composition and bone metrics in children and adolescents. Scientific achievements include three articles in international peer-reviewed journals, two presentations at international conferences, endorsement of paper of the year from Pediatric Exercise Science (PES). Additional contributions include active involvement in peer-review on the field of paediatric arterial health.

Publications in international peer-reviewed journals:
1. Kraav, J., Zagura, M., Viitasalo, A., Soininen, S., Veijalainen, A., Kähönen, M., Jürimäe, J., Tillmann, V., Haapala, E., & Lakka, T. (2024). Associations of cardiovascular health metrics in childhood and adolescence with arterial health indicators in adolescence: The PANIC Study. Journal of the American Heart Association, 13(22), e035790. https://doi.org/10.1161/JAHA.124.035790
2. Kraav, J., Tamme, R., Remmel, L., Mäestu, E., Zagura, M., Jürimäe, J., & Tillmann, V. (2023). Arterial structure in 18-year-old males is dependent on physical activity at 12 years and cumulative cardiorespiratory fitness from

puberty to late adolescence. Pediatric Exercise Science, 25(3), 144–154. https://doi.org/10.1123/pes.2022-0002
3. Kraav, J., Zagura, M., Remmel, L., Mäestu, E., Jürimäe, J., & Tillmann, V. (2023). Rapid trabecular bone growth in puberty associated with stiffer arteries in adulthood: Longitudinal study on healthy young males. Archives of Osteoporosis, 18(1), 62. https://doi.org/10.1007/s11657-023-01257-3

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Erialane töökogemus:

2022–…	õppejõud, Tartu Ülikool, Peremeditsiini ja rahvatervishoiu õppetool
2021–…	kliiniline hindaja, Ravimiamet
2023–2024	nooremteadur, Tartu Ülikool, Kliinilise meditsiini instituut, Lastekliinik
2017–2021	juhtivspetsialist, Ravimiamet
2016–2021	Kliiniliste uuringute osakonnajuhataja, OÜ Quretec
2014–2016	Kliiniliste uuringute andmehaldur/projektijuht, OÜ Quretec

Liikmelisus erialaseltsides:
Eesti Kardioloogide Selts
Eesti Arstide Liit

Teadustöö:
Minu teadustöö suunaks on arterite jäikuse, füüsilise aktiivsuse, kehalise võimekuse ja koostise ning luu näitajate vaheliste seoste uurimine. Olen olnud 3 rahvusvahelise teadusartikli publitseerimisel juhtivautor, millest üks on ära märgitud kui ajakirja aasta parim artikkel ja teinud 2 ettekannet rahvusvahelistel teaduskonverentsidel. Täiendava panusena olen osalenud aktiivselt oma valdkonnas retsensendina rahvusvaheliste ajakirjade töös.

Publikatsioonid:

1. Kraav, J., Zagura, M., Viitasalo, A., Soininen, S., Veijalainen, A., Kähönen, M., Jürimäe, J., Tillmann, V., Haapala, E., & Lakka, T. (2024). Associations of cardiovascular health metrics in childhood and adolescence with arterial health indicators in adolescence: The PANIC Study. Journal of the American Heart Association, 13(22), e035790. https://doi.org/10.1161/JAHA.124.035790
2. Kraav, J., Tamme, R., Remmel, L., Mäestu, E., Zagura, M., Jürimäe, J., & Tillmann, V. (2023). Arterial structure in 18-year-old males is dependent on physical activity at 12 years and cumulative cardiorespiratory fitness from

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3. Kraav, J., Zagura, M., Remmel, L., Mäestu, E., Jürimäe, J., & Tillmann, V. (2023). Rapid trabecular bone growth in puberty associated with stiffer arteries in adulthood: Longitudinal study on healthy young males. Archives of Osteoporosis, 18(1), 62. https://doi.org/10.1007/s11657-023-01257-3

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