ASSOCIATION BETWEEN RESTING BLOOD PRESSURE AND MAXIMAL BLOOD PRESSURE RESPONSE TO EXERCISE AND ARTERIAL HEALTH

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ABSTRACT

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We investigated the longitudinal associations of blood pressure, cardiorespiratory fitness, and arterial stiffness among children. Arterial stiffening has been repeatedly shown to be a cardiovascular mortality predictor and can be observed early in childhood. As such, it is crucial to understand whether a child's blood pressure, fitness level, and body composition can predict early signs of atherosclerosis and arterial stiffening. The current study examined the relationship between blood pressure, cardiorespiratory fitness, and arterial stiffness over time in children, using data from the Physical and Nutrition in Children (PANIC) Study. It is a physical and dietary intervention study conducted in Kuopio, Finland. A total of 504 children participated at baseline, 277 adolescents participated at 8-year follow-up, and 201 adolescents were available for data analysis. The study measured blood pressure before and after a maximal exercise test on an ergometer. The exercise test increased in intensity until the participant reached exhaustion, and blood pressure was measured again after the test. Wave Velocity (PWV) was only measured at 8-years follow up.

The main findings were that male adolescent (n=103) systolic blood pressure at rest in the supine position before to exercise, maximal workload during an exercise test, and systolic blood pressure immediately following exercise at baseline were significant predictors of pulse wave velocity in an 8-year follow-up ($p<.001^{b}$). Systolic blood pressure immediately after exercise ($p=.010$) and maximal workload during exercise ($p=.013$) were shown to be significant predictors of PWV in male adolescents only. Only females' fat mass ($p=.015$) and percentage of body fat ($p=.016$) was found to increase PWV, whereas males' lean soft tissue mass increased PWV ($p=.001$).

The findings support the notion that blood pressure regulation and weight management should be promoted from an early age, as prevention for early signs of atherosclerosis.

Key words: Atherosclerosis, blood pressure, endothelial function

Abbreviations

BMI	Body mass index
BP	Blood pressure
CF	Cystic Fibrosis
HDL	High density lipoprotein- cholesterol
HR	Heart rate
ICG	Impedance cardiography channel
IPG	Impedance plethysmography
LDL	Low density lipoprotein- cholesterol
NO	Nitric oxide
PA	Physical activity
PWV	Pulse wave velocity
Q	Cardiac output
SV	Stroke volume
VO_2	Oxygen consumption
VO_{2max}	Maximal oxygen uptake

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1. INTRODUCTION

Cardiovascular diseases cause premature death and serious health issues globally. Their genesis can be traced back to early childhood (McGill et al., 2000). In children, increased stiffness of arterial walls is one of the first signs of arteriosclerosis (Fernhall & Agiovlasitis, 2008). The stiffening of an arterial wall refers to the decreased elasticity and compliance of the artery in response to pressure changes (Zieman et al., 2005). Aging, repetitive stress, systemic inflammation, smooth muscle media calcification, altered cellular signaling, and endothelial dysfunction often lead to fractures in elastin, resulting in decreased arterial elasticity (Zieman et al., 2005). The emergence of arterial stiffening in childhood can be concerning as it is associated with cardiovascular morbidity and mortality in adulthood (Palombo & Kozakova, 2016).

Despite the common belief that young children are healthy, research has shown a high incidence of obesity and inactivity, which increase the risk of cardiovascular disease, including arterial stiffening. The process of arterial stiffening in children is accelerated by other coexisting conditions like dyslipidaemia and obesity. (Panchangam et al., 2018) Studies in children have found a direct association between elevated blood pressure and arterial stiffening (Hidvégi et al., 2012).

Pulse wave velocity (PWV) is the gold standard for evaluating arterial stiffness and predicting cardiovascular disease risk (Boutouyrie et al., 2021). PWV is typically measured using a device called a tonometer, which uses pressure sensors to detect the pulse wave at two different points on the arterial system, typically the carotid artery and the femoral artery. The time it takes for the pulse wave to travel between these two points is then used to calculate the PWV.

PWV has also been studied in paediatric populations, with some studies finding that higher PWV values are associated with an increased risk of cardiovascular disease in children and adolescents (Ryuno et al., 2016; Wang et al., 2019). These findings highlight the importance

of monitoring arterial health in young populations and the potential value of interventions aimed at reducing arterial stiffness in adolescents.

Longitudinal studies investigating the connection between blood pressure and arterial stiffness in paediatrics are limited in number. This study investigated the associations between body composition, resting and exercise blood pressure with arterial stiffness measured 8-years later among school-aged children from a cohort of Physical and Nutrition in Children (PANIC) Study conducted in Kuopio, Finland. The study investigated whether differences in fitness and blood pressure response can be used to predict arterial stiffening 8-years later. This review of the literature will address several topics regarding paediatric cardiovascular health. This includes the cardiovascular system and diseases in paediatrics, acute physiological and vascular responses to exercise, and the relationship between the cardiovascular system and arterial health.

2. CARDIOVASCULAR SYSTEM IN PAEDIATRICS

The physiological responses of the cardiovascular system to endurance exercise are truly remarkable. The cardiovascular system consists of the heart, blood, and blood vessels. The system is not only sophisticated and complex in nature but is also fine-tuned in response to the growing metabolic, thermal, and biochemical demands of the working muscles (Rowland et al., 2018). From foetal to neonatal period and infant to early childhood period, the cardiovascular system undergoes extensive changes. Therefore, it is only logical that cardiovascular physiology differs in young children, adolescents, and adults.

Veins, capillaries, and arteries are the major components of the vascular system, which pumps blood throughout the body (Martini & Bartholomew, 2020). Arteries carry blood from the heart to the capillaries. Circulating blood is in contact only with the tunica intima layer of the vessel. This layer is made of simple squamous epithelium, called the endothelium. The intermediate layer of the vessel, the tunica medium, is made up of smooth muscle and elastic connective tissue, which enables the constriction or dilation of arteries. Both intima and media layers play a key role in blood flow and pressure regulation. The medulla and autonomic nervous system regulate changes in the diameter of blood vessels. Tunica externa is a fibrous connective tissue layer that forms the outermost layer, and it is particularly strong and thick to avoid vessel ruptures under high pressure. (Martini & Bartholomew, 2020)

The major function of the heart, which is part of the cardiovascular system, is to circulate blood through the arteries, capillaries, and veins. During a cardiac cycle, a series of events occur to result in a heartbeat. A cardiac cycle is formed when the atrial systole is followed by a ventricular systole a hundredth of a second later. Systole refers to the contraction phase, and diastole refers to the relaxation phase of the cardiac cycle. Cardiac output is the volume of blood expelled by the left ventricle of the heart per minute (Q). Q is a function of the amount of blood that the ventricle pumps per beat (stroke volume; SV) combined with the heart rate (HR). (Rowland et al., 2018)

$$Q = SV \times HR$$

During strenuous exercise, a healthy young person's heart output can reach a maximum of four times their resting level yet will still be lower on average than adults, partly because young people have a lower SV (Martini & Bartholomew, 2020; Rowland, 1990) and smaller heart size (Washington et al., 1994). A decrease in stroke volume (SV) can be partially compensated for by an increase in heart rate (HR) to meet the metabolic demands of active muscles. The maximum HR of children and adolescents ranges from 195 to 200 beats per minute (exercise modality dependent). The HR of adults decreases with age (Tanaka et al., 2001) as it becomes less effective, resulting in a lower maximal Q. However, age may not affect the resting levels of HR.

Greater physical activity during childhood and adolescence has been linked to a lower incidence of obesity and cardiovascular disease, as well as improved musculoskeletal and mental health (Ortega et al., 2008). The heart and cardiovascular function are dependent on physical activity and fitness. Evidence has shown that children and adolescents' physical activity (PA) has decreased by half since 2020 all around the world, including in Finland, and even more in some due to the 2019 coronavirus pandemic (Ng et al., 2021). he incidence of overweight and obesity in children and adolescents in Finland has risen from 1974 to 2001. In Finland, the National Institute of Health and Welfare recently reported that 30% of adolescent boys and 21% of adolescent girls are overweight (Vuorela et al., 2011). Low PA rates in childhood predicts morbidity and mortality in later years (Shephard et al., 1968). This literature review will examine the role of physical inactivity and cardiovascular fitness and its predecessors on children's cardiovascular systems, more specifically their arterial health.

2.1. Paediatric Arterial Health

Cardiovascular risks in paediatrics can set the stage for future cardiovascular disease such as atherosclerosis in the future (Celermajer et al., 1993, 1994). Therefore, having healthy and functioning arteries are important to combat cardiovascular disease that could lead to early morbidity and mortality (Faxon et al., 2004). In order to have healthy and functioning arteries, an individual must combat risk factors that negatively affect the functioning of the endothelium. The endothelium was long thought of as a passive membrane that prevented macromolecule diffusion, but is now understood to be an important endocrine, autocrine and paracrine organ

(Esper et al., 2006). Healthy endothelium prevents platelets from accumulating in arteries, supports smooth muscle cell growth, and promotes adhesion and diapedesis of leukocytes through vascular walls (Hansson, 2005). Leukocytes exit the bloodstream by the process of diapedesis, which involves their breaking through the endothelium monolayer (Schoppmeyer & van Buul, 2021).

The endothelial lining also produces nitric oxide (NO), a relaxing factor derived from the endothelium. Nitric oxide (NO) is a molecule produced by the endothelial lining of blood vessels that plays several crucial roles in physiological functions. One of its key roles is as a vasodilator, meaning that it relaxes smooth muscle in the walls of blood vessels, leading to an increase in blood flow and a decrease in blood pressure (Hermann et al., 2006). This is important for preserving healthy arterial function because elevated blood pressure is a major contributor to cardiovascular disease (Chobanian, 2003). NO also has several other effects on the arterial system. For instance, it has been demonstrated to prevent the formation of plaque in arterial walls, thereby reducing the risk of arterial blockages, heart attack, and stroke (Gori, 2020).

Endothelial dysfunction can be simply explained as an imbalance between vasodilating and vasoconstricting substances produced by or affecting the endothelial cells (Deanfield et al., 2005). Endothelial cells are directly exposed to harmful factors such as BP and elevated lipid levels, which are common in obese individuals. Low levels of PA and excessive body fat in children and adolescents have been linked to endothelial dysfunction and arterial stiffening (Hopkins et al., 2011; Schack-Nielsen et al., 2005). Excessive body fat can impair endothelial function by high levels of low-density lipoprotein (LDL)-cholesterol by decreasing NO bioavailability (Faxon et al., 2004). On the other hand, high-density lipoprotein (HDL) cholesterol has shown to have positive effects on macrophage cholesterol efflux and NO production by the endothelium, and it can be used to treat patients with coronary artery disease and diabetes (Bruyndonckx et al., 2013). Childhood endothelial dysfunction may have lifelong health consequences. Researchers have discovered that childhood PA deficiency increases arterial stiffness in adolescence and adulthood (Chen et al., 2012; Pälve et al., 2014). Despite these findings, there is debate about the relationship between PA and arterial stiffness and in children (Sakuragi et al., 2009; Walker et al., 2013).

Endothelial dysfunction can be reversed and PA activity can assist in its reversal. Research suggests that participating in high-intensity PA can decrease arterial stiffness and improve endothelial function in children as well as in adults (Ashor et al., 2015; Haapala et al., 2017). In addition, PA may reduce adiposity and traditional cardiometabolic risk factors and enhance NO bioavailability, resulting in improved arterial stiffness and endothelial function (Gielen et al., 2010).

Regardless of cardiovascular disease status, the elasticity of blood vessels tends to decrease with age (Vaitkevicius et al., 1993). As a result, major blood vessels can no longer adequately expand in response to increases in pressure. The loss in arterial compliance that occurs as people age, as well as the lesser change in arterial diameter, appears to represent an independent risk factor for the development of cardiovascular disease (Joyner, 2000). Stiffening of the arteries can lead to ventricular hypertrophy, dilation of the aortic root, valve dysfunction, and heart failure (Arnett et al., 1994; Avolio et al., 1985; Tanaka et al., 2001). Adults with higher arterial stiffness have been found to be at higher risk for cardiovascular events, but there is currently insufficient evidence for children. Despite the lack of evidence, it is possible to identify impaired elastic properties of large arteries in young patients before the wall stiffens or before it occurs (Celermajer et al., 1992).

The onset of endothelial dysfunction, a forerunner to atherosclerosis, at an early age predicts cardiovascular disease and is exacerbated by obesity in children and adolescents (Celermajer et al., 1993, 1994). Other comorbidities accelerate cardiovascular disease as well, such as diabetes mellitus, hypertension and dyslipidaemia (Copeland et al., 2009). Since early risk factors of cardiovascular events can be identified in childhood, early prevention is possible and critical.

2.2. Arteriosclerosis

Arteriosclerosis refers to the stiffening of arteries and encompasses several diseases and pathological processes. At present, arteriosclerosis is classified according to three conditions: atherosclerosis, arteriolosclerosis and Monckeberg's medial calcific sclerosis, (Kumar et al., 2015). A rare, low-prevalence disease, Monckeberg's medial calcific sclerosis causes calcification of the elastic lamina of the small and medium arteries of the extremities as well as

the visceral vessels (Cuevas Castillo et al., 2020). Aging and comorbid conditions such as type 2 diabetes and renal dysfunction, as well as hormonal disorders and vitamin deficiencies are associated with the condition. The triggering causes of the condition are still unknown (Lanzer et al., 2014). Some studies link arteriosclerosis to aging and its related pathologic conditions like diabetes, osteoporosis, and renal failure (London, 2003).

Hypertension and diabetes are typically associated with arteriolosclerosis, which refers to the hardening of the walls of very small arteries by intimal fibromuscular tissue or deposits of hyaline (Fishbein & Fishbein, 2015). Arteriolosclerosis and Monckeberg's medial calcific sclerosis are prevalent among patients with chronic kidney disease, but they are less common in children or adolescents. Conversely, early signs of atherosclerosis can be detected in young individuals, as discussed in the following chapter (Vervloet & Cozzolino, 2017).

2.3. Atherosclerosis

Several of the most common cardiovascular diseases are caused by atherosclerosis; including coronary artery disease, carotid artery disease, and peripheral arterial disease, and are the leading cause of morbidity and mortality (Faxon et al., 2004). The disease progresses in the intima layer of large arteries over many years, with mortal outcomes after many decades (Griffin, 1999). Lesion-induced narrowing of artery lumens can be described as atherosclerosis. Not only is atherosclerosis a lipid deposition disorder but it is also a chronic inflammation characterised by lipid and fibrous element build-up on arterial walls (Lusis, 2000).

As a lipid-driven process, atherosclerosis is primarily caused by the accumulation of LDL and leukocytes in the vessel wall, leading to loss of vascular function and stenosis, narrowing of the blood vessel. As LDL enters the subendothelial space and becomes oxidized, the formation of foam cells is formed as illustrated in Figure 1. Whenever a vessel wall becomes stenotic, it disrupts the laminar flow of blood and, as the accumulation of these substances continues over time, the vessel may become completely occluded by a clot, resulting in acute myocardial infraction, stroke, and death. (Lusis, 2000)

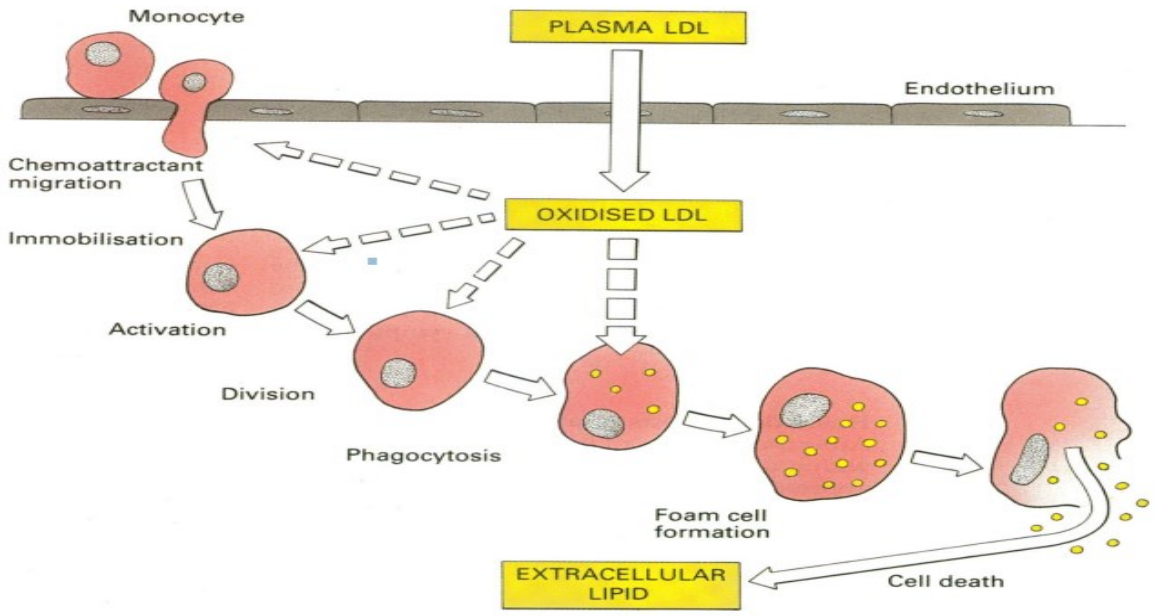

FIGURE 1. Illustration of Low-Density Lipoprotein (LDL) Oxidisation in Subendothelial Space and Forming Foam Cells (Davies & Woolf, 1993).

Early indications of arteriosclerosis, such as arterial stiffness and endothelial dysfunction, have been identified in children and adolescents, marking the start of this condition at a young age (Vervloet & Cozzolino, 2017). For some time, it has been known that pathological arterial processes, such atherosclerosis, begins in childhood and adolescence. Additionally, high blood cholesterol, hypertension, hyperglycaemia, smoking, and male gender contribute to its progression in youth (Böhm & Oberhoffer, 2019). Adolescents with low cardiorespiratory fitness have higher arterial stiffness in the carotid and femoral arteries, as well as thicker aortic intima media (Ferreira et al., 2003; Pahkala et al., 2013). On the other hand, better cardiorespiratory fitness in adolescence is associated with lower arterial stiffness and thinner carotid intima media thickness in middle adulthood (Ferreira et al., 2002). Those with physical disabilities or chronic conditions are more likely to develop endothelial complications, which can develop into atherosclerosis in the future (Cheung, 2010; Rimmer & Rowland, 2008). Studies suggest that the increased risk is due to lower levels of cardiorespiratory fitness and physical activity, as well as increased adiposity and obesity (Kotte et al., 2013; Neter et al., 2011). However, according to research by Martin et al, (2012), there was no difference in

arterial structure or function between children with cerebral palsy and those with typical development, despite comparable levels of body fat and physical activity.

3. ACUTE CARDIOVASCULAR RESPONSE TO PHYSICAL ACTIVITY IN NORMAL AND CHRONIC CONDITIONS

The cardiovascular system plays a crucial role in the body's ability to respond to increased demands during physical activity. It is widely believed that most of the increase in cardiac output (Q) during physical activity at intensities above 50% of the maximal capacity of the pulmonary and cardiovascular systems (VO_{2max}) is due to an increase in HR (Takken et al., 2017). HR increases linearly with rate of work until 75% of VO_{2max} and then may eventually plateau at maximal intensities in some (Turley, 1997). However, it is important to note that HR response is influenced by factors like body position, type of exercise, sex, fitness, age and environment (Washington et al., 1994).

Due to their smaller hearts, both boys and girls have a lower SV, which necessitates a higher HR at a given intensity of exercise; hence, a higher maximum HR than those of adults (Washington et al., 1994). A smaller SV of the left ventricle can limit the efficiency of the oxygen transport system (Takken et al., 2017). For a given exercise intensity, children might have a HR of 40-60 beats/min higher than adults (Turley & Wilmore, 1997). Post-puberty, females have higher HR than their male counterparts at any given intensity (Washington et al., 1994). Childhood obesity has been found to increase submaximal HR to those of healthy weight (Washington et al., 1994). Not only does childhood obesity increase submaximal HR, but among overweight and obese children of both sexes, SV were greater than among healthy weighted children (de Simone et al., 1997). An increase in levels of body fat mass decreases VO_{2max} (Rowland et al., 2018).

With progressive exercise, SV initially increases by approximately 25% at low intensities, then remains stable until exhaustion as seen in the control group of Figure 2 (Rowland et al., 2018). It is assumed that after 50% of VO_2, SV remains constant and HR becomes increasingly responsible for increases in Q (Takken et al., 2017). Similar responses occur in otherwise healthy individuals with high or low aerobic fitness levels. However, SV can decline with increasing exercise intensity in individuals with myocardial dysfunction due to a decrease in the capacity to produce contractile force while workload or intensity increases (T. Rowland et

al., 1999) (Figure 2). Hence SV response during exercise can be used as a methodology to detect myocardial dysfunction (Rowland et al., 2018).

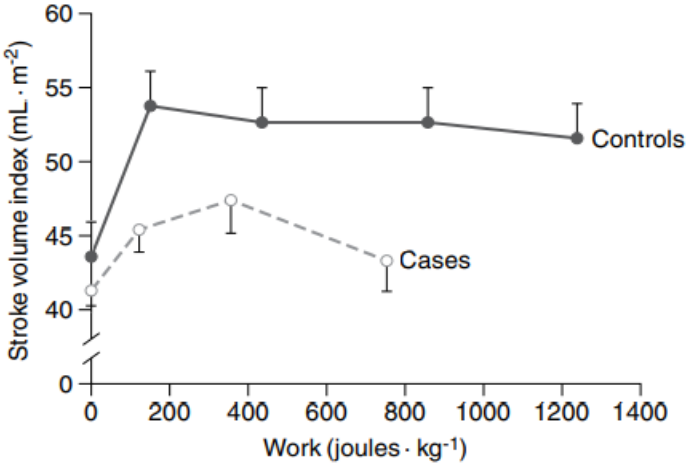

FIGURE 2. Stroke volume response to upright exercise was evaluated in children and adolescents with myocardial dysfunction (T. Rowland et al., 1999)

Numerous disorders have an impact on myocardial function that result in a reduction in SV. As an example, aortic or pulmonary stenosis create outflow obstruction; cardiomyopathies and obesity negatively affecting contractility; and disorders that result in a decreased forward SV, like ventricular septal defect (Bar-Or & Rowland, 2004). It is important to note that a low SV at peak exercise does not suggest poor myocardial function, since a low SV at peak exercise is found in both children with impaired myocardial function and with low aerobic fitness (Rowland et al., 2018).

Oxygen transport is accelerated as a result of increase in Q, ventilation rate, and arteriovenous oxygen difference (Takken et al., 2017). A plateau in oxygen consumption (VO_2) in children is rarely seen, therefore the peak VO_2 is most often assessed maximal cardiorespiratory capacity (Armstrong et al., 1996). The significance of the difference in arteriovenous oxygen levels and the ability of blood to transport oxygen during physical activity cannot be overstated. The term 'arterial-venous oxygen difference' refers to the variation in oxygen concentration between arterial and venous blood. This difference illustrates the amount of oxygen that has been extracted and utilized by the muscles and tissues during exercise. Prepubescent boys and girls have the same arteriovenous oxygen levels during maximal exercise, but post pubescent boys

have higher levels (Obert et al., 2003; Rowland et al., 2000). "It has been observed that, even in adulthood, men exhibit higher sub-maximal and maximal arteriovenous oxygen differences compared to women. Conversely, during sub-maximal physical activity, children tend to show higher oxygen difference levels compared to adults (Turley & Wilmore, 1997). This may be due to children's ability to compensate for their low Q by extracting more oxygen from the blood.

There is evidence that haemoglobin concentrations differ between sexes as we age. Both boys and girls exhibit similar haemoglobin concentrations prior to puberty (13.5 gm/dl), but the concentration for boys increases by around 12% at age 16. For girls, the concentrations tended to plateau at about 14 gm/dl concentrations (Dallman & Siimes, 1979). The sex difference on haemoglobin concentration is independent of iron status, and the higher male haemoglobin levels are also observed to occur in most mammal species (Kane et al., 2012; Yip et al., 1984). According to Murphy, (2014), this discrepancy may be explained by the direct effects of sex hormones on erythropoiesis, both oestrogen and androgen. Asthma, cyanotic heart disease, anaemia and hemoglobinopathies are among the conditions that impair oxygen carrying capacity (Bar-Or & Rowland, 2004).

3.1. Blood pressure response to acute exercise

In paediatric exercise testing, blood pressure is a commonly measured physiological response. The response of arterial BP to exercise is a crucial aspect of physiology, which is influenced by both systemic vascular resistance and Q(Sasaki et al., 2021). An increase in exercise intensity increases VO_2 and Q, which in turn increases BP. Age, body surface area, race, sex, and physical fitness all influence BP responses (Rowland et al., 2018). As body size and age play a key role, children have lower systolic and diastolic BP at rest and while exercising at any given intensity than adolescents and adults (Swan, 1998; Wanne & Haapoja, 1988). BP levels continue to increase in childhood and do not stabilise till the end of adolescence (Gidding et al., 1995).

A longitudinal study investigated the changes in peak systolic BP patterns between ages of 7 to 17 during a modified Bruce protocol CPET on a treadmill (Sasaki et al., 2021). Researchers found that peak systolic BP increased with age in both sexes, but to a greater extent in boys. One possibility is that there are differences in the physiological responses to exercise between the sexes. For example, it has been suggested that males may have a greater cardiovascular response to exercise due to higher levels of hormones such as testosterone, which can increase cardiac output and blood pressure. No gender differences have been observed in diastolic BP at peak levels or mean levels and the difference between the two only amounted to 18 mmHg between age groups. (Møller et al., 2010)

During exercise, a rapid rise in HR is initially a result of an increase in sympathetic nervous system activity (Rowland et al., 2018). Q rises rapidly in response to metabolic demand and peripheral resistance falls as a result of vasodilation of working muscles. As the increase in Q is greater than the decrease in vascular resistance, BP rises. Arterial baroreflex responds fast to the increased BP and provides continuous buffering of BP fluctuations and is required in keeping elevated BP levels during exercise (Benarroch, 2008). The systolic BP will typically rise curvilinearly during incremental exercise, plateauing towards the maximum effort (Schultz et al., 2017). Metabolic reflexes and vasoconstrictive mechanisms contribute to the high BP during moderate to vigorous exercise. Post exercise, the reduction in Q and systolic BP is due to the reduction of sympathetic activity and an increase in vagal tone (Rowland et al., 2018).

3.2. Blood pressure response to acute exercise for people with Chronic Conditions

People with chronic conditions may not have the same acute vascular response to exercise as healthy individuals due to changes in their vascular and respiratory physiology. This can affect their blood pressure response and exercise tolerance. Chronic conditions can lead to structural and functional changes in the blood vessels and cardiovascular system, which can alter the body's response to physical activity. Understanding these physiological changes can help identify interventions for improving exercise tolerance in the following populations.

Cystic Fibrosis

Cystic Fibrosis (CF) is recognised as a pulmonary disease associated with reduced airway function (Baño-Rodrigo et al., 2012). Although cardiovascular complications have been poorly described, there is evidence to suggest there are abnormalities in right ventricular systolic and diastolic function in adolescence with CF (Baño-Rodrigo et al., 2012). Children with CF may have enlarged left ventricles due to changes in blood flow and increased pulmonary resistance, which places an extra demand on the right ventricle (Morgan, 1967). During exercise, adults with CF had similar HR and BP responses at 60%max HR but had significantly higher left ventricular wasted pressure energy (Hull et al., 2011). However, there have been few paediatric studies on BP response in children with CF. There is evidence that CF patients have a reduced alveolar membrane diffusion capacity during rest and during exercise (Godfrey & Mearns, 1971). Exercise increases blood flow into the lungs, which is not adequately met by poor alveolar membrane diffusion capacity, resulting in low oxygen saturation (Godfrey & Mearns, 1971). Due to the cardiorespiratory constraints and alveolar diffusion capacity, there is a decrease in exercise tolerance.

Aortic Stenosis

Aortic stenosis is a condition whereby the left ventricular ejection time is prolonged at rest and in exercise. When an aortic valve stenosis progresses, systolic BP response decreases significantly. In some cases, peak exercise systolic BP may only rise by 20 mmHg above resting levels, and, in severe cases, it may even fall below resting levels (Rowland et al., 2018). A maximal treadmill exercise test was conducted on 29 adolescents of the age of 11.8± 3.9 (SD) (Alpert et al., 1982). Among participants with aortic stenosis, systolic BP increased by 30.3 mmHg from resting levels, whereas controls had an increase of 43.1 mmHg. In summary, adults and adolescents with aortic stenosis have smaller BP in responses to acute exercise.

Sickle Cell Disease

Children with sickle cell disease appear to exhibit lower exercise values of their BP and reduced peak VO_2 (Das et al., 2008). At rest as well as during exercise, children with sickle cell disease show left ventricular systolic dysfunction, a finding also observed in cystic fibrosis, and other cardiac abnormalities (Lester et al., 1990; Zilberman et al., 2007). A submaximal cycle ergometer test was conducted on 61 sickle cell disease patients of ages ranging from 5 to 23 years. According to the results, patients with ST segment depression on the electrocardiogram wave responded with higher systolic BP. It is suggested that a depression in the ST segment may be associated with myocardial ischemia and decreased oxygen supply (McConnell et al., 1989).

Type 1 diabetes

Individuals with Type 1 diabetes have a reduced vasodilator response during dynamic exercise. A maximal cycle ergometer test was undertaken with 15 healthy weight normoglycemic controls, 23 overweight/obese normoglycemic controls and 23 adolescences with dysglycemia (Matteucci et al., 2006). The BP response during exercise increased in adolescents who were obese and dysglycemic, despite working at lower workloads. We can conclude from this study that systolic BP response to maximal exercise is similar in dysglycemic adolescents and obese adolescents.

Renal transplant

Although kidney transplantation reduces the risk of cardiovascular mortality and illness, it has been shown to cause an increase in blood pressure after the procedure (Neale, 2015; Stoumpos et al., 2015). Following renal transplantation, children's exercise tolerance and BP response to

treadmill exercise were evaluated by Giordano et al, (1998). In comparison with healthy controls, transplant patients had a higher HR, higher maximum systolic BP, and a lower exercise tolerance.

3.3. Endothelial response to acute exercise

Acute exercise has been shown to alter endothelial function. Shear stress, which plays a crucial role in stimulating NO production, is a significant for vascular remodelling and blood vessel formation (Resnick et al., 2003). The increase in blood flow to working muscles during exercise causes increased shear stress in the vessels supplying blood to the active cardiac and skeletal muscles (Laughlin et al., 2008). As a result of increased shear stress during exercise, endothelial NO synthase, messenger RNA, and protein expression levels rapidly increase (Haram, 2008). In response to moderate exercise, increases in shear stress stimulates endothelial NO production and subjacent smooth muscle cell vasodilation. After prolonged exercise, vessels adapt structurally partly by NO-mediated remodelling, resulting in a drastic increase in vessel diameter (Di Francescomarino et al., 2009). The exercise-induced vasodilation is also attributed to several endothelial-dependent vasoactive compounds, such as prostaglandin I2 (inflammation mediating hormone) and endothelin-1 (potent vasoconstrictor peptide) (Di Francescomarino et al., 2009).

Endothelium also produces prostacyclin that mediates vasodilation (Deanfield et al., 2007). As BP drops after exercise, the endothelium produces NO to prevent excessive myogenic vasoconstriction (Levick & Michel, 2010). Adults exhibit a greater vasodilator response to high intensity exercise than adolescents (Birk et al., 2012). Repeated episodes of elevated blood flow during exercise may improve endothelial function that would lead to long-term benefits of reducing complications of cardiovascular disease in youth and in adults (Hopkins et al., 2011).

3.4. Endothelial response to acute exercise in people with chronic conditions

Exercise may not incite the same acute vascular response as it does for people without chronic conditions such as hypertension, diabetes, and inactivity. Endothelial dysfunction is a key factor

in the development of atherosclerosis, which can be triggered by several factors such as high blood pressure, diabetes, dyslipidaemia, smoking, metabolic disorders, high salt intake, and physical inactivity. Therefore, impaired endothelial function may hamper exercise adherence and tolerance in the following populations.

Hypertension

Hypertension is a significant risk factor for atherosclerosis and can either cause or result from endothelial dysfunction. High BP can compromise the integrity of endothelial cells and lead to activation or dysfunction of these cells (Chobanian, 1996). High blood pressure during adolescence has the potential to negatively impact endothelial function in adulthood (Juonala et al., 2006). Hypertension impairs vascular endothelial NO bioavailability and endothelial function in adolescents and adults (Juonala et al., 2006; Panza et al., 1990). Aortic stiffening can increase as a result of endothelial dysfunction exacerbated by hypertension (Wallace et al., 2007).

However, hypertensive individuals can benefit from exercise as it can improve NO-dependent endothelial vasodilator function (Green et al., 2004). Significant increases in systolic BP may indicate an increased risk of hypertension in the future. Trained athletes tend to experience greater increases than untrained individuals, but this does not necessarily indicate the development of hypertension. Fortunately, short-term exercise has shown to reduce arterial stiffness in adults with hypertension (Madden et al., 2009).

Type 2 diabetes

Diabetes can negatively impact the endothelium's ability to release NO, which is a crucial aspect of endothelial function (Fuchsjäger-Mayrl et al., 2002). A comparison between obese and diabetic children and adolescents and their lean and BMI-matched peers was conducted by Naylor et al, (2016). Individuals with co-morbid obesity and diabetes showed early indicators of vascular dysfunction compared to lean and BMI- matched peers. However, the study showed improvements in endothelial function, NO mediated function, body composition and strength after a 12- week exercise intervention. These findings are backed by a study on adults, which showed that acute exercise resulted in significant reductions in vascular stiffness, thus enhancing endothelial function in individuals with type 2 diabetes (Madden et al., 2009).

Physical inactivity

A study by Abbott et al. in 2002 showed that in children aged 5-10, there is a strong correlation between endothelial function and physical activity. Another study showed that even as little as 5 days of reduced physical activity can negatively impact macrovascular endothelial function in young active men (Boyle et al., 2013). Furthermore, a decrease in vigorous PA over a period of 4-6 months was also observed to result in decreased endothelial function in children (Hopkins et al., 2011).

It is widely recognized that regular PA improves endothelial function in adults. Similar results have been observed in studies on children, where it has been shown that moderate to intense physical activity has a positive impact on endothelial function (Ascenso et al., 2016). PAcan improve endothelial function in children with obesity, even without changes in body mass index or weight (Penha et al., 2019; Watts et al., 2005).

4. RELATIONSHIP BETWEEN CARDIOVASCULAR FUNCTION AND ARTERIAL HEALTH

The relationship between cardiovascular function and arterial health in children is important for overall health. Poor cardiovascular function can lead to arterial dysfunction, and this can have a negative impact lead to several health problems, including heart disease and stroke. To ensure good arterial health, it is crucial to maintain a healthy cardiovascular system. Having an ideal level of cardiovascular health occurs when an individual does not smoke, exercises regularly, has a BMI of 25 or less, follows a diet consistent with national guidelines, has a total cholesterol level of 200mg/dl, a BP level of 120/80mm Hg, and has fasting blood sugar between 100 and 200 mg/dl (Crichton et al., 2014). The ideal cardiovascular factors and behaviours have shown to be identified as strong predictors of both all-cause mortality and circulatory system related diseases (Ford et al., 2012).

As discussed earlier, the onset of coronary artery diseases, such as atherosclerosis, can be identified in childhood. Atherosclerosis symptoms in adulthood are associated with childhood obesity, high BP, and serum cholesterol (Berenson et al., 1998). The negative health factors in childhood contribute to arterial stiffness and endothelial dysfunction, worsening arterial health. Changes to structural and functional characteristics of arteries can be measured to reflect the progression of cardiovascular disease (Thijssen et al., 2016).

Behavioural actions such as exercise, has been found to improve overall arterial health in children, adolescents, and adults. Children with high fitness levels are associated with improved cardiovascular function and arterial health (Agbaje et al., 2019; Hopkins et al., 2009). However, the lack of PA also impairs the function of endothelium in both children and adults (Hopkins et al., 2011; Boyle et al., 2013).

This literature review has identified several aspects of paediatric cardiovascular health, including physiologic and cardiovascular changes, acute physiological and vascular responses to exercise, and the relationship between the cardiovascular system and arterial health. Research has identified that PA can be used as a tool to reduce cardiovascular risks, improve endothelial function, and hinder the development of coronary artery diseases like atherosclerosis.

5. PURPOSE

The purpose of the present study was to provide new scientific insights into the association between blood pressure and arterial health and how fitness level affects a child's arterial stiffness in the future. Currently, there are very few studies investigating how blood pressure and fitness levels influence and predict arterial stiffness. This study investigated whether differences in blood pressure and fitness in young healthy children, can predict early signs of atherosclerosis. In Addition, the study investigated whether body composition could be used as independent predictor of arterial stiffness.

5.1. Research hypothesis

According to current literature, arterial stiffness can be observed as early as childhood. "Given the potential long-term effects of arterial stiffness, it is important to understand the factors that contribute to this condition and to identify strategies for preventing or mitigating its development. Research suggests that children with elevated blood pressure may have a heightened risk for arterial stiffness and other cardiovascular health risks. As arterial stiffness has been found to be significantly associated with blood pressure in children (Hidvégi et al., 2012), therefore, understanding the factors that influence blood pressure responses in children, and whether these responses are predictive of future cardiovascular risk, may provide important insights into the development of arterial stiffness and other cardiovascular conditions.

Another factor that may affect arterial stiffness in children is cardiorespiratory fitness. "Studies have indicated that children and adolescents with higher levels of cardiorespiratory fitness are correlated with lower levels of arterial stiffness (Noortman et al., 2019; Veijalainen et al., 2016). Therefore, understanding the relationship between cardiorespiratory fitness and arterial stiffness in children may provide important information for developing strategies to prevent or mitigate the development of arterial stiffness and other cardiovascular conditions in children and adolescents.

A greater maximal systolic BP response during exercise has been associated with endothelial dysfunction (Stewart, 2004) and carotid atherosclerosis in adults (Jae et al., 2006), and in children it has been linked to metabolic risk factors such as impaired insulin sensitivity and

adiposity (Møller et al., 2010). This suggests that higher maximal blood pressure response to exercise may be risk factors for the development of arterial stiffness. A recent study by Lona et al. (2022) showed a relationship between high levels of cardiorespiratory fitness and low levels of arterial stiffness in children and adolescents. This implies that those with high levels of fitness may have a decreased risk for the development of arterial stiffness, leading to better long-term arterial health outcomes.

The research questions and hypothesis regarding the research objectives were as follows:

1. Investigate the association between resting blood pressure and maximal blood pressure response to exercise and arterial health. My hypothesis is that there is a significant positive association between maximal blood pressure response to exercise and arterial stiffness.

2. Investigate the association between cardiorespiratory fitness, blood pressure at baseline, and arterial health in children at 8-year follow-up. My hypothesis is that children with higher cardiorespiratory fitness levels and high blood pressure response to exercise at baseline have better arterial health at 8-year follow-up compared to those with poor cardiorespiratory fitness and high blood pressure.

6. METHODS

6.1. Study design and population

The current study is based on 8-year follow-up data from the Physical and Nutrition in Children (PANIC) Study in Kuopio, Finland, which focused on the effects of physical activity and diet on primary school-aged children (see Figure 3 for detailed outline of intervention, and Figure 4 for study flowchart). The study was given approval by the Northern Savo Hospital District Research Committee, and parental consent and child assent were obtained for participation. A total of 504 children aged 6-9 years from primary schools in Kuopio were included in the study, which took place from 2007-2009. The inclusion criteria for the study were being a boy or girl, between the ages of 6-9 years, and living in Kuopio, Finland.

The exclusion criteria for the study were physical disabilities that would prevent a child from participating in the intervention, and lack of time or motivation to attend the study. The study included follow-up examinations at 2 and 8 years after the initial baseline assessments. For the 8-year follow-up, complete data on variables related to resting blood pressure, maximal systolic blood pressure, maximal watts, DXA lean soft tissue mass, DXA percent body fat, DXA fat mass, and pulse wave velocity (PWV) were available for 201 children (103 boys and 98 girls).

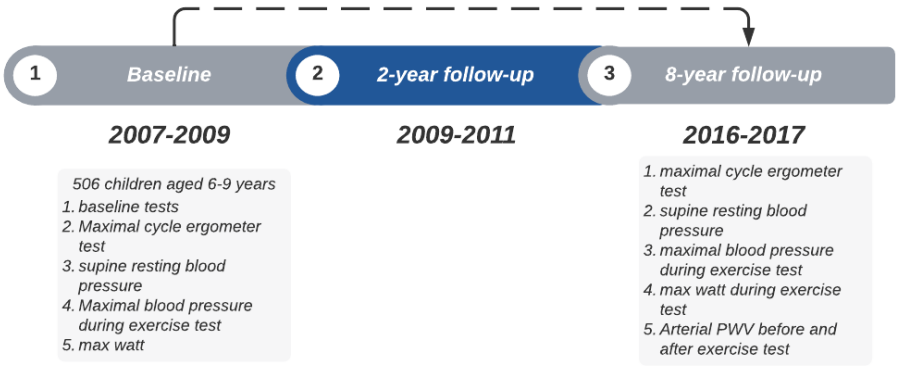

FIGURE 4. Detailed Timeline of Intervention

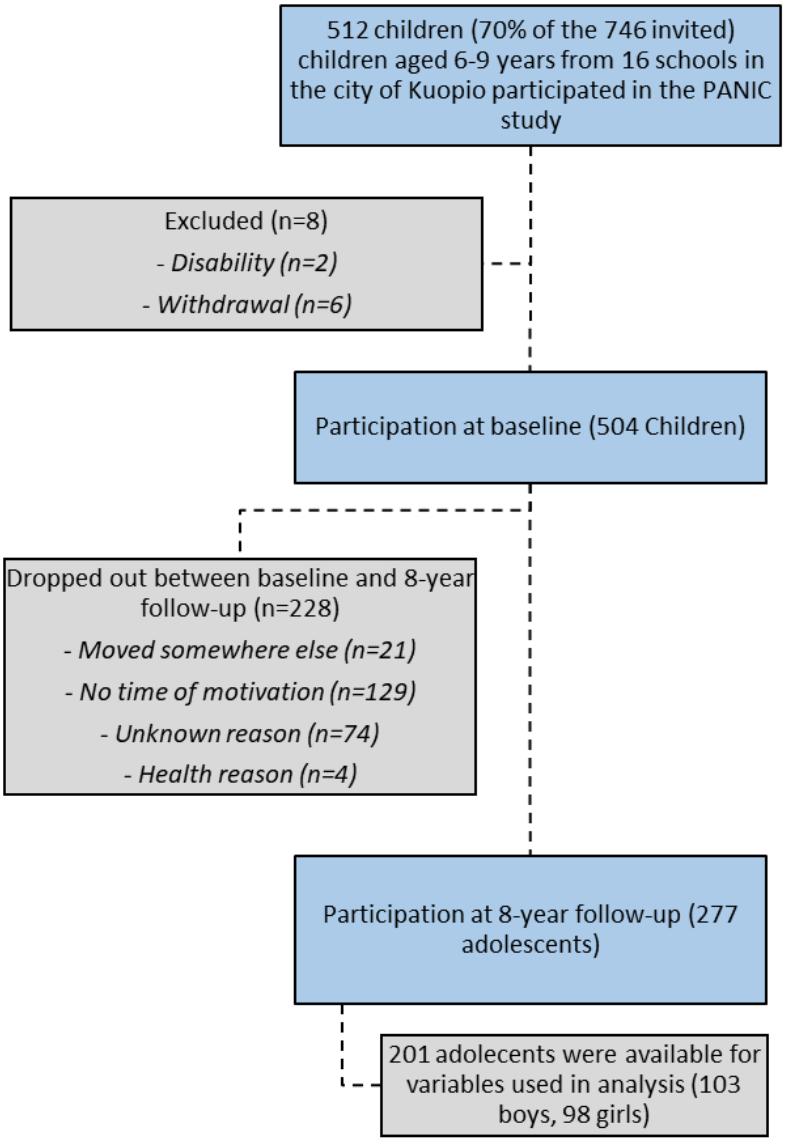

FIGURE 3. Flowchart of the PANIC study

6.2. Experimental design

Biometric data, body composition, maximal cycle ergometer performance, and blood pressure indices were all assessed at both baseline and at the 8-year follow-up. Arterial stiffness measurements were only conducted at the 8-year follow-up. Subjects for the study arrived at the Institute of Biomedicine's exercise and health laboratory after a 12-hour fast, accompanied by their parents or caregivers, to undergo the study procedures. They were instructed to avoid anti-inflammatory drugs, caffeine, and strenuous physical activity before the visit. If a child was sick or had a condition that could affect the test results, the visit was rescheduled. A research nurse measured the children's height and weight, and then the children's body weight was measured using a bioelectrical impedance device. This was all done in light clothing and after emptying their bladders to ensure accuracy.

After the initial measurements were taken, the children were offered breakfast and then allowed to rest to standardise conditions before the exercise test. The research nurse and physician provided instructions on how to perform the test, and the children were allowed to practice on the ergometer for 10 minutes before lying down. The children were instructed to lie down in a supine position for 15 minutes prior to the test. During this time, the research physician evaluated the arterial indices multiple times in the last 5 minutes.

The cardiorespiratory fitness of the children was evaluated using a maximal exercise test performed on a cycle ergometer equipped with electromagnetic brakes and a specialized saddle designed for children. The test was conducted using the Ergoselect 200 K cycle ergometer. The test began with a 2.5-minute period of preparation and a 3-minute warm-up at 5 watts. This was followed by a 1-minute steady-state period at 20 watts, a workload that gradually increased by 1 watt every 6 seconds until the child reached exhaustion. After the exercise, a 4-minute recovery period at 5 watts was completed. The test was considered maximal if the child was unable to maintain the cadence of 60-70 revolutions per minute and had reached the maximum effort and capacity of their cardiorespiratory system. After the exercise protocol was completed, arterial indices were measured again at least three times during a 5-minute period of supine rest. The parents and caregivers were allowed to be with their children during the assessments, including the exercise test.

The PWV was measured using the Circmon® B202 whole-body impedance cardiography device manufactured by JR Medical Ltd. The device works by measures the electrical conductivity of the body as an electrical current is passed through it using electrodes placed on the wrists and ankles, and a voltage electrode positioned 5 cm proximal from the electrode centres (see Figure 5). As the current passes through the body, it encounters resistance, known as impedance, from the tissues and fluids. Distal impedance plethysmography was performed from the popliteal artery utilizing an active electrode on the lateral knee joint and a reference electrode placed on the calf, with about 20 cm between the two electrodes. The CircMon software was used to estimate the impedance plethysmogram (IPG) signal and the foot of the impedance cardiography channel signal, which correspond to pulse transmission in the aortic arch and the popliteal artery, respectively. Before measurement, the participants were instructed to rest in a supine position for 15 minutes. PWV was then determined by the estimated distance (L) and pulse transit time (t) between the two recording sites using the following equation (Koivistoinen et al., 2011):

$$PWV\ (m/s) = L/\Delta t$$

A Heine Gamma Gamma® G7 aneroid sphygmomanometer was used to measure systolic and diastolic BP in the right arm to a precision of 2 mmHg. The participants' body composition, including lean mass (LM), body fat mass, and body fat percentage (BF%), were assessed using the Lunar Prodigy Advance DXA device and Encore software (both from GE Medical Systems). The measurement was performed in accordance with the manufacturer's standardized protocols and the same DXA device was used for all measurements.

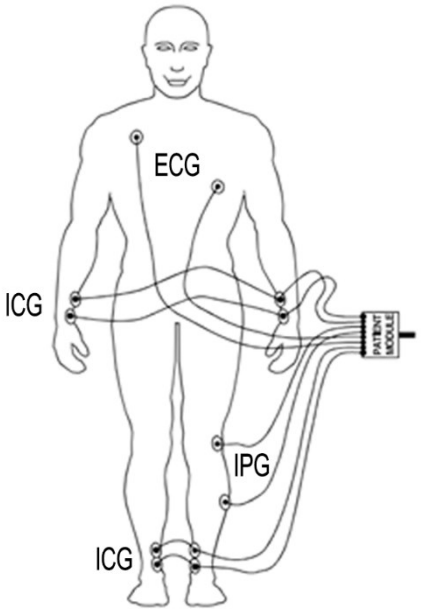

FIGURE 5. The placement of electrodes in whole-body impedance cardiography, including a voltage-sensing channel on the left calf, was used to measure PWV. The ECG was recorded simultaneously, and the difference in time between the ICG and IPG was used to determine the pulse transit time from the aortic arch to the popliteal artery.

6.3. Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics, Version 28 (IBM Corp., Armonk, NY, USA). The associations between PWV and systolic blood pressure post exercise, systolic blood pressure supine, maximal workload, maximal workload per kg of lean body mass, DXA lean soft tissues mass, DXA percept body fat and DXA fat mass were investigated with linear regression analyses adjusted for age and sex. Standardised coefficients were used to compare associations and unstandardized coefficient was used to get clinical findings. ANOVA Group Comparison was used to compare results in order to further analyse the relationship between differences in maximal blood pressure during exercise and maximal watt production on PWV across and between sexes. Subjects were split into four different groups : Girls High BP = <120mmHg, High Watt = <3.61w/kg LM, boys High BP= <1200mmHg, High Watts = < 3.81w/kg LM (see Table 4).

7. RESULTS

Female adolescent (n=98) systolic blood pressure at rest in the supine position before to exercise, maximal workload during an exercise test, and systolic blood pressure immediately following exercise at baseline were insignificant predictors of pulse wave velocity at the 8-year follow-up (significance value of p=.608) (TABLE 1. Independent variables at baseline in predicting pulse wave velocity in 8-year follow-up. In males (n=103), these predictors were shown be significant in predicting pulse wave velocity (p<.001[b]) (TABLE 1. Independent variables at baseline in predicting pulse wave velocity in 8-year follow-up

TABLE 1. Independent variables at baseline in predicting pulse wave velocity in 8-year follow-up. * p < 0.05 for statistically significant association.

ANOVA

Model	Female		Male	
Regression	df	Sig.	df	Sig.
	3	.603[b]	3	<.001*[b]

a. Dependent Variable: PWV_log

b. Predictors: (Constant), Systolic blood pressure at supine rest before exercise test at baseline (mmHg), Maximal workload during exercise test at baseline (W), Systolic blood pressure immediately (0.5 minute) after exercise test at baseline (mmHg)

Systolic blood pressure immediately after exercise (p=.010) and maximal workload during exercise (p=.013) were shown to me significant predictors of PWV in male adolescents (Table 3) (scatter plot of relationships displayed in Figure 6). Females fat mass (p=.015) and percentage of body fat (p=.016) was found to increase PWV, whereas males' lean soft tissue mass increased PWV unstandardised B (p=.001) (Table 3). Maximal workload per kg of lean body mass measured by DXA at baseline was not a significant predictor of pulse wave velocity in either females (p=.193) or males respectively (p=.836) (Table 3).

TABLE 2. Regression coefficients of both sexes. * $p < 0.05$ for statistically significant difference between measurement time points.

Coefficients

Model	Both sexes			
	Unstandardized B	Standardized Coefficients Beta	t	Sig.
Systolic blood pressure immediately after exercise (0.5 minute) after exercise test at baseline	.000	.109	1.494	.137
Systolic blood pressure at supine rest before exercise test at baseline (mmHg)	.001	.145	1.992	.048*
Maximal workload during exercise test at baseline (W)	-.001	-.187	-1.738	.084
Maximal workload per kg of lean body mass measured by DXA at baseline (W/kg)	-.009	-.105	-1.428	.155
DXA Lean Soft Tissue Mass at baseline (kg)	.006	.302	2.556	.011*
DXA percent Body Fat at baseline (%)	.001	.146	2.012	.046*
DXA Fat Mass at baseline (kg)	.001	.081	1.059	.291
Age at first baseline examination (year)	.016	.008	1.968	.051
Sexes	-.011	-.125	-1.516	.131

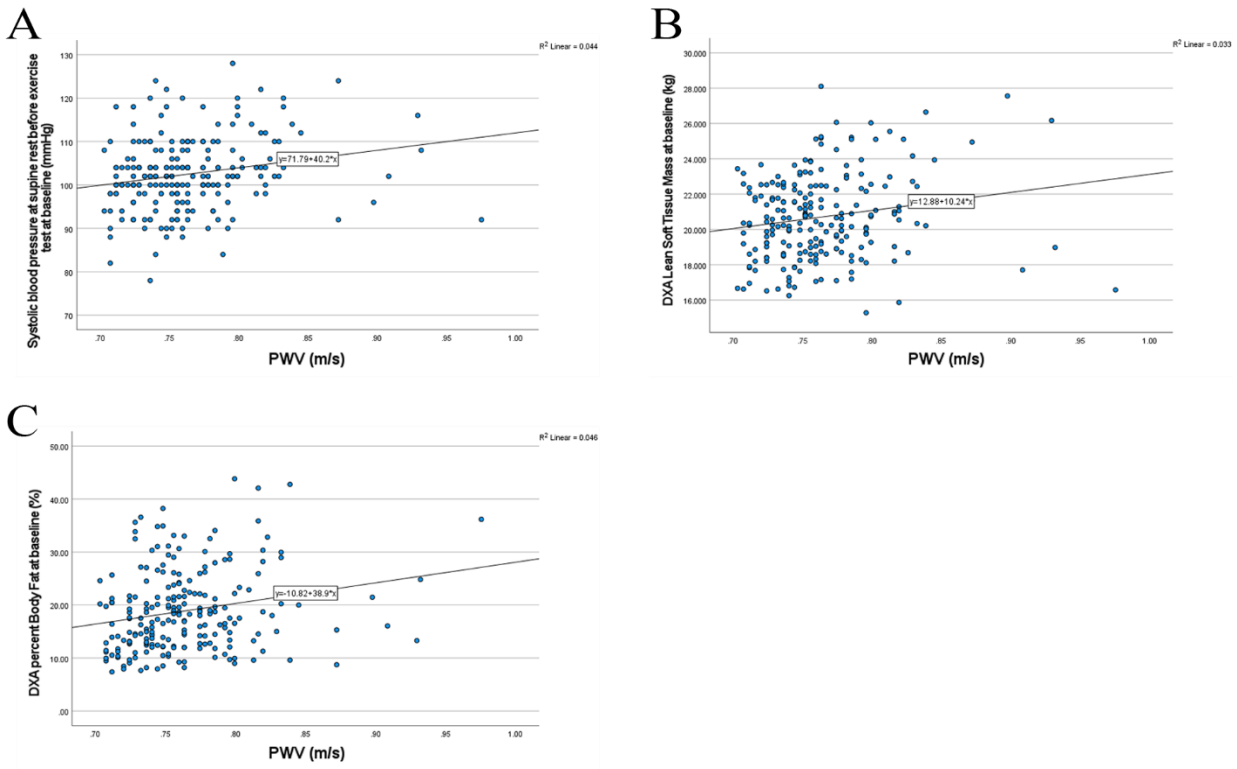

FIGURE 6. Regression analysis of PWV and dependent variables. (A) Relationship between PWV and systolic BP immediately after exercise test at baseline, (B) Relationship between PWV and DXA lean tissues mass at baseline, (C) Relationship between PWV and maximal workload during exercise test.

The linear regression analysis of both sexes only reveals substantial correlation of systolic blood pressure at rest before exercise (p=.048) and DXA lean soft tissue mass (p=.011) and percent of body fat (p=.046) at baseline in predicting PWV (Table 2) (scatter plot of relationships displayed in Figure 7). Lean soft tissue mass determined to be a significant predictor of PWV in both sexes in a regression analysis (p=.011) (Table 2).

TABLE 3. Regression coefficients of both female and male participants. * $p < 0.05$ for statistically significant associations.

Coefficients

Model	Female				Male			
	Unstandardised B	Standardised Coefficients Beta	t	Sig.	Unstandardised B	Standardised Coefficients Beta	t	Sig.
Systolic blood pressure immediately after exercise (0.5 minute) after exercise test at baseline	.000	.068	.618	.538	.001	.245	2.624	**.010***
Systolic blood pressure at supine rest before exercise test at baseline (mmHg)	.000	.098	.881	.380	.000	.139	1.369	.145
Maximal workload during exercise test at baseline (W)	-9.542E-5	-.027	-.260	.795	.001	.239	2.515	**.013***
Maximal workload per kg of lean body mass measured by DXA at baseline (W/kg)	-.012	-.139	-1.31	.193	-.008	-.083	-.408	.836
DXA Lean Soft Tissue Mass at baseline (kg)	.000	.008	.060	.952	.010	.483	3.372	**.001***
DXA percent Body Fat at baseline (%)	0.002	.262	2.473	**.015***	.000	.077	.797	.427
DXA Fat Mass at baseline (kg)	.004	.284	2.445	**.016***	-.001	-0.067	-.653	.515
Age at first baseline examination (year)	.013	.115	1.102	.273	.026	.205	2.184	**.031***

a. Dependent Variable: PWV_log

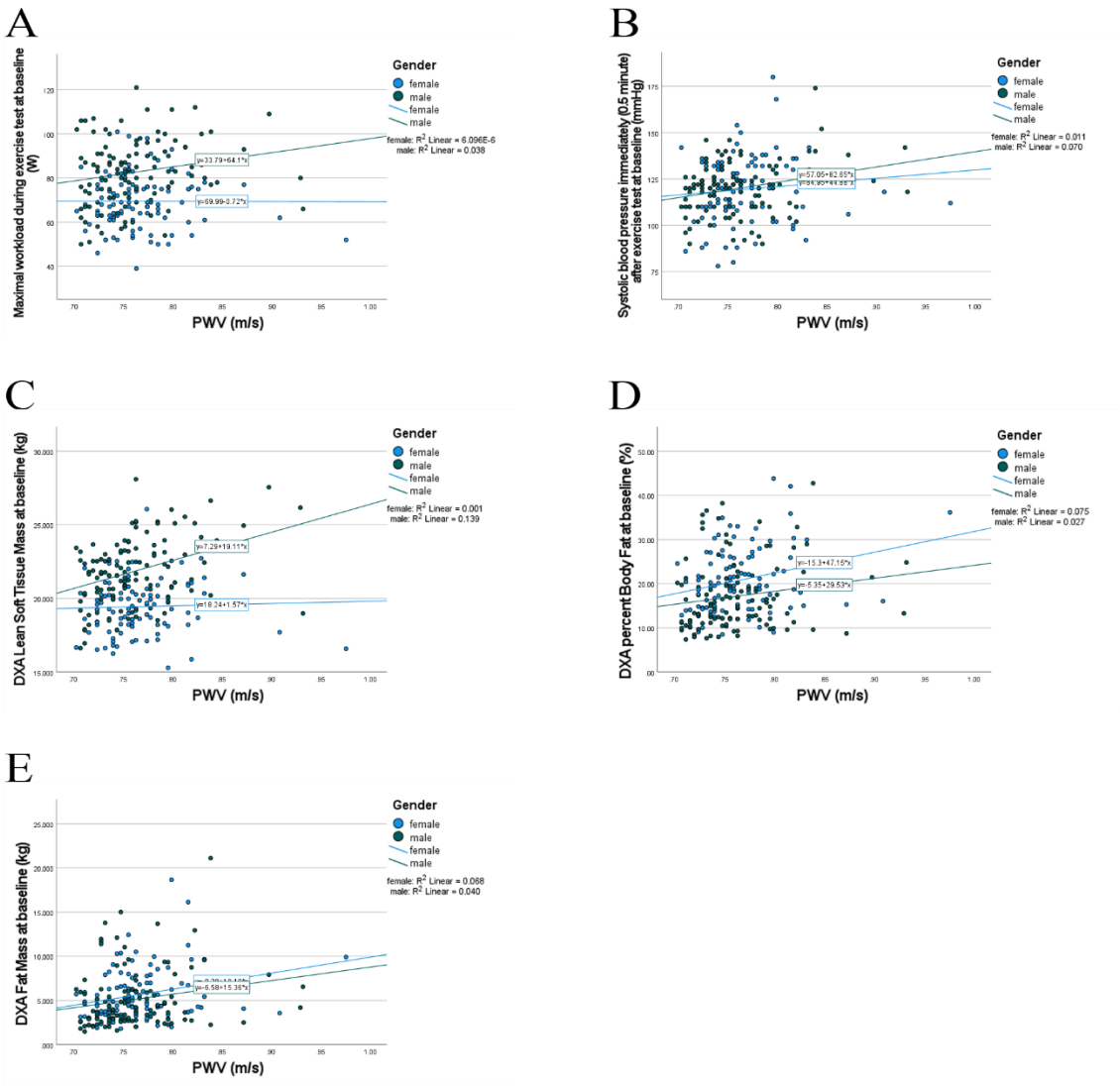

FIGURE 7. Regression analysis of PWV and dependent variables between the sexes. Female participants presented in blue, and male in green, (A) Relationship between PWV and maximal workload during exercise test, (B) Relationship between PWV and systolic BP immediately after exercise test at baseline. (C) Relationship between PWV and DXA lean tissues mass at

baseline, (D) Relationship between PWV and DXA percent body fat at baseline, (E) Relationship between PWV and DXA fat mass at baseline.

Group Comparison ANOVA was used to examine four groups controlled for sex. Number of participants in each group and sex shown in Table 4. There were no significant findings between sexes and no difference in subjects (Figure 8).

TABLE 4. Group comparison ANOVA between groups and sexes.

Group Comparison ANOVA	Male		Female	
Max workload per kg of lean body mass and max Systolic BP after exercise test	N	Mean PWV log (m/s)	N	Mean PWV log (m/s)
Group 1 Low Systolic BP, Low Watts	26	.757	23	.778
Group 2 Low Systolic BP, High Watts	27	.747	30	.757
Group 3 High Systolic BP, Low Watts	29	.776	23	.768
Group 4 High Systolic BP, High Watts	19	.771	21	.763

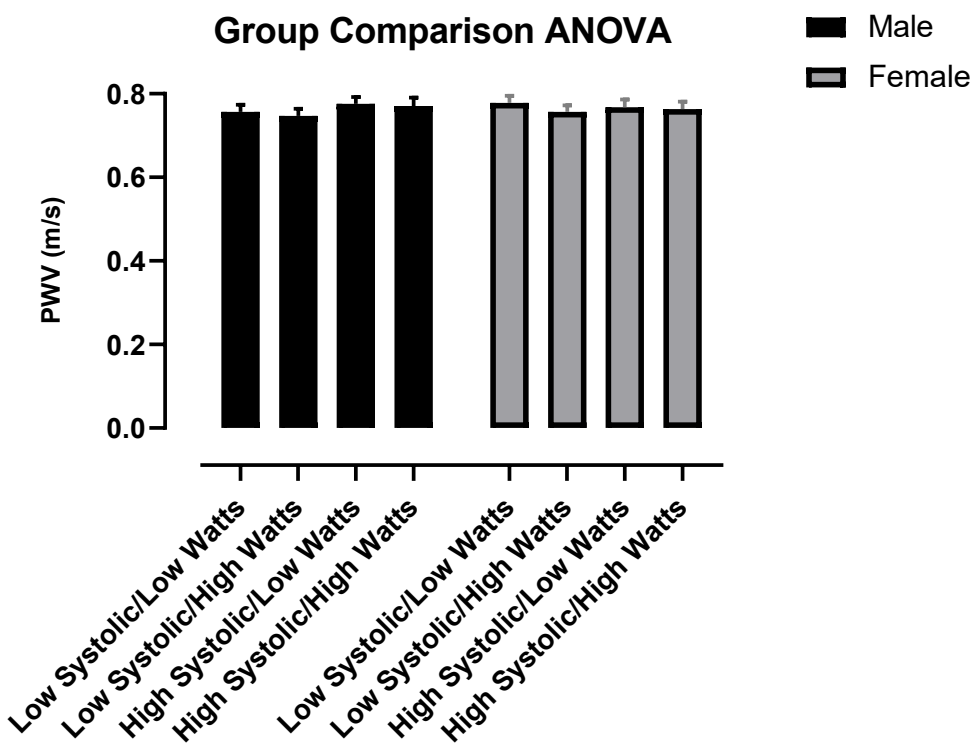

FIGURE 8. Group comparison ANOVA between groups and sexes. Values are means; box and whisker plot represent 95% Confidence Interval. 8-year follow-up PWV differences in sexes with different levels of systolic blood pressure immediately after exercise test at baseline and maximal workload per kg of lean body mass measured by DXA.

No significant differences were found in maximal systolic blood pressure immediately after exercise or maximal workload per kilogram of lean body mass at baseline when comparing the different groups and sexes in predicting arterial stiffening 8 years later.

8. DISCUSSION

This study investigated the association independent factors on PWV at follow-up in 201 adolescents. The aim of our study was to investigate the associations between resting blood pressure, maximal blood pressure response to exercise, cardiorespiratory fitness, and arterial health in children. We hypothesized that there would be a significant positive association between maximal blood pressure response to exercise and arterial stiffness, and that children with higher cardiorespiratory fitness levels and high blood pressure response to exercise at baseline would have better arterial health at 8-year follow-up compared to those with poor cardiorespiratory fitness and high blood pressure.

Increase in resting supine systolic BP was associated with higher PWV 8-years follow-up. These findings were consistent with findings by Lona et al, (2020) in a follow-up study on 262 prepubertal children who found that high BP in children predicts future cardiovascular disease events and mortality, even when adjusted for BP in adulthood. An increase in lean tissue mass was associated with an increase in PWV at follow-up, however sex disparities were revealed by regression coefficient analysis shows only boys had this strong association. It is challenging to interpret the differences between males and females when taking chronological age into account, as the development of vascular properties is influenced by the stage of maturation (Radtke et al., 2012). Boys generally experience puberty later than girls, and young athletes typically experience it later than their peers (Brix et al., 2019). The disparities in vascular properties between boys and girls may be due to differences in hormone levels. Boys experience an increase in testosterone during puberty, which activates the sympathetic nervous system and renin-angiotensin system, leading to higher systolic BP (Albin & Norjavaara, 2013). The higher testosterone levels may contribute to the variations in arterial stiffness and left ventricular mass between the sexes, providing a potential explanation for the disparities (Bittencourt et al., 2016).

The demographic of boys in our study and their athletic past could potentially play a role as well. The available evidence suggests that physical activity has a positive effect on the vascular health of healthy children and adolescents, with total physical activity being considered beneficial for the vascular characteristics in children and adolescents (Baumgartner et al.,

2020). However, It has been found that boys with a high exercise training length and intensity had greater carotid intima media thickness (Baumgartner et al., 2021).

There is also evidence that the type of exercise plays a decisive role in arterial stiffness. D'Andrea et al. (2012) conducted a study that involved 190 strength athletes, 220 endurance athletes, and 240 controls. The results showed that endurance athletes had better aortic distensibility compared to strength athletes and controls, while strength athletes had higher aortic stiffness than endurance athletes and controls. Considering our results, an increase in arterial stiffness in boys may be dependent on the type of exercise they engage in, with certain modalities potentially leading to higher degree of arterial stiffness compared to others. A recent study reported that better cardiovascular fitness in children was associated with a risk of developing arterial stiffness. Populations who engage in high intensity resistance training, increases in proximal aortic stiffness is often observed, and higher incidences of left ventricular hypertrophy is associated with greater arterial stiffness, which seems to be a normal physiological adaptation to exercise.

This study found that a higher percent of body fat was independently associated with higher arterial stiffness 8 years later. These findings are in line with those of an Australian study on 573 healthy elementary school students, which found that the percentage of body fat was independently linked to carotid-femoral PWV even after taking into account factors such as sex, age, and BP (Savant et al., 2014). It is worth noting that some studies have reported no correlation or even an inverse relationship between obesity and measures of arterial stiffness. However, these inconsistent results may be due to differences in methodology used in these studies (Herouvi et al., 2013; Lurbe et al., 2012). When the regression coefficient analysis was performed on the two sexes separately, there was a relationship between the body fat percentage and PWV in the female population. This finding contradicts the results of a study by Agbaje et al. (2019), which found no relationship between a girl's body fat content and arterial stiffness. One possible explanation for this discrepancy is that a higher body fat content may be associated with decreased arterial dilation ability, as suggested by Agbaje et al. (2019). Since more girls may have already attained puberty (at the time of the follow-up), It's possible that the disparity between the sexes in the connection between body fat percentage and PWV when it comes to exercise may be due to a greater increase in body fat content in girls during maturation

compared to boys (Meyer et al., 2017). In a 2-year follow-up study on the same cohort of children, (Korhonen et al., 2021) found that girls participated in lesser vigorous physical activity than boys; which may be a potential reason for the disparities in outcomes between the sexes.

Our results found a positive association between maximal blood pressure immediately after exercise and PWV in boys, but not in girls. Systolic blood pressure typically rises due to the increase in cardiac output in response to exercise demands (Paridon et al., 2006). However, systolic BP increases much less in children compared to adult counterparts, due the improved arterial compliance and significant reduction in total peripheral resistance during PA (Gardner & Parker, 2010). Only a few studies have previously investigated the relationship between arterial stiffness and BP response during exercise in adolescent populations Adult studies show that an increased carotid femoral PWV is correlated with higher BP response in submaximal treadmill tests (Thanassoulis et al., 2012). A study on young healthy Finnish adults investigated the relationship between arterial stiffness and blood pressure in an incremental ergometer test (Haarala et al., 2020). They showed that a high PWV at baseline was associated with exaggerated exercise blood pressure. Adults exhibiting elevated systolic BP during a maximal exercise test have been found to have a heightened vulnerability to hypertension and cardiovascular disease (Laukkanen & Kurl, 2012). Additionally, in children, an elevated rise in systolic blood pressure during an exercise test has been associated with metabolic risk factors (Møller et al., 2010). It is then possible that an exaggerated systolic BP response to exercise test in children could serve as a predictor of future metabolic and cardiovascular disease.

For boys, this study found that a higher maximal workload during the test at baseline was associated with a greater PWV over the 8-year follow-up. It is surprising that maximal workload per kilogram of lean body mass was not associated with PWV in neither sex. The differences found may be explained by the sex differences in cardiovascular fitness and hemodynamic response during a maximal exercise test. Eiberg and collegues (2005) observed that young boys aged 6-7 years displayed a higher degree of cardiovascular fitness and physical activity compared to girls of the same age.

Group comparison ANOVA was used to investigate the difference between systolic blood pressure immediately after exercise and maximal workload per kg of lean body mass on PWV

controlled for sex (Figure 8). There were no notable distinctions between the groups or between the sexes. These findings suggest that differences in blood pressure response to maximal strenuous exercise and fitness level do not predict arterial stiffening 8 years later in paediatrics.

The strength of our study is that we were able to investigate the long-term effects of blood pressure and fitness levels in response to exercise on future arterial health in childhood. Another strength of the study was that we were able to use maximal workload per lean mass and maximal systolic BP to predict PWV. The PANIC study was also able to control several factors, including physical activity, diet intake, insulin resistance and maturation. We also had multiple other factors in the analysis thanks to the comprehensive and thorough assessments. The primary drawback of the study was the inability to utilize the most accurate measures of arterial stiffness and endothelial function, such as PWV between the carotid and femoral artery, or brachial artery flow-mediated dilation (FMD). Because the study sample consisted of Caucasian children, the results may not be generalized to children of other ethnic backgrounds. Different ethnicities may have different genetic and environmental factors that could affect the relationship between variables such as blood pressure, exercise, and arterial stiffness. It would be necessary to conduct additional studies with more diverse samples in order to fully understand the relationship between these variables in different ethnicities.

9. CONCLUSION

In conclusion, this 8 year follow up study investigated the early factors that mediate arterial stiffening in adolescents. The results showed that a higher total body fat percentage in girls and lean mass in boys were predictive of arterial stiffening 8 years later. In addition, only in boys was a higher systolic blood pressure after exercise found to predict arterial stiffening in the follow-up. A higher baseline resting systolic blood pressure was also associated with higher arterial stiffness.

These gender differences in predicting arterial stiffening highlight the need for further research to fully understand the development of cardiovascular disease in adults and inform interventions to prevent it. These findings also underscore the importance of controlling blood pressure regulation and weight management from a young age to potentially prevent the development of cardiovascular disease in the future. However, it is unclear whether changes in arterial stiffness are the result of exercise-induced normal structural adaptations, and further research is needed to fully understand the mechanisms by which cardiovascular fitness and blood pressure in response to exercise impact arterial health in adolescents.

To inform future guidelines for preventing cardiovascular disease in this population, future studies should examine the long-term effects of different exercise intensities and modalities on adolescents' arterial health.

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