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LEFT VENTRICULAR STRUCTURE AND FUNCTION – ASSOCIATIONS WITH CARDIOVASCULAR RISK FACTORS FROM CHILDHOOD TO ADULTHOOD

The Cardiovascular Risk in the Young Finns Study

Jarkko Heiskanen

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To my family

UNIVERSITY OF TURKU
Faculty of Medicine
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Cardiology and Cardiovascular Medicine
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Centre for Population Health Research
JARKKO HEISKANEN: Left Ventricular Structure and Function –
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ABSTRACT

Background: Despite improvements in the treatment of cardiovascular diseases, heart failure remains a challenge that causes considerable morbidity and mortality in aging populations. Left ventricular (LV) remodeling and changes in LV diastolic function, which precede heart failure, are suggested to stem from lifestyle factors during the whole life course. However, the determinants of LV remodeling and diastolic function in healthy populations are inadequately known.
Aims: The first aim was to examine the associations between cardiovascular risk factors and LV diastolic function in adulthood. The second aim was to examine the effects of early-life adiposity and systolic blood pressure on LV mass and remodeling. The third aim was to investigate whether early life exposure to cardiovascular risk factors is associated with LV diastolic function in adulthood.
Materials and Methods: This thesis uses data from the Cardiovascular Risk in Young Finns Study, a population-based follow-up study that recruited n=3596 participants aged 3 to 18 in 1980. Cardiovascular risk factors have been measured repeatedly in follow-up visits between the years 1980–2011. In 2011, a follow-up with cardiac ultrasound was performed on n=1994 participants aged 34–49 years. Acquired data were analyzed using standard statistical methods.
Results: In adulthood, the determinants for LV diastolic function included systolic blood pressure, waist circumference, alanine aminotransferase, smoking, shorter stature, and female sex. Exposure to high body mass index in early life was associated with higher adulthood LV mass and risk for eccentric hypertrophy independently of adult obesity status. Early life risk factors for lower LV diastolic function in adulthood included the cumulative burden of higher adiposity and lower levels of physical activity.
Conclusions: The longitudinal burden of cardiovascular risk factors is associated independently with changes in LV diastolic function and LV remodeling. If these associations turn out to be causal, these results can be applied to guiding the primordial prevention and targeting the early interventions for individuals with increased cardiovascular risk factor burden.

KEYWORDS: Cardiovascular risk factors, left ventricular diastolic function, left ventricular remodeling, echocardiography, longitudinal study

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Väitöskirja, 118 s.
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TIIVISTELMÄ

Tausta: Sydämen vajaatoiminta lisää merkittävästi iäkkäiden sairastavuutta ja kuolleisuutta. Tutkimuksissa on havaittu, että sydämen vajaatoimintaa voi edeltää vasemman kammion muovautuminen -ja diastolisen toiminnan muutokset. Niiden arvioidaan johtuvan elintapojen aiheuttamasta pitkäkestoisesta altisteesta. Ei ole kuitenkaan selvää, mitkä ovat itsenäisiä riskitekijöitä sydämen muovautumiseen ja vasemman kammion diastolisen toiminnan muutoksiin terveessä väestössä.
Tavoite: Tutkimuksen tavoitteena oli tutkia vasemman kammion diastolisen funktion ja kardiovaskulaaririskitekijöiden välisiä yhteyksiä aikuisuudessa. Tavoitteena oli myös tutkia lapsuuden ja nuoruuden kardiovaskulaaririskitekijöiden altisteen yhteyttä vasemman kammion diastoliseen toimintaan aikuisuudessa sekä lapsuuden ja nuoruuden systolisen verenpaineen ja kehonkoostumuksen yhteyttä vasemman kammion massaan ja muovautumiseen aikuisuudessa.
Materiaalit ja menetelmät: Tämä väitöskirja on osa Lasten Sepelvaltimotaudin Riskitekijät -seurantatutkimusta. Seuranta alkoi vuonna 1980, jolloin tutkimuspopulaatio koostui n=3596 3–18-vuotiaasta lapsesta ja nuoresta. Kardiovaskulaaririskitekijöitä mitattiin säännöllisesti seurantakäynneillä ja vuonna 2011 seurantakäynnillä tehtiin sydämen ultraäänitutkimus n=1994 34–49-vuotiaille tutkittaville. Data on analysoitu standardoiduilla tilastomenetelmillä.
Tulokset: Aikuisuudessa vasemman kammion diastolisen funktioon muutoksiin yhdistettiin systolinen verenpaine, vyötärönympärys, alaniiniaminotransferaasientsyymi, tupakointi, pituus ja sukupuoli. Lapsuuden riskitekijät matalammalle vasemman kammion diastoliselle funktiolle olivat rasvaisempi kehonkoostumus ja vähäisempi liikunnan määrä. Lisäksi korkeampi painoindeksi lapsuudessa ja nuoruudessa oli yhteydessä korkeampaan vasemman kammion massaan ja eksentrisen hypertrofian riskiin riippumatta painoindeksistä aikuisuudessa.
Johtopäätökset: Pitkäaikainen kardiovaskulaaririskitekijöiden altiste on yhteydessä vasemman kammion diastoliseen toimintaan ja vasemman kammion muovautumiseen. Jos taustalla on syy-seuraussuhde, voidaan tuloksia hyödyntää ennaltaehkäisyssä ja elintapamuutosten kohdistamisessa.

AVAINSANAT: Kardiovaskulaaririskitekijä, vasemman kammion diastolinen funktio, vasemman kammion muovautuminen, sydämen ultra-äänitutkimus, pitkittäistutkimus

Table of Contents

Abbreviations

2DE	Two-dimensional echocardiography
ALT	Alanine aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CRP	C-reactive protein
CVD	Cardiovascular disease
GGT	Gamma-glutamyltransferase
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
mmHg	millimeters of mercury
LA	Left atrium
LAVi	Left atrial volume index
LDL-C	low-density lipoprotein cholesterol
LV	Left ventricle
LVDD	Left ventricular diastolic dysfunction
LVEF	Left ventricular ejection fraction
LVM	Left ventricular mass
PA	Physical activity
PLAX	Parasternal long axis
PW	Pulsed wave
RWT	Relative wall thickness
SD	Standard deviation
SE	Standard error
SBP	Systolic blood pressure
TDI	Tissue Doppler imaging
WHO	World Health Organization
YFS	The Cardiovascular Risk in the Young Finns Study

List of Original Publications

This Dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Heiskanen, J. S., Ruohonen, S., Rovio, S. P., Kytö, V., Kähönen, M., Lehtimäki, T., Viikari, J. S. A., Juonala, M., Laitinen, T., Tossavainen, P., Jokinen, E., Hutri-Kähönen, N., & Raitakari, O. T. (2019). Determinants of left ventricular diastolic function — The Cardiovascular Risk in Young Finns Study. Echocardiography, 36(5), 854–861. https://doi.org/10.1111/echo.14321

II. Heiskanen, J. S., Hernesniemi, J. A., Ruohonen, S., Hutri-Kähönen, N., Kähönen, M., Jokinen, E., Tossavainen, P., Kallio, M., Laitinen, T., Lehtimäki, T., Viikari, J. S. A, Juonala, M., Nevalainen, J., & Raitakari, O. T. (2021). Influence of early-life body mass index and systolic blood pressure on left ventricle in adulthood — The Cardiovascular Risk in Young Finns Study. Annals of Medicine, 53(1), 160–168. https://doi.org/10.1080/07853890.2020.1849785

III. Heiskanen, J. S., Ruohonen, S., Rovio, S. P., Pahkala, K., Kytö, V., Kähönen, M., Lehtimäki, T., Viikari, J. S. A., Juonala, M., Laitinen, T., Tossavainen, P., Jokinen, E., Hutri-Kähönen, N., & Raitakari, O. T. (2021). Cardiovascular Risk Factors in Childhood and Left Ventricular Diastolic Function in Adulthood. Pediatrics. https://doi.org/10.1542/peds.2020-016691

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1 Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVD) are the leading cause of death globally, causing an estimated 18.6 million deaths worldwide each year. (Roth et al., 2020) CVD is a class of diseases that affect the heart or blood vessels. Hypertension, diabetes, smoking, physical inactivity, obesity, poor-quality diet, and dyslipidemia are established as major cardiovascular risk factors. (Piepoli et al., 2016) All these risk factors have a shared element; they are modified by lifestyle choices. Naturally, not all risk factors are modifiable, for instance, genetics, age, and sex. However, the primary cardiovascular risk factor burden originates from individuals' selections.

Due to the development in treatments and prevention through profuse scientific research, the overall mortality rate of CVD has decreased. Especially in Finland, the reductions in cardiovascular risk factor levels and CVD mortality during the past decades have been remarkable. (Jousilahti et al., 2016) Although there are significant improvements in the treatment of virtually all CVD, heart failure (HF) is an exception. HF, especially heart failure with preserved ejection fraction (HFpEF), is the cardiac disease observed with non-declining prevalence, and only small prolongations in survival rate and life expectancy are reported. (Braunwald, 2013)

HF is a clinical syndrome with symptoms and or signs caused by structural and functional cardiac abnormalities and corroborated by elevated natriuretic peptide levels or objective evidence of pulmonary or systemic congestion. (Bozkurt et al., 2021) HF has been categorized into three subtypes by left ventricular ejection fraction (LVEF):

- heart failure with preserved ejection fraction; (HFpEF LVEF ≥ 50%) in which the relaxation of the left ventricle (LV) is diminished.
- heart failure with reduced ejection fraction; (HFrEF; LVEF ≤ 40%) in which the contractility of the LV is diminished.
- heart failure with mildly reduced ejection fraction; (LVEF 41–49%) a condition typically presenting characteristics of both HF subtypes above.

In addition, the universal definition of HF established a new HF category; heart failure with improved ejection fraction: HF with a baseline LVEF of ≤40%, a ≥10-

point increase from baseline LVEF, and a second measurement of LVEF of >40%. (Bozkurt et al., 2021)

The estimated number of HF patients in the United States was 924 000 in 2017. (Agarwal et al., 2021). In Finland, according to the Social Insurance Institution of Finland, 27 490 patients had reimbursement for HF medication in 2018, with the amount slightly declining compared to the year 2015 when the number of patients was 30 692. (Agarwal et al., 2021; the Social Insurance Institution of Finland, 2018). Approximately half of the patients with the clinical syndrome of HF have a preserved ejection fraction. (Dunlay et al., 2017). HF causes a significant burden of mortality and hospitalization; in 2017, there were 1.2 million HF hospitalizations in the United States. (Agarwal et al., 2021). This represents a 26% increase in HF hospitalizations and in the number of patients hospitalized with HF compared to the year 2014. If there is no significant progress in the treatment of HF, the direct costs have been projected to reach $53 billion by 2030 in the United States. (Heidenreich et al., 2013) Therefore, for better prevention of HF there is a need for a better understanding of how and which cardiovascular risk factors are affecting HF.

The pathogenesis of HFrEF is well known; the three main risk factors are ischemic heart disease, valvular heart disease, and uncontrolled hypertension. (Schwinger, 2021; Vedin et al., 2017) However, the pathology behind HFpEF is multifactorial and not as well understood. HFpEF is associated with several cardiovascular comorbidities, including obesity, diabetes mellitus, and hypertension. It is considered that the cumulation of cardiovascular comorbidities causes cardiomyocyte hypertrophy, fibrosis, and inflammation, all leading to decreased LV diastolic function, including prolonged isovolumic LV relaxation, slow LV filling, and increased diastolic LV stiffness. (B. A. Borlaug & Kass, 2011; Nagueh et al., 2016; Simmonds et al., 2020) Currently, no pharmacological therapy has been proven effective in improving long-term prognosis in patients with HFpEF. As LV diastolic function is decreased considerably when the symptoms of HFpEF appear, it is of interest to improve the knowledge of the etiology and preventive methods. In previous studies among elderly populations, hypertension, obesity, diabetes, LV mass (LVM), LV remodeling, and high age has been associated with lower LV diastolic dysfunction (LVDD). (B. A. Borlaug & Kass, 2011; Kitzman & Little, 2012) The knowledge of the effects of early-life cardiovascular risk factor burden on LV diastolic function or even associations of LV diastolic function and cardiovascular risk factors in the general population is limited, as most of the studies concerning LVDD have been produced in elderly populations. The main objectives of this thesis were to identify the determinants of LV diastolic function in the study population of early middle-aged participants and examine associations of the cardiovascular risk factor burden from childhood and adolescence with LV diastolic function and LV remodeling.

This thesis uses The Cardiovascular Risk in the Young Finns Study (YFS) -population to study the associations between CVD risk factors and LV function and remodeling. YFS is an ongoing population-based follow-up study of 3,596 participants that began in 1980 to study the risk factors of CVD and their determinants. (Raitakari et al., 2008) The YFS -population represents the general Finnish population aged 34–49 at the time of the echocardiographic measurements in the year 2011. YFS-population is an ideal population for these studies for several reasons. First, the longitudinal study design of YFS and the long follow-up of well-phenotyped participants in childhood and adulthood. (Juonala et al., 2013) Second, the study population represents the non-elderly general Finnish population. Third, the study population allows studying the associations before the confounding caused by the onset of severe CVD endpoints, i.e., myocardial infarct, which may alter the cardiac geometry and function significantly.

2 Review of the Literature

2.1 Left ventricular structure and function

2.1.1 General cardiac structure and function

In principle, the human heart is an efficiently designed four-chamber pump consisting of the left- and right atrium and -ventricle. The main function is to pump blood through the entire circulation to meet the metabolic demands of the body. The left atrium (LA) receives oxygenated blood from the lungs and pumps it to LV. LV, the largest and strongest chamber of the heart, pumps oxygen-rich blood to the rest of the body. The right atrium receives the oxygen-depleted blood from the peripheral circulation and pumps it to the right chamber of the heart, which pumps it under low pressure into the lungs.

Cardiac function is maintained by electrical activity. Electrical stimuli are initiated from the sinoatrial node regulated by the autonomic nervous system. The pacemaker cells in the sinoatrial node can spontaneously generate an electrical impulse, which conducts to the right atrium and then through the rest of the heart's electrical conduction system, eventually resulting in myocardial contraction and blood distributed to the rest of the body. (Airaksinen et al., 2016)

Commonly, the cardiac cycle is simplified and divided into two phases (Figure 2.1.2):

1. Ventricular diastole; when the ventricles fill with blood and the atriums contract. The time that the atriums contract is the point that the cardiac cycle is considered to start.
2. Ventricular systole; when the ventricles contract and pump blood into the circulation. In the electrocardiogram, the ventricular systole starts at QRS-complex, representing depolarization of the ventricles, and ends with ventricular repolarization.

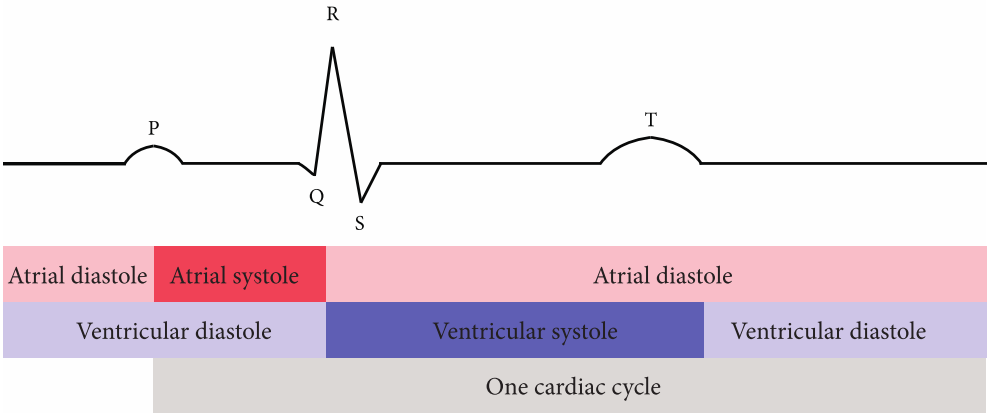

Figure 2.1.2 Illustration of a typical electrocardiogram. The wave represents atrial depolarization. Q wave represents the depolarization of the interventricular septum. R wave represents early ventricular depolarization. S wave represents the depolarization of the Purkinje fibers. T wave represents ventricular repolarization.

However, when analyzed in detail, the cardiac cycle is divided into 7 phases. Phases 1 and 5–7 are part of the diastole and phases 2–4 are part of the systole. Only the left side of the heart is reported below.(Klabunde, 2012)

1. LA contraction; The cardiac cycle is considered to begin with the last part of the diastole in which LA contracts and continues to fill the LV.
2. Isovolumetric contraction; LA pressure drops at the end of LA contraction, and the pressure in the LA is exceeded by the pressure in the LV, causing the mitral valve to close, starting the isovolumetric contraction of LV. During the isovolumetric contraction, the LV pressure rises as the cardiomyocytes contract with no corresponding volume change.
3. Rapid ejection; When the LV pressure exceeds the pressure within the aorta, rapid ejection starts, and the blood rushes to the aorta.
4. Reduced ejection; When LV has fully contracted, the ejection rate falls but continues due to the kinetic energy of the blood, known as reduced ejection.
5. Isovolumetric relaxation; At the end of the reduced ejection, the aortic valve closes. LV starts to relax during the isovolumetric relaxation until the mitral valve opens and diastole begins again.
6. Rapid filling; Early diastole starts when the mitral valve opens, and blood rushes from the LA to the LV.
7. Reduced filling; As the ventricles continue to fill with blood during early diastole, they become less compliant, the LV ventricular pressure rises, and the filling slows.

2.1.1.1 Left ventricular diastolic function

Normal LV diastolic function requires synchrony of LV ejection and relaxation and is an active energy-requiring process. (Kitzman & Little, 2012) Energy is required during the LA contraction and the rapid filling in early diastole as LV actively and passively relaxes. (Nagueh et al., 2016; Opdahl et al., 2009) The LV relaxation depends on the length of the sarcomeres, and as the ventricular volume increases (i.e., longer muscle), more time is needed to relax the myocardium; likewise, the diastolic relaxation prolongs. (Janssen & Hunter, 1995) Similarly, myocardial wall thickening affects the relaxation of the myocardium due to increased LV wall stiffness. Heart rate affects diastolic relaxation of LV by shortening the diastasis (the time between the early filling and contraction of LA) and increasing the atrial contraction. (Chung et al., 2004) Beta-adrenergic stimulation increases the heart rate. Additionally, it impacts several processes affecting cardiac relaxation, i.e., phosphorylation of phospholamban and L-type calcium channels, affecting the intracellular levels of Ca2+. (Najafi et al., 2016)

On a cellular level, three main events can limit LV relaxation rate: the rate of intracellular calcium decline, the rate of thin-filament deactivation, and the rate of myosin cross-bridge cycling. (Biesiadecki et al., 2014) These events interact with each other and are impacted by several other molecular events, making myocardial relaxation a complicated process. An increase of Ca2+ in the cytosol is required for cardiomyocyte contraction, and a lowering of Ca2+is needed for cardiomyocytes to relax. This is acquired through four transport mechanisms: 1. sarcoplasmic reticulum ATPase, which transports Ca2+ from the cytosol into the sarcoplasmic reticulum. 2. mitochondrial calcium uniporter, which transports Ca2+ to the mitochondria. 3. the sodium-calcium exchanger, and 4. sarcolemmal Ca2+-ATPase, which transports Ca2+ out of the cardiomyocyte. (Biesiadecki et al., 2014; Nagueh, 2020a, 2020b) When intracellular Ca2+ -levels drop, it acts as a signaling molecule to the tropomyosin and the troponin complex, causing thin filament inactivation, thus blocking the interaction between myosin and actin. The rate of this thin filament inactivation is regulated by troponin isoform switching, mutations, and post-translational modifications. (Biesiadecki et al., 2014) The rate of myosin cross-bridge cycling during diastole is affected by myosin light chain isoform switching and phosphorylation, myosin-binding protein-C phosphorylation level, and isoform switching and phosphorylation of titin. (Biesiadecki et al., 2014; Linke & Hamdani, 2014)

2.1.2 Echocardiography

Ultrasound in cardiac imaging is typically used as transthoracic echocardiography or transesophageal echocardiography. Cardiac echocardiography is a non-invasive and effective method to image the heart's structure and function. In addition, because of

the low price and small size of ultrasound machines, it has the best availability of cardiac imaging methods. As an imaging modality, the main strengths of cardiac echocardiography are the short time needed for the imaging, no need for pre-imaging procedures (in transthoracic echocardiography), and a live view of the function and structure of the heart non-invasively. The main limitation of transthoracic echocardiography is limited visibility of the heart in some patients; e.g., in obese patients, the visibility may be severely reduced. In addition, specific cardiac structures are hard to visualize even if the view is not limited, I.e., the LA appendage. Furthermore, the quality, reliability, and reproducibility of cardiac echocardiography are highly user-dependent. This thesis uses transthoracic echocardiography, hereinafter referred to as echocardiography.

In echocardiography, several ultrasound modalities are used to gather information on the cardiac structure and function. M-mode visualizes a single line of the myocardium with time on the x-axis. M-mode allows for precise measurement of specific time points of the cardiac cycle. The contrast of myocardial walls is clear, and the frame rate is high in M-mode. However, M-mode's main limitation is the possibility of having inaccurate measurements due to off-axis beam orientation, causing oblique linear measurements. Two-dimensional echocardiography (2DE) allows a cross-sectional view of the heart by producing an arc of ultrasound beams. Most of the typical echocardiography is done by this modality as it allows a global view of the heart and visualization of local abnormalities. 2DE is used to acquire single plane images of the heart and to guide linear or Doppler measurements to the correct localization.

The current guideline by the American Society of Echocardiography and the European Association of Cardiovascular Imaging suggests that the linear measurements of LV are obtained either with a 2DE or 2DE guided M-mode approach, measured at or immediately below the level of the mitral valve leaflet tips perpendicular to the LV long axis in the parasternal long-axis (PLAX) view. (Lang et al., 2015) Volumetric measurements of the LV are recommended to do either with 2DE or three-dimensional echocardiography. To study LVM in large populations, the guideline points out that M-mode based method has advantages because it is simple, quick, and subject to less measurement variability. It is noted that there is a large body of evidence to support the accuracy of this method, and most studies that relate LVM to prognosis are based on this method. (Armstrong et al., 2012) However, the limitations include the critical need for truly perpendicular measurement in M-mode; the 2DE and M-mode-based calculations may not be directly interchangeable. As the linear measurements in M-mode are raised at the power of 3 in the calculation of LVM, measurement errors may have significant effects on the calculated LVM.

Doppler imaging is based Doppler effect on ultrasound waves reflecting from the circulation of the red blood cells. By calculating the frequency shift of a particular sample volume, fluid speed and direction can be determined. Doppler imaging in echocardiography is used to visualize blood flow through valves and to measure the speed of the blood flow. Pulsed wave (PW) Doppler allows the measurement of blood velocity small window of space, whereas continuous wave Doppler allows measurement of high velocities but does not allow spatial localization of the velocity measured. Tissue Doppler imaging (TDI) uses the Doppler effect from reflecting waves from myocardial motion to acquire the velocity of the myocardial walls.

2.1.2.1 Assessing left ventricular diastolic function by echocardiography

The current guideline for evaluation of LV diastolic function by echocardiography by the American Society of Echocardiography and the European Association of Cardiovascular Imaging states: “When performing an echocardiographic study in patients with potential diastolic dysfunction, one should search for signs of impaired LV relaxation, reduced restoring forces and increased diastolic stiffness.” (Nagueh et al., 2016) These factors form the basis for the evaluation of LV diastolic function. Furthermore, when evaluating LV diastolic function, the natural progression of LV diastolic function by aging should be considered.

As LV fills with blood during diastole, the filling velocity of the blood can be measured by PW Doppler echocardiography, from the apical four-chamber view with color flow imaging for optimal alignment, with sample volume paced in between the mitral leaflet tips (Figure 2.1.2.1A). The peak blood flow velocity measurement taken in the early diastole is E (cm/s) and in the late diastole A (cm/s). Similarly, the mitral annular peak velocity is measured from the apical four-chamber view with PW TDI (é and á). The sample volume is placed either at the side of the mitral annulus (Figure 2.1.2.1B). These parameters are commonly used as ratios: E/A-ratio and E/è-ratio.

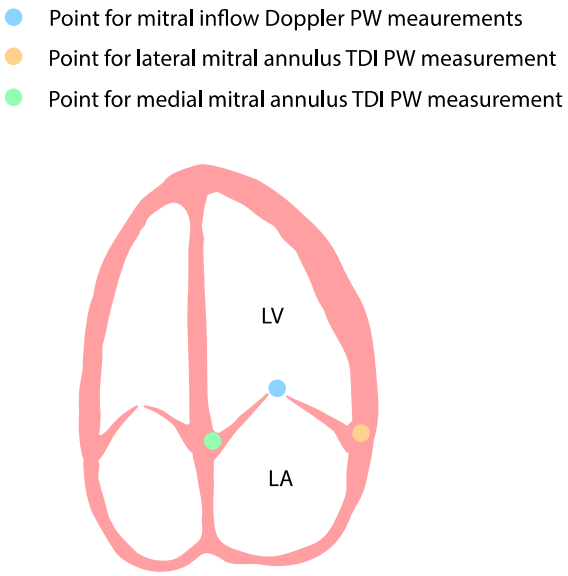

Figure 2.1.2.1A. Illustration of the measurement points of mitral inflow velocities and mitral annulus velocities, using the apical four-chamber view.

When LV diastolic function is normal, the diastolic filling occurs predominantly during early diastole. Thus E/A ratio is > 1. In addition, the mitral annulus early diastolic velocity (é) is high as the LV wall moves effortlessly, causing the normal E/é ratio to be < 8. (Nagueh et al., 2016) When LV relaxation impairs in LVDD, the filling of the LV shifts from early diastole to late diastole, causing the E/A-ratio to decrease (Figure 2.1.3.1B). (Nagueh, 2020a) As the relaxation impairs, the é decreases, and the E/é ratio rises. In a patient with LV diastolic dysfunction and decompensation, LA pressure rises. In this situation, the early diastolic E velocity increases, and due to higher late diastolic LV pressure and LA afterload, A velocity decreases, causing the "pseudonormalisation" of E/A-ratio. (Nagueh, 2020a) However, LV relaxation must be considerably impaired to cause a shift in LV filling from early to late diastole.

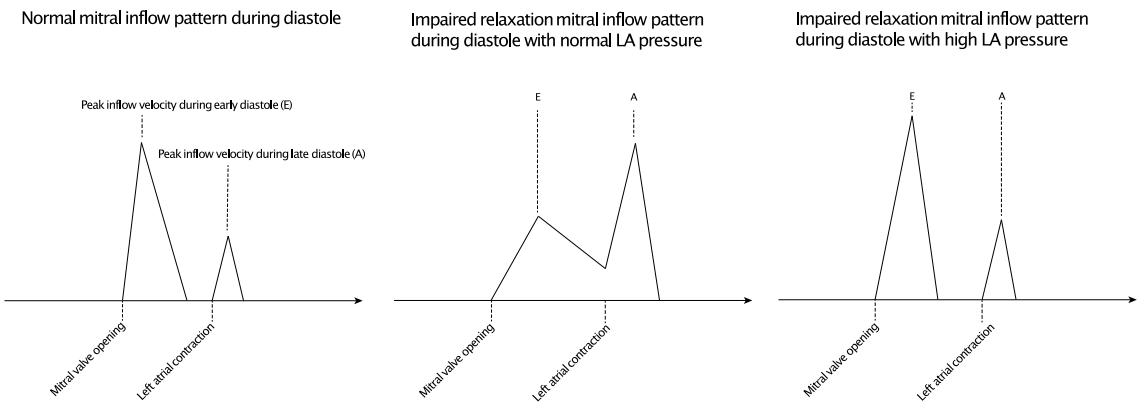

Figure 2.1.2.1B. Illustration of the mitral inflow patterns measured with PW Doppler echocardiography.

At a population level, a higher E/é-ratio has been shown to associate with an increased incidence of HF and has been used in multiple studies to predict all-cause mortality, cardiovascular death, and HF hospitalizations in several disease states. (Halley et al., 2011; Redfield et al., 2003) Additionally, in a population-based follow-up study by Kane et al., baseline E/é-ratio was a predictive factor for worse LV diastolic dysfunction in the follow-up examination. (Kane et al., 2011) In previous studies, early diastolic annular velocity é decrease predicted mortality in a general population of patients, mostly without apparent systolic and diastolic dysfunction. (Kuznetsova et al., 2014; Mogelvang et al., 2009)

Assessment of LA volume is recommended in the evaluation of LV diastolic dysfunction. (Nagueh et al., 2016) LA volumes indexed to body surface area (LAVi) remain nearly stable until the seventies. Thus, an increase in LA size before the seventies is likely to represent a pathological change except in elite-level athletes in whom LA dilatation has been reported. (Maron Barry J. & Pelliccia Antonio, 2006) An increase in LA volume has been associated with a worse prognosis of coronary disease, HF, higher incidence of atrial fibrillation, and has been associated with alterations in LV diastolic relaxation. (Ahmeti et al., 2021; Boyd et al., 2011; Nagueh et al., 2016; Patel et al., 2011) The increase in LA volume is considered to be a consequence of increased LV filling pressures in LVDD, causing LA to adapt to increased wall stress by increasing the LA volume. (Tsang et al., 2002) Therefore, LA volume is an insensitive biomarker of the early phases of LVDD. (Thomas et al., 2019)

2.1.3 Left ventricular diastolic dysfunction and heart failure with preserved ejection fraction

LVDD is an early-onset alteration in cardiac function and is common in elderly populations, and the prevalence increases with age in middle-aged populations. (Fischer et al., 2003; Kane et al., 2011). It has been shown that even in healthy individuals, the diastolic function parameters decrease by aging. (Carrick-Ranson et al., 2012) In LVDD, due to LV relaxation impairment, LV cannot fill with enough blood, and the chamber filling is slowed. Therefore, LV filling becomes more dependent on LA contraction and higher atrial pressures. LV diastolic function is impaired by several pathological processes that affect LV function or cause LV hypertrophy or fibrosis, including hypertension, diabetes, obesity, smoking, and infiltrative cardiomyopathies. (B. J. Borlaug & Paulus, 2011; Kitzman & Little, 2012) In addition, LVDD has been associated with coronary microvascular dysfunction, mortality, and increased risk of HFpEF. (Aljaroudi et al., 2012; Kane et al., 2011; Taqueti et al., 2018) HFpEF is a condition where an individual has HF symptoms and findings; however, LVEF is normal, and instead, the echocardiographic findings represent LVDD. (Pfeffer et al., 2019) However, at the time HF symptoms appear, the level of LVDD is already significant as the cardiovascular system cannot compensate for the decrease in LV diastolic function.

The overall prevalence of HFpEF is increasing, and the proportion of HF due to HfpEF is rising, accounting now ~50% of HF incidence overall. (B. J. Borlaug & Paulus, 2011; Pfeffer et al., 2019) The factors causing the increase in prevalence are increased life expectancy and aging of the population, the epidemic of cardiac and non-cardiac comorbidities caused by the increasing prevalence of obesity and physical inactivity, and increased clinical recognition of HFpEF. (Oktay et al., 2013; Pandey et al., 2018; World Health Organization, 2022) Patients with HFpEF have poor life quality, comparable to patients with end-stage renal disease. (Hoekstra et al., 2011) HFpEF is associated with high in-hospital, short-term, and long-term mortality rates. (Chan & Lam, 2013) Long-term prognostic treatment has not been established for HFpEF. However, recent studies showed that the use of sodium–glucose cotransporter 2 inhibitor reduced the combined risk of cardiovascular death or hospitalization for HF in patients and showed clinical benefit in acute HF regardless of LVEF. (Anker et al., 2021; Voors et al., 2022) Medication for HFpEF is currently an active field of research, with more ongoing clinical trials registered on ClinicalTrials.gov than HFrEF. However, preventive methods are essential to reduce the prevalence of HFpEF. The cardiovascular risk factors and their associations to LVDD and HFpEF are discussed one by one in later chapters.

In HFpEF, more pressure is needed to achieve a certain LV volume during diastole, and the rate at which pressure declines after the aortic valve closes is reduced. (Westermann et al., 2008; Zile et al., 2004) Systemic countermeasures are

triggered to restore cardiac output. These countermeasures include increasing sympathetic activity, activation of the renin-angiotensin-aldosterone axis, and the cytokine system. (Mann & Bristow, 2005) These responses are compensatory at first. Eventually, they become part of the disease process itself, leading to further worsening cardiac function. (Triposkiadis et al., 2009) It has been suggested that the main etiologic factors for HFpEF are metabolic comorbidities that trigger a systemic inflammatory resulting in coronary microvascular endothelial dysfunction. (Paulus & Tschöpe, 2013) This causes stiffening and hypertrophy of cardiomyocytes through altered paracrine signaling and nitric oxide levels. These alterations cause leukocyte infiltration, which leads to activation of myofibroblasts and interstitial collagen deposition. (Paulus & Dal Canto, 2018) The amount of collagen cross-linking has been associated with elevated filling pressures in patients with HF, and it may be a more important contributor to LV stiffness than the absolute amount of collagen in the myocardium. (López et al., 2012) It has been reported that HFpEF patients represent titin (a protein responsible for the passive elasticity of striated muscle) isoforms in different ratios than healthy individuals. (Borbély et al., 2005) However, the effects of titin are also controlled by post-translational modifications such as phosphorylation and calcium binding. (Hidalgo & Granzier, 2013) Ca2+ concentration plays a major part in cardiomyocyte contraction and relaxation, as described earlier, and it has been hypothesized that the dysregulation of Ca2+ plays a part in HFpEF. (Campbell & Sorrell, 2015) However, no studies have been comparing Ca2+ handling in healthy individuals and HFpEF patients. In addition, it has been hypothesized that strain-rate-dependent detachment of myosin cross-bridges changes as the LA pressure increases. (Campbell & Sorrell, 2015)

Alterations in cardiac energy metabolism contribute to the development and severity of HF. These changes are complicated and affected by comorbidities, i.e., diabetes, which changes the energy metabolism. A healthy adult heart can use multiple energy substrates, of which 60% originate from fatty acid metabolism. Oxygen requiring mitochondrial oxidation processes consists of 95% myocardial energy production. In HFpEF, mitochondrial oxidative capacity is reduced, fatty acid oxidation is increased, glucose oxidation is decreased, and the rate of glycolysis increases. (De Jong & Lopaschuk, 2017) Overall, the changes in energy substrate preferences that occur in HFpEF are controversial and not completely understood. (Lopaschuk, 2017)

2.1.4 Left ventricular mass and remodeling

The heart is an adaptive organ responding to the increased need for blood circulation by increasing the heart rate or to increased pressure overload by increasing contractility. However, prolonged exposure to the same factors, i.e., hypertension

and volume overload due to valvular disease, may cause adaptive or maladaptive processes in the heart. (Kehat & Molkentin, 2010; Vega et al., 2017) As LV produces a significant part of the heart's output, most of these adaptations are typically seen as LV changes, such as an increase in LVM and LV remodeling. Furthermore, several unmodifiable factors influence cardiac growth and remodeling, i.e., age, genetics, sex, and height. (Malcolm et al., 1993; Petersen et al., 2017) These adaptations can be small and unnoticeable or lead to cardiac diseases, i.e., in the YFS population aged 34–49, the mean LVM is 110g in women and 152g in men, and still untreated hypertension may cause hypertensive heart disease and a significant increase of LVM, to over 400g. (Nadar et al., 2005; Ruohonen et al., 2016) An increased LVM is associated with increased morbidity and mortality in adults. (Casale et al., 1986; Levy et al., 1990) Increased LVM in children has been shown to be predictive of increased adulthood LVM. (Daniels et al., 1998; de Simone et al., 1995)

Current evidence suggests that average and exercise-induced cardiac growth are regulated in large part by the growth hormone and insulin-like growth factor. (Dorn & Force, 2005) In contrast, pathological or reactive cardiac growth is triggered by neurohormonal factors (most importantly epinephrine, norepinephrine, angiotensin II, and aldosterone) released during biomechanical stress. (Dorn & Force, 2005) In addition, homeostatic, fibrinolytic mechanisms and inflammatory pathway activation have been observed. (Velagaleti et al., 2008) Moreover, microvascular endothelial dysfunction in HFpEF has been associated with cardiomyocyte hypertrophy. (Paulus & Tschöpe, 2013)

By classical definition, two different hypertrophic LV remodeling patterns are distinguished (Figure 2.1.4): 1. concentric hypertrophy, caused by pressure overload, characterized by parallel addition of sarcomeres and lateral growth of individual cardiomyocytes, defined by an increase in both LVM indexed to BSA and relative wall thickness (RWT). (Dorn et al., 2003; Lang et al., 2015) 2. eccentric hypertrophy, caused by volume overload or prior infarction, characterized by the addition of sarcomeres in series and longitudinal cell growth, defined by an increase in LVM/BSA index but normal RWT. (Dorn et al., 2003; Lang et al., 2015; Lorell & Carabello, 2000) In addition, the third category of LV remodeling without LV hypertrophy is used; concentric remodeling. In concentric remodeling, the LVM/BSA index is normal, but the RWT is increased. (Lang et al., 2015) The definition and calculation of LVM and RWT are shown in chapter 4.4.1. Concentric remodeling can be considered as a preceding condition before concentric hypertrophy, and if the unideal exposure does not decrease, it can develop into concentric hypertrophy.

Several modifiable cardiovascular risk factors associate strongly with LVM in children and adults, including blood pressure, physical activity, exposure to tobacco

smoking, overweight, and obesity. (Gidding et al., 2013; Hegde et al., 2016; Malcolm et al., 1993; Petersen et al., 2017) These risk factors and their associations with LVM will be discussed one by one in further chapters.

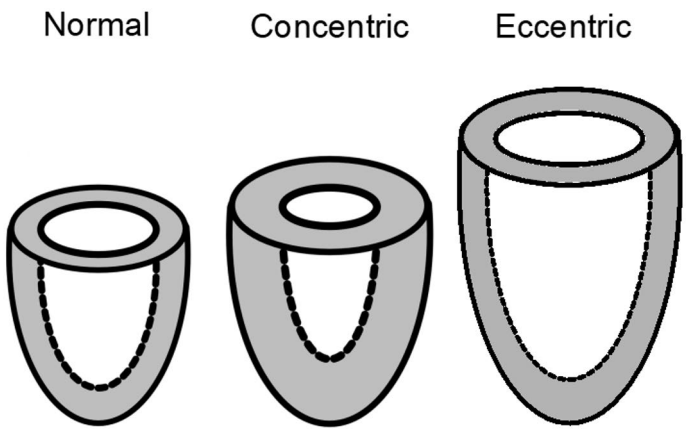

Figure 2.1.4 Visualization of the LV remodeling patterns. Compared to normal geometry, concentric remodeling is characterized by increased LVM and RWT. Compared to normal geometry, eccentric remodeling is characterized by increase an in LVM but normal RWT.

2.2 Cardiovascular risk factors

2.2.1 Blood pressure and hypertension

Increased blood pressure is one of the main cardiovascular risk factors associated with cardiovascular mortality and events. (Whelton et al., 2018) Lowering elevated blood pressure levels has been shown to reduce major cardiovascular events significantly. (Neal et al., 2000) Studies show that blood pressure levels in children and adolescents have increased, explained partially by the rise in obesity. (De Ferranti et al., 2019) In prospective studies, elevated blood pressure in children and adolescents has been associated with preclinical vascular changes, suggesting that childhood elevated blood pressure may increase the CVD risk in adulthood (Juonala et al., 2006; Mahoney et al., 1996; Raitakari et al., 2003)

Hypertension is strongly associated with increased LVM, and especially concentric LV hypertrophy is a common finding in hypertensive populations. (Cuspidi et al., 2011) Hypertension causes the heart to work against higher pressure, and the increased workload causes an adaptive response in LV to normalize systolic wall stress. (Frohlich et al., 2011) Cardiomyocytes respond to pressure overload by 1. slowing the maximum shortening velocity allowing the cardiac fiber to contract at a normal energy cost, 2. modifications that lead to increased cell size, which will

multiply the contractile units to normalize wall stress and preserve LV chamber function. (Swynghedauw et al., 2010)

Hypertension has been reported as the most important risk factor for LVDD and a major contributor to HF development. (Nadruz et al., 2017; Redfield et al., 2003) Also, hypertension is a significant risk factor for coronary atherosclerosis, and LVDD is aggravated in hypertensive subjects with coronary artery disease. (Vlasseros et al., 2013) Hypertension causes hypertrophic arteriolar remodeling and capillary rarefaction, causing a reduction in coronary flow reserve. (Abhayaratna et al., 2008; Feihl et al., 2009) This results in reductions of coronary perfusion during diastole, which may induce myocardial ischemia, and apoptosis of the cardiomyocytes. (Strøm et al., 2005) In addition, neurohumoral activation by the renin-angiotensin-aldosterone system in hypertension promotes collagen synthesis and cardiac fibrosis in hypertension through angiotensin II endothelin and aldosterone. (Janardhanan et al., 2009) Hypertension is also associated with systemic inflammation, which is related to the development of LVDD. (De Miguel et al., 2015; Nadruz et al., 2017)

2.2.2 Overweight and obesity

Obesity has tripled since 1975, and overweight and obesity have reached epidemic levels worldwide. (Carter et al., 2013) In 2016, 39% of all adults were overweight, and 13% of the world's adult population were obese. (Abarca-Gómez et al., 2017) Furthermore, under 1% of children and adolescents aged 5–19 were obese in 1975, and in 2016 6% of girls and 8% of boys (over 124 million children and adolescents) were obese. (Abarca-Gómez et al., 2017) Overweight and obesity are linked to more deaths worldwide than being underweight. (World Health Organization, 2020) The current cardiovascular health promotion goals highlight the importance of primordial prevention of obesity already in children to avoid long lifetime exposure to obesity. (Lloyd-Jones et al., 2010; World Health Organization, 2020) This is important as obesity tracks significantly from youth to adulthood, and offspring's body mass index (BMI) in adulthood is partly predicted by parental BMI. (Raitakari et al., 2005; Serlachius et al., 2016) Furthermore, previous cohort studies have reported encouraging results by showing that the cardiovascular risk factor profile associated with overweight in childhood and adolescence is reversible. (Ayer et al., 2015; Juonala et al., 2011)

Being overweight and obese are associated with numerous cardiac complications such as coronary heart disease, HF, and sudden death. (Poirier et al., 2006) Besides, obesity is associated with major cardiovascular risk factors; hypertension, dyslipidemia, and type 2 diabetes. (Lavie, Arena, et al., 2018; Lavie, Laddu, et al., 2018) Even in childhood, being overweight is associated with an adverse lipid

profile, hypertension, and insulin resistance. (Dahlström et al., 1985) Naturally, being overweight is crucial in the pathophysiology of metabolic syndrome, which is a substantial risk factor for CVD morbidity and mortality. (Haffner et al., 1998) Hormonal changes occur in obesity, causing leptin resistance and lower levels of adiponectin. (Carter et al., 2013) A proinflammatory and prothrombotic state often accompanies excessive adipose tissue and has been suggested as one pathway through which obesity may cause LVDD. (Rost et al., 2001; Wu et al., 2012) Overall, obesity acts as a cardiovascular risk factor through multiple underlying mechanisms.

A variety of cardiac structure and function alterations occur as excess adipose tissue accumulates, even in the absence of hypertension or underlying organic heart disease. (Poirier et al., 2006) Obesity increases excess body mass, causing increased blood volume, thus requiring the heart to pump more blood. (Lavie, Arena, et al., 2018; Poirier et al., 2006) Already in children, obesity is associated with higher LVM, increased LV volume, and decreased LV systolic and diastolic function. (Cote et al., 2013) However, the results regarding LV function in childhood obesity are heterogeneous and typically seen only when the degree of obesity is severe. (Aurigemma et al., 2013; Tadic & Cuspidi, 2015) In adults, associations between obesity and cardiac structural and functional changes are well established. Obesity is associated with increased LVM and LV hypertrophy, (Alpert, Lavie, et al., 2014; Alpert, Omran, et al., 2014; Aurigemma et al., 2013) elevated cardiac output, (Poirier et al., 2006) and changes in cardiac pressure levels. (Lavie et al., 2013) In addition, an increase in LVM in obesity is associated with eccentric and concentric hypertrophy in adults. (Aurigemma et al., 2013; Avelar et al., 2007; Cuspidi et al., 2014) Furthermore, longstanding obesity is associated with lower LV diastolic and systolic function in early middle-aged adults. (Aurigemma et al., 2013; Kishi et al., 2014; Powell et al., 2006)

2.2.3 Physical activity

The cardiovascular health benefits of physical activity and exercise are well established. Persistent aerobic exercise has positive morphological and physiological cardiovascular adaptations in apparently healthy individuals, irrespective of age and sex at all ages. (2018 Physical Activity Guidelines Advisory Committee, U.S. Department of Health and Human Services, 2018, 2018; Lavie et al., 2015) Therefore, WHO highlights the importance of regularly undertaking aerobic and muscle-strengthening activities in the general population. (Bull et al., 2020)

Higher amounts of physical activity and higher cardiorespiratory fitness are associated with a lower risk for CVD and HF. (Giannuzzi et al., 2003; Warburton et al., 2006) Instead, a sedentary lifestyle and low cardiorespiratory fitness have been associated with increased CVD risk and mortality and increased HF risk. (Lavie et

al., 2019; Young et al., 2016) The mechanisms through which physical activity affects cardiovascular health are numerous, affecting glucose homeostasis, lipids, blood pressure, and low-grade inflammation. (Booth et al., 2012) Physical activity also enhances endothelial function, and the aging-related decline in cardiac function is significantly attenuated when exercising across the lifespan. (2018 Physical Activity Guidelines Advisory Committee, U.S. Department of Health and Human Services, 2018, 2018; Arbab-Zadeh et al., 2004) In childhood, physical activity is beneficially associated with cardiometabolic risk factor profile, endothelial function, and carotid intima-media thickness. (Ekelund et al., 2012; Pahkala et al., 2011)

Exercise causes beneficial morphological LV adaptations through (1) increased early diastolic filling secondary to a combination of increased preload and increased myocardial relaxation; and (2) increased contractile strength. (Baggish et al., 2008; Weiner & Baggish, 2012) These changes increase LVM, cardiac output, and cardiorespiratory fitness. Elite-level training is associated with a significant increase in LVM, LV dilatation, and LA dilatation. These changes can progress even to a condition called “athletes heart”, which resembles patterns found in pathological conditions. (Maron Barry J. & Pelliccia Antonio, 2006) However, a longitudinal study of elite-level athletes found no increase in the risk for cardiac death. (Pelliccia et al., 2010) Moreover, in previous studies, diastolic LV diastolic function has been shown to stay normal in athletes with LV hypertrophy, whereas in patients with pathologic LV hypertrophy LV diastolic function decreases. (Caselli et al., 2014; Schannwell et al., 2002) Patterns resembling pathological conditions associated with continuous strenuous exercise only influence a small specific elite-level athlete population. In the general population, higher levels of physical activity are associated with higher LVM but with a better cardiovascular prognosis. (Joseph et al., 2020)

LVDD and HFpEF have been associated with low levels of physical activity and a sedentary lifestyle. (Abarca-Gómez et al., 2017; Hegde et al., 2017; Lavie et al., 2019) However, in a short-term follow-up, exercise training was not associated with reduced hospitalization or mortality in HFpEF patients in a recent meta-analysis. (Edwards & O’Driscoll, 2022) Instead, exercise training in patients with HFpEF is associated with improved cardiorespiratory fitness and quality of life. (Pandey et al., 2015) Furthermore, a study by Bhella et al. showed that 4 to 5 exercise sessions a week in adulthood might prevent age-related LV stiffening. (Bhella et al., 2014) Even in healthy male adolescents, physical activity beneficially influences endothelial function, and higher cardiorespiratory fitness in young adulthood is associated with lower LV diastolic filling pressure in middle age, independent of the cardiovascular risk factor burden. (Pahkala et al., 2008; Pandey et al., 2017)

Low physical activity is an important risk factor for CVD and is associated strongly with several cardiovascular risk factors, e.g., higher blood pressure and obesity, the two main factors causing LV hypertrophy and LVDD. (Lavie et al.,

2019; Lee et al., 2012; Roth et al., 2020) As the prevalence of obesity is rising, and the use of antihypertensive medication is rising in western countries, the promotion of physical activity is crucial. (Abarca-Gómez et al., 2017; Gu et al., 2012) Thus, the American College of Cardiology and American Heart Association, the European Heart Association, and the WHO have recommendations for physical activity, including lifelong physical activity implementation from childhood, and recommend avoiding low levels of physical activity and sedentary time. (Arnett et al., 2019; Chaput et al., 2020; Piepoli et al., 2016)

2.2.4 Blood glucose and diabetes

Individuals with diabetes mellitus have over two times the risk of developing HF than individuals without diabetes mellitus. (Dei Cas et al., 2015; Nichols et al., 2001) In addition, diabetes mellitus is associated with LV hypertrophy and remodeling. (Kenny & Abel, 2019; Yap et al., 2019) Notably, about 45% of patients with HFpEF have diabetes mellitus, and the prevalence of comorbid diabetes mellitus is increasing most significantly in those with new-onset HFpEF. (Echouffo-Tcheugui et al., 2016; McHugh et al., 2019) Furthermore, increases in plasma glucose levels have been suggested to be a predictor of the future development of HF, and blood glucose levels have been correlated with the severity of HF. (Shaye et al., 2012) Impaired glucose metabolism and insulin resistance have been shown to be associated with abnormal LV diastolic function and structure independent of age, gender, and blood pressure. (Hwang et al., 2012) In a study by Eguchi et al., diabetes mellitus increased the risk of LV hypertrophy by about 1.5-fold. (Eguchi et al., 2008) This effect is considered to be caused by both insulin resistance, which causes higher levels of insulin that acts like a growth hormone, and comorbid obesity, which causes higher peripheral resistance and increased workload of the heart.

Impaired glucose metabolism affects the remodeling and dysfunction of the myocardium through several mechanisms: hyperglycemia, systemic inflammation, hyperinsulinemia, and changes in glomerular function. (Paulus & Dal Canto, 2018) Hyperglycemia increases protein kinase C activity in fibroblasts, which augments collagen production and deposition. (Asbun & Villarreal, 2006) Systemic inflammation causes leukocyte infiltration into myocardial cells, which leads to activation of myofibroblasts and interstitial collagen deposition. (Paulus & Dal Canto, 2018) In addition, insulin induces cardiomyocyte hypertrophy, partly explaining the cardiomyocyte hypertrophy observed in HFpEF patients with diabetes mellitus.

2.2.5 Cholesterol, triglycerides, and lipoproteins

The strong cumulative evidence demonstrates a causal relation between hypercholesterolemia and CVD. (European Atherosclerosis Society, 1987; Levine et al., 1995; the National Institutes of Health, 1985) The majority of cholesterol in the bloodstream is contained in low-density lipoprotein cholesterol (LDL-C) particles. It has been shown that low-density lipoprotein is an atherogenic lipoprotein. (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002) In addition, high concentrations of triglycerides raise CVD risk. (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002) Multiple trials and meta-analyses have demonstrated that treatment with a statin and thus lowering LDL-C levels significantly reduces the risk of major coronary events. (Gould et al., 1998; Nissen et al., 2005) Though cholesterol, triglyceride, and lipoprotein concentrations have a high role in atherosclerosis, no significant evidence supports cholesterol as a significant independent risk factor for LV hypertrophy or LVDD. By current knowledge, there are a limited number of studies showing associations between lipid metabolism and HFpEF. In previous studies, impaired coronary flow reserve, suggesting microvascular disease, a risk factor for HFpEF, has been associated with high LDL-C levels in asymptomatic patients. (D'Amario et al., 2019; Kaufmann et al., 2000) In a study by Mahmod et al., high myocardial triglyceride accumulation has been associated with impaired diastolic strain rate and HFpEF. (Mahmod et al., 2018) Furthermore, in rat experiments, high rates of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. (Liu et al., 2002) In humans, hyperlipidemia leads to myocardial triglyceride accumulation and can induce cell death. (Bayeva et al., 2013) Overall, there is no conclusive understanding of the effects of cholesterol, triglycerides, and lipoproteins on LV diastolic function or HFpEF. However, as patients with HFpEF typically have multiple impairments in their cardiovascular system and several comorbidities, achieving the guideline-recommended cholesterol levels essential in these patients.

2.2.6 Smoking

Longitudinal evidence indicates that exposure to tobacco smoke is causally related to CVD. (National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014) Cigarette smoking has many adverse effects on the vascular wall. (Messner & Bernhard, 2014) The key processes are endothelial dysfunction and damage, increase in and oxidation of proatherogenic lipids, induction of inflammation, and the shift toward a prothrombotic state in the

circulation. (Csordas & Bernhard, 2013) Many cigarette-smoke-mediated prothrombotic changes are quickly reversible upon smoking cessation. (Csordas & Bernhard, 2013) Smoking bans in public places and workplaces are associated with significant ischemic heart disease incidence reductions among adult populations. (Meyers et al., 2009) Exposure to cigarette smoking during childhood appears to have an adverse effect on long-term vascular health; In a study by Gall et al., children exposed to their parents' smoking had preclinical vascular changes.

In adults, cigarette smoking is associated with LV hypertrophy, lower LV diastolic function, and HF hospitalization. (Kamimura et al., 2018; Nadruz et al., 2016) Smoking acutely increases systolic blood pressure (SBP), total systemic vascular resistance, pulmonary artery pressure, pulmonary vascular resistance, and changes in LV relaxation are all known risk factors for HF. (Lichodziejewska et al., 2007; Nicolozakes et al., 1988) However, in population-level data, smoking also has been associated with reduced SBP. (Karvonen et al., 1959; Leone, 2011) Furthermore, smoking is associated with carbon monoxide exposure, which has been reported to increase oxidative stress and lead to impaired mitochondrial function and inflammation, all of which have been implicated in the pathophysiology of HF and LVDD. (Levitzky et al., 2008; Morris et al., 2015; Reboul et al., 2017) However, long-term smoking cessation lowers the risk of HF significantly, even to the level of never-smokers. (Ahmed et al., 2015)

3 Aims

This thesis uses data from YFS. The primary purpose was to study the associations between cardiovascular risk factor burden in early life and LV structure and function in adulthood.

The specific aims of this study were:

1. Identify the predictors of LV diastolic function in YFS-population (Study I)
2. To study whether the childhood BMI and SBP have an independent association with adulthood LVM and LV remodeling (Study II)
3. To examine associations between the cumulative exposure to early-life cardiovascular risk factors and LV diastolic function in adulthood (Study III)

4 Materials and Methods

4.1 The Cardiovascular Risk in Young Finns Study

The study population comprised participants of YFS, a population-based follow-up study on cardiovascular risk factors from childhood through adulthood. (Raitakari et al., 2008) The first cross-sectional survey was conducted in 1980. To produce a representative subsample of Finnish children, the participants were haphazardously recruited from the population registers of all five Finnish university cities with medical school and their rural surroundings. Of the recruited 4,320 children and adolescents aged 3, 6, 9, 12, 15, and 18 years, a total of 3,596 (83%) participated in the original study, which included clinical examination, laboratory testing, and questionnaires. Follow-up studies were performed in 1983, 1986, 1989, 1992, 2001, 2007, and 2011. The participation rates have been relatively high (Figure 4.1). Detailed assessments of the representativeness have previously demonstrated no significant differences between the participants and non-participants in the age and sex-adjusted analyses. (Juonala et al., 2013) Furthermore, many patients lost to follow-up early in the study have returned to the study later on. (Raitakari et al., 2008) Echocardiographic analysis was done at the follow-up in 2011 when the participants were 34–49 years old. In this thesis, longitudinal data throughout the follow-up was used. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and is approved by the ethics committee of the University of Turku. Informed consent was obtained from all participants.

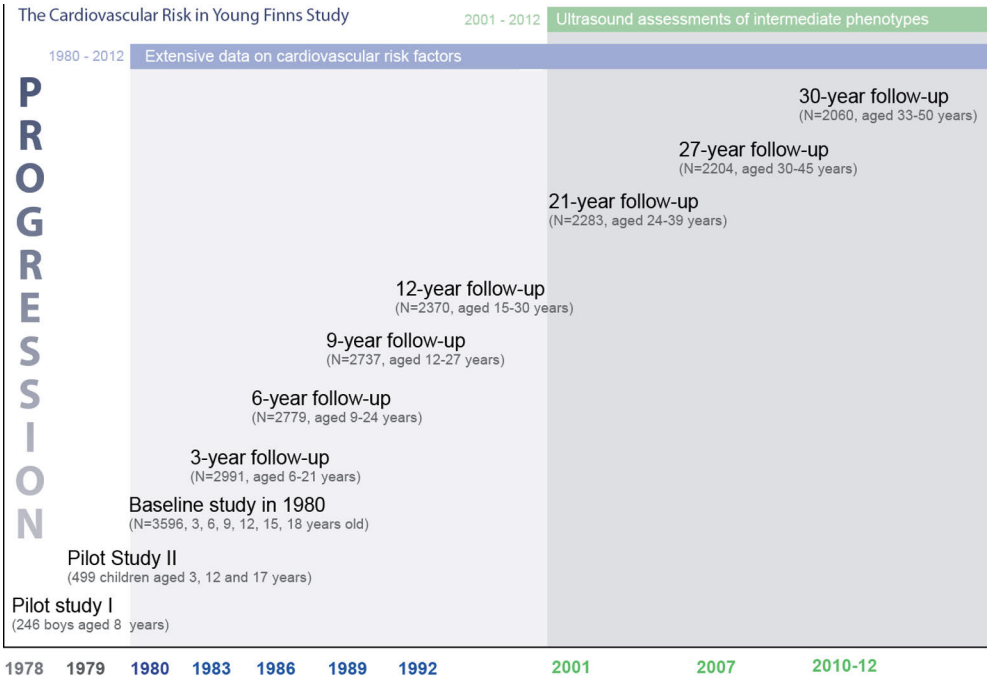

Figure 4.1 Progression of the Cardiovascular Risk in Young Finns Study. (Photo reprinted with the permission of the original author Markus Juonala, https://youngfinnsstudy.utu.fi/studydesign.html)

4.2 Study design and participants

Study I examined biochemical, physiological, and lifestyle determinants of LV diastolic function in 34–49-year-old participants of the YFS. The study population consisted of N=1,928 participants (46% men, aged 34–49 years). The main aim was to identify the determinants of LV diastolic function in the YFS population.

Study II used longitudinal data of the YFS to examine the independent associations of the cumulative burden of BMI and SBP between ages 6–18 on LVM and LV remodeling in adulthood. After exclusions, the study population included N=1,864 participants (45% men, aged 34–49 years).

Study III examined whether childhood exposure to cardiovascular risk factors predicts LV diastolic function in adulthood. We used the longitudinal data from the YFS, with repeated risk factor measurements beginning from childhood that allowed us the unique assessment of cumulative risk factor burden during early life (between ages 6–18). After exclusions, the study population included N=1,873 participants (46% men, aged 34–49 years).

In all three studies of this thesis, participants were excluded from the study population if they had missing cardiac ultrasound measurement that was used as an outcome variable. 5 individuals were excluded due to myocardial infarction, 1 individual due to atrial fibrillation, 1 individual due to bicuspid aortic valve, 1 due to patent foramen ovale and stroke, and 3 individuals were excluded due to laboratory measurement outliers. By 2011, 93 of the original participants had died, with only 14.0% (n=13) of the deaths attributable to cardiovascular causes. In studies II and III, insufficient longitudinal data on childhood parameters was used as an exclusion criterion. In study II 11 women were excluded due to pregnancy at the time of the echocardiography. In study III, type 1 diabetic patients were excluded (n=10).

4.3 Data acquisition in the Cardiovascular Risk in Young Finns Study

4.3.1 Physical examination

Height, weight, and waist circumference were measured during each study visit. Weight was measured with weighing scaled to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm by a wall-mounted stadiometer. Waist circumference was measured midway between the iliac crest and the lowest rib at the midaxillary line with a non-stretchable plastic-covered cloth measuring tape to an accuracy of 0.1 cm. BMI was calculated as weight (kg) / height squared (m^2). Between ages 6–18, participants were defined as overweight if I) their age- and sex-specific BMI values exceeded the international BMI percentiles corresponding to adult BMI of 25 kg/m^2 in at least 50% of the measured values between ages 6 and 18 or II) their BMI burden between years 6–18 calculated as area under the curve (AUC) exceeded AUC value derived from the international BMI corresponding to adult BMI of 25 kg/m^2. (Cole et al., 2000) Adult participants were stratified by obesity status using a cut-off of 30 kg/m^2. Body surface area (BSA) was calculated using the Du Bois formula (BSA = 0.007184 x weight $(kg)^{0.425}$ x height $(cm)^{0.725}$). (Du Bois & Du Bois, 1916) In adults, overweight was defined as having BMI $\geq$ 25 kg/m^2 and obese as BMI $\geq$ 30 kg/m^2. In the follow-up studies conducted in 1980, 1983, and 1986, adiposity was measured by using subscapular, biceps, and triceps skinfold measurements in triplicate from the nondominant arm by using a Harpenden skinfold caliper. (Dahlström et al., 1985) In the follow-up studies conducted in 2001, 2007, and 2011, waist circumference was used to indicate adiposity.

Blood pressure was measured in a sitting position after a 5-minute rest, using a random zero sphygmomanometer, except for the year 1980, when blood pressure was measured with a standard mercury sphygmomanometer. Korotkoff's first sound

was used as a sign of SBP, and the fifth sound as a sign of diastolic blood pressure. Readings to the nearest number of millimeters of mercury (mmHg) were taken at least two times on each subject. The average of systolic and diastolic readings was used as the measure of blood pressure in analyses. Hypertension was defined as 1) SBP > 140 mmHg, or 2) diastolic blood pressure > 90 mmHg, or 3) using antihypertensive medication. Heart rate was reported directly from the electrocardiography readings.

4.3.2 Questionnaires

Smoking habits were assessed by a self-administrated questionnaire beginning at the age of 12 years. Those smoking daily were considered smokers. Pack-years of smoking were calculated. Alcohol consumption was enquired by standardized questionnaires and calculated in standard doses (12 g pure ethanol) per day by dividing the total number of doses consumed per week in the year 2011 (0.33 l doses of beer or cider, 0.12 l doses of wine, and 0.04l doses of hard liquor). The use of prescription medications was queried from the participants and confirmed from the electronic Patient Data Repository of the Social Insurance Institution of Finland.

4.3.2.1 Physical activity questionnaire

Physical activity (PA) and participation in sports of the 9- to 18-year-old participants (1980 to 1989) were measured through a short self-report questionnaire administered individually in connection with a medical examination.(Telama et al., 1985). The questionnaire has previously been validated against objectively measured PA in adults obtained with the use of a pedometer, and the PA defined by the questionnaire has been shown to be associated with several common CVD risk factors e.g. SBP, BMI, and serum triglycerides. (Hirvensalo et al., 2017; Mansikkaniemi et al., 2012; Raitakari et al., 1997; Telama et al., 2005) The questions concerned the frequency and intensity of leisure-time PA, sports club training participation, competitive sports event participation, everyday activity during leisure time, school physical education grades, and type of school commute. The answers were coded from 1 to 3, with 1 representing inactivity or very low activity, 2 moderately intensive or frequent activity, and 3 frequent or vigorous activity. The grade received in physical education, which has been shown to be a good predictor of PA and commuting to school as a measure of daily activity, were coded from 1 to 4. After coding, a sum index of PA was calculated. Among the 9- to 15-year-olds, the PA index comprised eight variables with a total score ranging from 8 to 25. Among the cohort aged 18 years, five variables with a score ranging from 5 to 15. The extra three variables in

the questionnaire administrated to the younger group related to going to school and did not apply to the older group.

For participants aged 6 years, PA was measured using parents' ratings. Parents were asked questions concerning their child's outdoor playtime (hours in a day) in summer and in winter, the amount of PA in play as compared with other children, the vigorousness of PA, the child's enjoyment of indoor/outdoor play, the child's general level of activity as compared with other children, the encouragement given to participate in sports, and the patterns of PA. Each item was coded from 1 to 3, except for encouragement to engage in sport (1–2). By summing the variables, the PA index of preschool children was formed with scores ranging from 8 to 23.

Table 4.3.2.1 Physical activity questionnaire for 9- to 18-year-old participants

How often do you engage in leisure-time physical activity for at least half an hour per session?	
Not at all	1
Less than once a month	1
Once a month	1
2–3 times a month	1
Once a week	2
2–6 times a week	2
Every day	3
How much breathlessness and sweating do you experience when you engage in physical activity and sport?	
Not at all	1
Moderate amount	2
A lot	3
How many times a week do you usually engage in training sessions organized by a sports club?	
Not at all	1
Occasionally	1
Less than once a month	1
Once a month or more	2
Once a week	2
Several hours and times a week	3
Do you participate in sports competitions?	
Not at all	1
Sports club level	2
Regional level	3
National level	3

What do you usually do in your leisure time?	
I am usually indoors and read or do other sedentary activities	1
I spend my time indoors and outdoors	2
I usually walk or spend time with my friends	2
I am usually outdoors and exercise quite a lot	3
The questions below apply only for participants aged the 9- to 15-year-old	
Do you participate in a sports club at school?	
No	1
Yes	2
What was your grade for physical education in your last school report?[a]	
Grades 4–7	1
Grade 8	2
Grade 9	3
Grade 10	4
How far and by what means do you usually go to school?	
By car/bus	1
By bicycle <400m	2
By bicycle <700 m or walking <400 m	3
By bicycle over >700 m or walking over 500 m	4
Physical activity index total, range	8–25

[a] In Finland, school-subject grades range from 4 to 10, 4 being the lowest. The mean physical education grade is 8. From the Original publication III, supplemental material.

4.3.3 Biochemical analyses

In childhood, venous blood samples were drawn after a 12-hour fast from the right antecubital vein with the subject lying recumbent. Venipuncture was attempted only once. An aliquot for serum lipid analyses was stored at -25°C until thawed for the first time for the analyses. Venous blood samples were drawn from the right antecubital vein after an overnight fast, and serum was separated, aliquoted, and stored at -70°C until analysis. All lipid determinations were done in duplicate and in the same laboratory. In 1980, total cholesterol concentrations were measured using a fully enzymatic CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany) with OLLI 3000 and Kone CD analyzers (Kone Co., Espoo, Finland). In 1980, serum High-density lipoprotein cholesterol (HDL-C) concentrations were measured from the supernatant after precipitation of very-low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein particles with dextran sulphate-MgCl2 (Pharmacia, Uppsala, Sweden). (Kostner, 1976) In 1980 the precipitation was done in the laboratory, whereas in 1983 and 1986, the precipitation was done at the blood collection site. The time between blood collection and

precipitation was thus longer in 1980 and may have caused slightly biased (presumably lower) HDL-C concentrations in 1980. In 1980, serum triglycerides were determined by using a fully enzymatic method (Boehringer Mannheim). All analyses were performed as simultaneously as possible in the laboratory of the Rehabilitation Centre of the Social Insurance Institution, Turku, Finland.

In adulthood, venous blood samples were drawn from the right antecubital vein of recumbent subjects after a 12-hour fast, and serum was separated, aliquoted, and stored at -70°C until analysis. C-reactive protein (CRP) was determined immunoturbidimetrically. (Suomela et al., 2015) The concentration of serum insulin was determined with an immunoassay. (Suomela et al., 2015) Serum glucose concentration was determined by enzymatic methods. (Suomela et al., 2015) Homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as (insulin x fasting serum glucose)/22.5. (Matthews et al., 1985) Fasting serum alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) were measured by enzymatic methods. (Suomela et al., 2015) Serum creatinine was determined spectrophotometrically with the Jaffe method. (Slot, 1965)9/30/2022 11:29:00 AM Glomerular filtration rate was counted using the Chronic Kidney Disease Epidemiology Collaboration equation. (Levey et al., 2009)

Triglyceride concentration was determined using the enzymatic glycerol kinase–glycerol phosphate oxidase method (Triglyceride reagent, Beckman Coulter Biomedical, Ireland). Total cholesterol levels were measured by the enzymatic cholesterol esterase–cholesterol oxidase method (Cholesterol reagent, Beckman Coulter Biomedical). The same reagent was used for estimating HDL-C levels after precipitation of very-low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein particles with dextran sulphate-MgCl2. (Kostner, 1976) All the above assays were performed on an AU400 instrument (Olympus, Japan), and the same methods were used both in 2007 and 2011. LDL-C was calculated by the Friedewald formula. (Friedewald et al., 1972) Participants with triglyceride levels above 4.0 mmol/L were excluded from this analysis (n=32 in 2001, n=46 in 2007, and n=47 in 2011). Also, LDL-C concentrations were measured in 2007 by a direct enzymatic method. The analysis methods for total cholesterol and triglycerides have been accredited by the Finnish Accreditation Service according to standard ISO/IEC17025. All analyses were performed as simultaneously as possible in the laboratory of the Research and Development Unit of the Social Insurance Institution (Turku, Finland) in 2001 and in the laboratory for Population Research of the National Institute for Health and Welfare (Turku, Finland) in 2007 and 2011.

Because of changes in determination methods and kits during the study years, lipid levels from 1980, 1983, and 1986 and triglycerides from 2007 were corrected by using correction factor equations to correspond to the samples taken in 2001.(Juonala et al., 2004a; Porkka et al., 1997) These equations were determined

with linear regression analysis utilizing standardized principal component adjustments.

4.3.4 Definition of metabolic syndrome, type 2 diabetes, and hypertension

The harmonized definition was used for metabolic syndrome. (Alberti et al., 2009) Metabolic syndrome was diagnosed if participants had at least three of the following five factors:

1. waist circumference ≥102 cm for males and ≥88 cm for females
2. raised triglycerides: >1.7 mmol/l (>150 mg/dl), or specific treatment for this lipid abnormality
3. reduced HDL-C: <1.036 mmol/l (<40 mg/dl) in males and <1.3 mmol/l (<50 mg/dl) in females, or specific treatment for this lipid abnormality
4. raised blood pressure: blood pressure ≥130/85 mmHg, or treatment of previously diagnosed hypertension
5. raised fasting plasma glucose ≥5.6 mmol/l (100 mg/dl), or previously diagnosed type 2 diabetes.

Participants were classified as having type 2 diabetes if they had fasting plasma glucose of 7.0 mmol/l or higher, reported use of oral glucose-lowering medication or insulin but had not reported having type 1 diabetes, or reported a diagnosis of type 2 diabetes by a physician. Participants were also classified as having type 2 diabetes if they had Hemoglobin A1c ≥6.5% (48 mmol/mol). Participants were classified as having hypertension if they had SBP ≥140 mmHg or a diastolic blood pressure ≥90 mmHg or if they reported use of the blood-pressure-lowering medication.

4.4 Echocardiographic measurement of cardiac structure and function

All echocardiographic measurements were conducted according to American and European guidelines. (Lang et al., 2015; Nagueh et al., 2016) Trained sonographers performed echocardiographic examinations at five study centers in Finland. A single cardiac imaging specialist trained all sonographers. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Acuson, Mountain View, CA, USA) ultrasonography, using a 3.5 MHz scanning frequency phased-array transducer. Analysis of the echo images was carried out by one observer blinded to the clinical details using ComPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program. (Ruohonen et al., 2016)

4.4.1 Left ventricular mass and remodeling

LVM and RWT were calculated from M-mode PLAX views based on diastolic values. LVM was calculated with the standard formula: (0.8[1.04((LV end-diastolic diameter + end-diastolic posterior wall thickness + end-diastolic interventricular septum thickness)^3 – LV end-diastolic diameter)^3] + 0.6 g. RWT was calculated as (2 x end-diastolic posterior wall thickness) / LV end-diastolic diameter. For specific analyses, LVM was indexed to body height ($m^{2.7}$) expressed in $g/m^{2.7}$ and to BSA expressed in g/m^2. LVEF was calculated as follows: LVEF = 100 x (LV end-diastolic volume - LV end-systolic volume)/LV end-diastolic volume. End-diastole was defined by the onset of the QRS complex or the widest diameter if the QRS complex signal was not optimal. LAVi was calculated as LA volume/BSA.

Because the YFS population is relatively young and healthy, the number of cardiac morbidities and changes in the myocardium are minor. Thus, LV remodeling patterns were defined by the population 85th percentile cut-off values for LVM/BSA and RWT. By using this method, we can identify the individuals with the trait of LV hypertrophy. Concentric remodeling was defined as high RWT without LV hypertrophy. Concentric hypertrophy was defined as LV hypertrophy with a high RWT. Eccentric hypertrophy was defined as LV hypertrophy without high RWT.

4.4.2 Left ventricular diastolic function

PW Doppler imaging was used to measure peak E-wave velocity (cm/s). E wave describes the mitral blood flow during the early diastole measured at the level of mitral leaflet tips. Color flow imaging was used to optimally align the PW Doppler with the blood flow in the apical four-chamber view. Peak modal velocity in early diastole was at the leading edge of the spectral waveform. A-wave peak velocity (cm/s) was measured similarly at the time of LA contraction. E/A-ratio was calculated by dividing E-wave peak velocity by A-wave peak velocity.

PW TDI was used to measure é peak velocity (cm/s). é represents mitral annular early diastolic velocity towards LA. The apical four-chamber view was used, and PW TDI sample volume was placed at lateral and septal mitral annular regions. Peak modal velocity in early diastole was measured at the leading edge of the spectral waveform. In this thesis, E/é-ratio was calculated using the average of lateral and septal values of é velocity.

4.5 Statistical methods

The statistical analyses were performed using the R statistical packages from 3.3.2 to 4.02. (R Core Team 2016. R: A language and environment for statistical

computing, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/) The distributions of the study variables were confirmed by visual evaluation and the Kolmogorov-Smirnov test. The study center was used as a technical covariate in the statistical models to ensure that the results were not driven by differences between the study centers.

4.5.1 Study I

Mean and standard deviations (SD) were calculated for the variables used in the study to describe the study participants' characteristics. For smoking, type 2 diabetes, hypertension, and metabolic syndrome number of participants and percentage of participants were reported. Parameters with skewed distributions were log-transformed: ALT, GGT, CRP, triglycerides, fasting serum glucose, insulin, and HOMA-IR. To study the differences between men and women, Welch Two-Sample t-test was used for each continuous variable with a normal distribution, while an independent 2-group Mann-Whitney U-Test was used for continuous variables with skewed distribution. For categorical variables, a Pearson's chi-squared test with Yates' continuity correction was used. Adjusted means were calculated using least-squares means. Pearson's correlation analysis was used to analyze correlations between echocardiographic parameters. Linear regression and multivariable linear regression analyses were conducted to study the associations between studied determinant parameters and LV diastolic function parameters. The possible effect modification by sex was analyzed by adding interaction terms to the multivariable linear regression analyses.

4.5.2 Study II

The study used AUC parameters to evaluate the long-term burden of BMI and SBP between ages 6–18. The methodology for AUC calculation is described below in chapter 4.5.4. The AUC values were standardized for analysis (z-transformed with mean 0 and SD 1). The primary outcome variable was LVM, and the secondary endpoints were LV volume and LV remodeling patterns. The remodeling phenotypes were defined by using the population 85th cut-off values for LVM and RWT. Multivariable linear regression analysis was used to analyze the association between exposure and outcome variables and to analyze differences between study groups. Unadjusted group differences were analyzed with 2-tailed t-tests. We calculated inverse probability weights to fit marginally structural models to verify the magnitude of observed associations and correct for possible issues due to collinearity and multicollinearity in regression analysis.

4.5.3 Study III

The study used AUC parameters to evaluate the long-term burden of cardiovascular risk factors between ages 6–18 with Adulthood E/é-ratio. The methodology for AUC calculation is described below in chapter 4.5.4. Variables were standardized (mean 0 and SD 1) to ensure the comparability of the point estimates among the studied risk factors. Multivariable linear regression analyses were conducted to study associations between childhood risk factors and adulthood LV diastolic function. Variance inflation factors were used to detect multicollinearity in multivariable models. We calculated a childhood risk score (0 to 3) by defining having a risk factor as having the AUC value within the highest quartile for adiposity and systolic blood pressure and in the lowest quartile for PA. Least-squared means were calculated to study adjusted means between cardiovascular risk factor groups. Sensitivity analyses were conducted by using arithmetic means instead of least-squares means or cut-off limits of 80th/20th for the risk factors to calculate the childhood cardiovascular risk score indicating the childhood risk factor accumulation.

4.5.4 Participant-specific curves by mixed model regression splines

The covariance structure for the longitudinal setting was modeled by allowing for participant-specific regression spline coefficients, which were incorporated as random effects into the model.(Rovio et al., 2017; S. Welham et al., 2009; S. J. Welham et al., 2006) To avoid overfitting on a subject level, we reduced the number of knots (two knots on the calendar time from 1980 to 2011) for the participant-specific part from that of the fixed effect's part (four knots on age from 3 to 34 years). To be more specific, we model the average and the participant-specific deviations from the average profile (and in-so-doing the covariance structure) by the mixed model regression spline.

$$Y_{ij} = (\alpha + a_i) + (\beta + b_i)t_{ij} + \sum_{k=1}^{5} \gamma_k B_k(t_{ij}) + \sum_{l=1}^{3} c_{il} B_l(v_{ij}) + e_{ij}$$

where

- Y_{ij} is the log of the studied variable of the ith participant at the jth occasion.
- T_{ij} is the age of the participant, and v_{ij} is the (calendar time – 1980) at the jth measurement occasion.
- The B-functions are the mathematical basis functions for the spline construction.

Thus, the fixed effect's part, $\alpha + \beta t_{ij} + \sum_{k=1}^{5} \gamma_k B_k(t_{ij})$, of the model estimates the average profile over the follow-up period. The role of the spline part is to allow departures from the linear mean trend in a flexible manner given by the data. In the final model, we allowed the intercept (α) to depend on the birth cohort and sex, and the slope (β) and the spline coefficients (γ) to be different for boys and girls.

The random-effects a_i, b_i and c_{i1}-c_{i3}, represent heterogeneity in trajectories across individuals, are assumed to be independent across participants, and normally distributed with zero mean and unstructured covariance matrix; finally, e_{ij} is the independent and normally distributed error term. The predicted values of the random effects for each participant, added to the estimated average trajectory, give the estimate of the individual trajectory (best linear unbiased prediction). The individual trajectories were then integrated to obtain AUC (Figure 4.5.4). The mean profile was allowed to vary across birth cohorts and sex in terms of possibly different fixed effects parts. For these studies, the AUC variables were defined between ages 6–18.

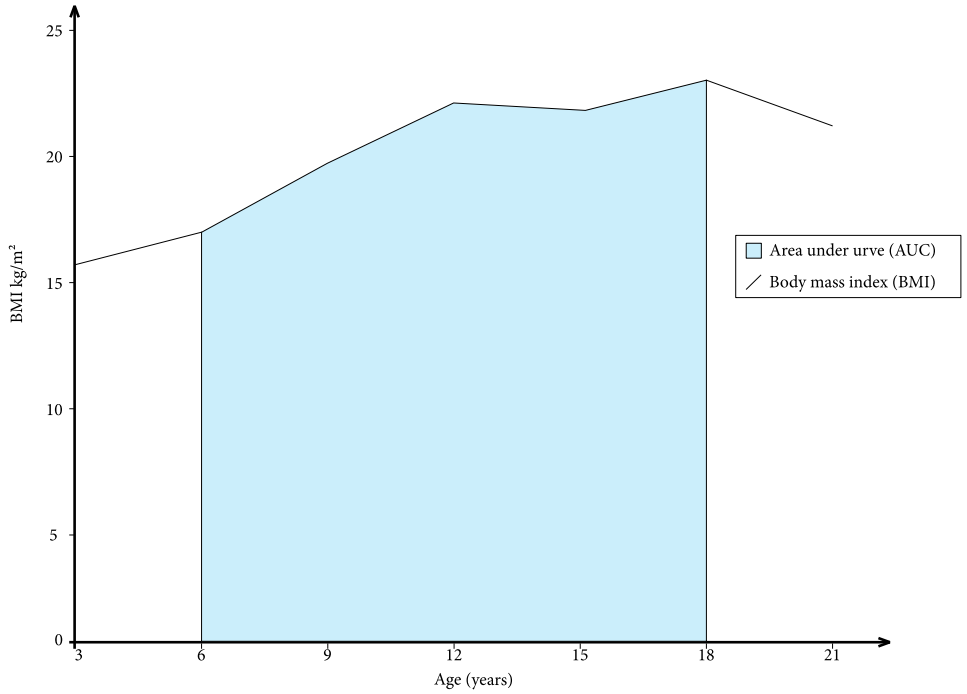

Figure 4.5.4 Graphical illustration for the calculation of AUC. From original publication II, supplemental material.

4.6 Ethics

YFS study protocol was approved by the ethics committee of the University of Turku and Turku University Hospital. Informed consent was obtained from all participants, and their parents provided it for the under-aged participants.

5 Results

5.1 Characteristics of the participants

The study population's clinical and biochemical characteristics at the baseline and at the time of the cardiac ultrasound (in the year 2011) are shown in tables 5.1A and 5.1B. At the baseline, ages ranged from 3 to 18, and in the year 2011 from 34 to 49 years. Echocardiographic characteristics of the patients are shown in Table 5.1C Study participant characteristics are shown according to the exclusions of Study I, no significant changes to participant characteristics are seen if study II or III exclusion criteria are used.

Table 5.1A Study participant characteristics in the year 1980.

	Men		Women	
	n	Mean ± SD	n	Mean ± SD
Age (years)	880	10.7 ± 5.0	1048	11.0 ± 5.0
Systolic blood pressure (mmHg)	868	113.6 ± 13.0	1043	112.1 ± 10.9
Diastolic blood pressure (mmHg)	742	68.6 ± 9.6	911	21.8 ± 6.0
Height (cm)	870	144.7 ± 27.4	1045	142.0 ± 23.7
Weight (kg)	872	40.7 ± 20.0	1045	38.4 ± 16.5
BMI (kg/m2)	870	18.0 ± 3.1	1044	17.9 ± 3.1
Total cholesterol (mmol/l)	870	5.0 ± 0.8	1035	5.2 ± 0.8
Triglycerides (mmol/l)	870	0.6 ± 0.3	1035	0.6 ± 0.3
HDL-C (mmol/l)	870	1.5 ± 0.3	1035	1.5 ± 0.3
LDL-C (mmol/l)	870	3.3 ± 0.8	1035	3.4 ± 0.8
Insulin (mU/l)	865	9.0 ± 5.5	1030	10.6 ± 6.3

Table 5.1B Study participant characteristics in the year 2011.

	Men		Women	
	n	Mean ± SD	n	Mean ± SD
Age (years)	880	41.7 ± 5.0	1048	42.0 ± 5.0
Heart rate (beats/min)	830	61.0 ± 10.1	1012	63 ± 9.3
Systolic blood pressure (mmHg)	876	122.9 ± 13.3	1043	115.4 ± 13.6
Diastolic blood pressure (mmHg)	876	77.6 ± 10.9	1043	72.3 ± 9.4
Height (cm)	880	179.8 ± 6.6	1046	166.1 ± 6.0
Weight (kg)	880	87.1 ± 15.4	1048	71.8 ± 15.1
Waist circumference (cm)	880	96.6 ± 12.2	1047	87.4 ± 13.8
BMI (kg/m2)	880	26.9 ± 4.2	1046	26.0 ± 5.4
GFR (mL/min/1.73 m2)	875	97.2 ± 5.2	1040	103.4 ± 5.8
ALT (U/l)	875	23.0 ± 15.2	1040	13.2 ± 9.7
GGT (U/l)	875	44.8 ± 43.9	1040	24.4 ± 28.8
CRP (mg/l)	875	1.5 ± 2.6	1040	1.8 ± 2.6
Total cholesterol (mmol/l)	875	5.3 ± 1.0	1040	5.1 ± 0.9
Triglycerides (mmol/l)	875	1.6 ± 1.2	1040	1.1 ± 1.2
HDL-C (mmol/l)	873	1.2 ± 0.3	1040	1.4 ± 0.3
LDL-C (mmol/l)	838	3.4 ± 0.9	1032	3.1 ± 0.8
Fasting serum glucose (mmol/l)	875	5.5 ± 0.8	1040	5.2 ± 1.0
Insulin (mU/l)	873	10.4 ± 10.7	1036	9.6 ± 16.0
HOMA-IR	873	2.8 ± 4.2	1036	2.6 ± 8.6
Alcohol consumption	808	1.2 ± 1.4	995	0.5 ± 0.7
Leisure-time physical activity index	786	8.9 ± 1.9	980	9.1 ± 1.9
	n	n (%)	n	n (%)
Smoking	821	137 (17 %)	1009	133 (13 %)
Type 1 diabetes	880	3 (0.3 %)	1048	7 (0.7 %)
Type 2 diabetes	880	33 (4 %)	1048	36 (3 %)
Hypertension	880	206 (23 %)	1048	151 (14 %)
Metabolic syndrome	870	222 (26 %)	1025	180 (18 %)
Overweight	880	386 (43 %)	1046	319 (30 %)
Obese	880	180 (20 %)	1046	207 (20 %)
Overweight or obese	880	566 (64 %)	1046	526 (50 %)

Table 5.1C Echocardiographic characteristics of the study population in the year 2011.

	Men		Women	
	n	Mean ± SD	n	Mean ± SD
E/é-ratio	880	4.6 ± 0.9	1048	5.0 ± 1.0
E/A-ratio	880	1.16 ± 0.2	1047	1.2 ± 0.3
LVEF (Four-chamber view)	866	57.7 ± 3.4	1030	58.9 ± 3.6
LVM	838	157.9 ± 32.7	1020	115.2 ± 23.2
LVM/height$^{2.7}$	838	32.4 ± 6.8	1018	29.3 ± 6.0
LVM/BSA	838	76.7 ± 14.3	1018	64.3 ± 10.8
RWT	838	0.3 ± 0.04	1020	0.3 ±0.04
LV diastolic diameter (PLAX, M-mode)	841	5.4 ± 0.5	1020	5.0 ± 0.4
LV diastolic volume (Four-chamber view)	868	151.2 ± 29.9	1030	114.1 ± 21.8
LA systolic diameter (PLAX, M-mode)	872	4.0 ± 0.4	1032	3.6 ± 0.4
LAVi	862	23.4 ± 6.8	1019	21.8 ± 6.0
Interventricular septum diastolic thickness (PLAX, M-mode)	839	0.8 ± 0.09	1021	0.7 ± 0.07
LV posterior wall diastolic thickness (PLAX, M-mode)	838	0.7 ± 0.08	1021	0.7 ±0.07

5.2 Determinants of the left ventricular diastolic function in adulthood (Study I)

Figure 5.2. shows the association between E/é-ratio and studied parameters in both sexes. E/é-ratio was inversely associated with height and directly with age, LVM, SBP, diastolic blood pressure, weight, waist circumference, BMI, ALT, GGT, CRP, total cholesterol, triglycerides, fasting serum glucose, insulin, HOMA-IR, hypertension, and the metabolic syndrome, and inversely with height. Additionally, among women, E/é-ratio was indirectly associated with glomerular filtration rate and directly with heart rate, BSA, and alcohol consumption.

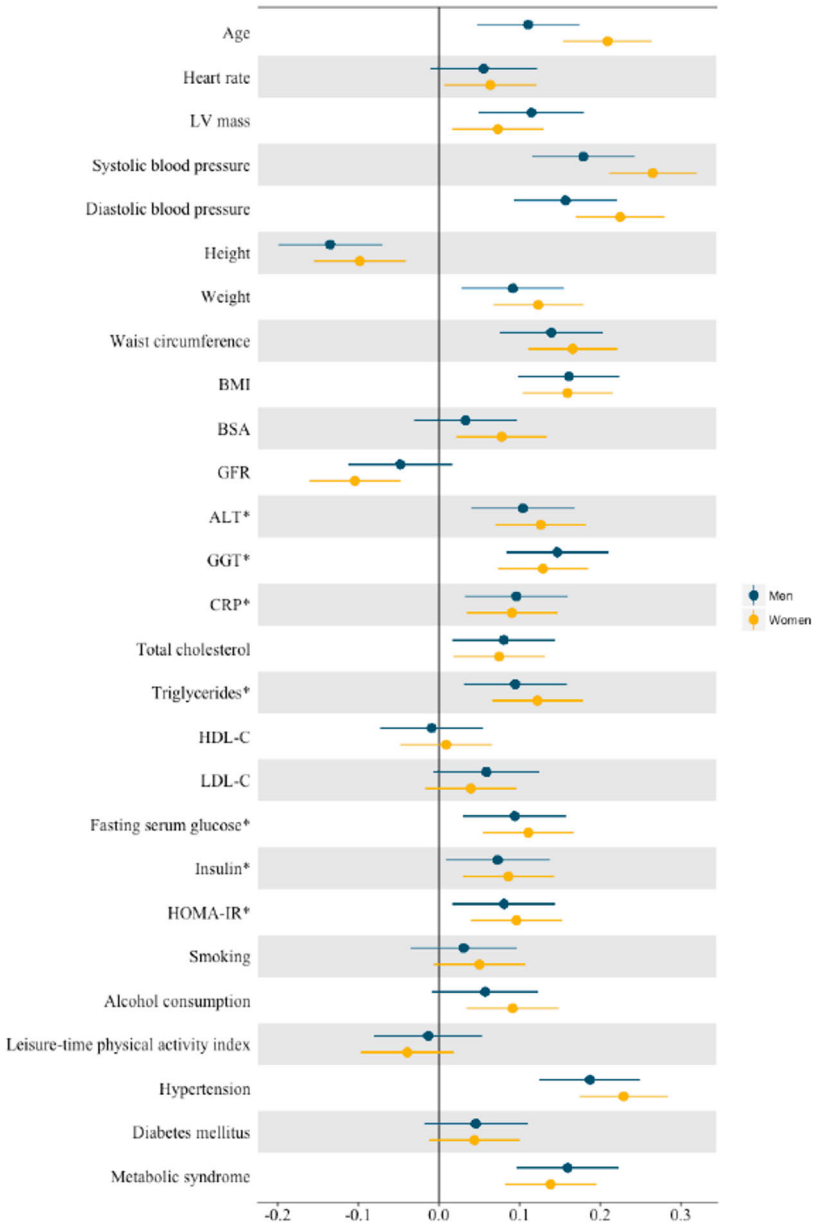

Figure 5.2. The association between E/é-ratio and studied parameters in both sexes. Linear regression analyses were adjusted for the study center, and parameters were standardized for visualization in forest plot (mean 0 and SD 1). Error bars denote 95%confidence intervals. *Variable log- transformed prior to modeling. E/é-ratio was inversely associated with height and directly with age, LVM, SBP, diastolic blood pressure, weight, waist circumference, BMI, ALT, GGT, CRP, total cholesterol, triglycerides, fasting serum glucose, insulin, HOMA-IR, hypertension, and the metabolic syndrome, and inversely with height. Additionally, among women, E/é-ratio was indirectly associated with glomerular filtration rate and directly with heart rate, BSA, and alcohol consumption. Modified from the original publication I.

Results of the multivariable analysis are shown in table 5.2. Age, SBP, and PA-index were significantly associated with all diastolic function parameters. E/é- and E/A-ratios had significant associations also with sex and waist circumference. E/A-ratio and LAVi had significant associations with LVM. In addition, E/é-ratio had a significant association with height, ALT, and smoking, whereas LAVi was associated significantly with GFR. Height and waist circumference were not studied with LAVi as BSA correlates strongly with both parameters, not reflecting the actual association with LA volume.

In further analyses fasting serum glucose was replaced with insulin in the otherwise similar multivariate models. Insulin was inversely associated with E/A-ratio and LAVi ($P < 0.005$ for both), whereas no association was found for E/é-ratio ($P = 0.6$). When SBP, waist circumference, total cholesterol, and fasting serum glucose were replaced with the diagnosis of the metabolic syndrome in the multivariable models, the metabolic syndrome was found to have a significant association with higher E/é-ratio (unadjusted mean values between groups: 5.05±1.02 vs 4.74±1.02) and lower E/A-ratio (1.40±0.32 vs 1.59 ± 0.41) ($P < 0.005$ for both), whereas no association was found for LAVi (22.79 ± 6.56 vs 22.49 ± 6.39) ($P = 0.2$).

Table 5.2 Results of multivariate linear regression models.

	E/é			E/A			LAVi[a]		
	β[e]	SE	P-value	β[e]	SE	P-value	β[e]	SE	P-value
Female sex	0.443	0.081	< 0.005	0.099	0.034	< 0.005	-0.465	0.496	0.348
Age (Years)	0.019	0.006	< 0.005	-0.016	0.002	< 0.005	0.121	0.041	< 0.005
LV mass (g)	0.002	0.001	0.081	0.001	0.000	< 0.005	0.050	0.006	< 0.005
Systolic blood pressure (mmHg)	0.011	0.002	< 0.005	-0.004	0.001	< 0.005	0.044	0.012	< 0.005
Height (cm)	-0.018	0.004	< 0.005	0.002	0.002	0.289			
Waist circumference (cm)	0.005	0.002	0.024	-0.006	0.001	< 0.005			
Glomerular filtration rate (mL/min/1.73 m2)	-0.004	0.005	0.443	-0.001	0.002	0.582	0.123	0.037	< 0.005
ALT[b] (U/l)	0.100	0.047	0.032	-0.031	0.020	0.107	-0.471	0.313	0.133
Total cholesterol (mmol/l)	0.005	0.024	0.836	-0.015	0.010	0.128	-0.146	0.166	0.380
Fasting serum glucose[b] (mmol/l)	0.146	0.186	0.434	-0.065	0.078	0.406	-2.479	1.326	0.062
Smoking (yes/no)	0.140	0.064	0.028	-0.022	0.027	0.400	0.219	0.444	0.623
Alcohol consumption[c]	0.011	0.021	0.604	0.010	0.009	0.267	0.140	0.145	0.334
Leisure-time physical activity index[d]	0.002	0.012	0.888	0.014	0.005	< 0.005	0.429	0.082	< 0.005

[a]Height and waist were not included in the model [b]Log-transformed prior to modeling. [c]Alcohol consumption was measured as drinks per day. [d]An index score ranging between 5-15. [e]β-estimate of the multilinear regression model. Additionally, to the variables shown in the table, study center was included as an independent variable in the model. SE = Standard error. Reproduced from the original publication I.

5.2.1 Association between left ventricular remodeling patterns and E/é-ratio

Participants with concentric hypertrophy had statistically significantly higher adjusted mean E/é-ratio than participants with normal cardiac geometry. The E/é-ratio was similar in participants with concentric remodeling, eccentric hypertrophy and normal cardiac geometry.

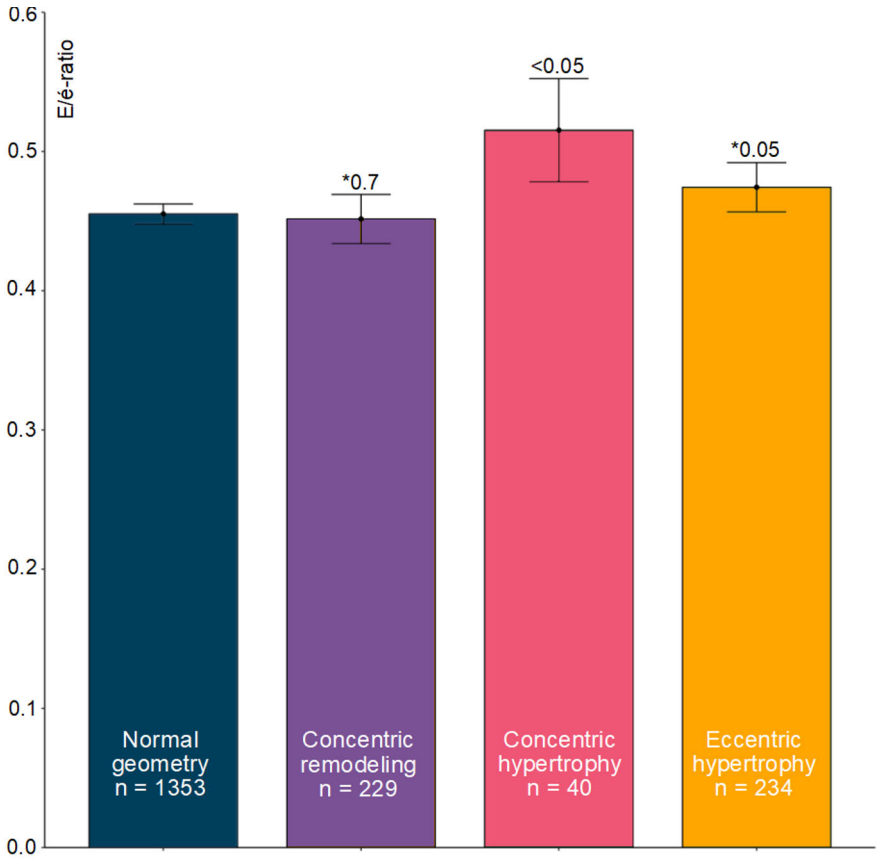

Figure 5.2.1 The adjusted means for adulthood E/é-ratio in different LV remodeling groups. Error bars denote 95% confidence intervals. P-values compared to the normal geometry group are displayed at the top of each bar. Model adjusted with study center, sex, and age. Corresponding results were seen with unadjusted mean values. The LV geometry groups were defined by the population 85th percentile cut-off values for LV hypertrophy (indexed LV mass/BSA) and RWT. Modified from the original publication I.

5.3 Associations between the early-life burden of BMI and adulthood LV structure (Study II)

In stratified analyses, the study population was divided into four groups by overweight/obesity status in early life and adulthood. Participants overweight in early life had ~14% increased LVM regardless of BMI status in adulthood (Figure 5.3). Overweight in early-life combined with obesity in adulthood (BMI > 30 kg/m^2) resulted in a 21% (17.3–32.9%, p < 0.0001) increase in LVM. Furthermore, after adjusting for the adulthood risk factors (as in Table 5.3) of LVM, the LVM increase of early-life overweight stayed significant at 4.7% (2.5–6.9 %, p<0.0001) as the continuous exposure to high BMI through early-life and adulthood 17.5% (14.9–20.1%, p < 0.0001)

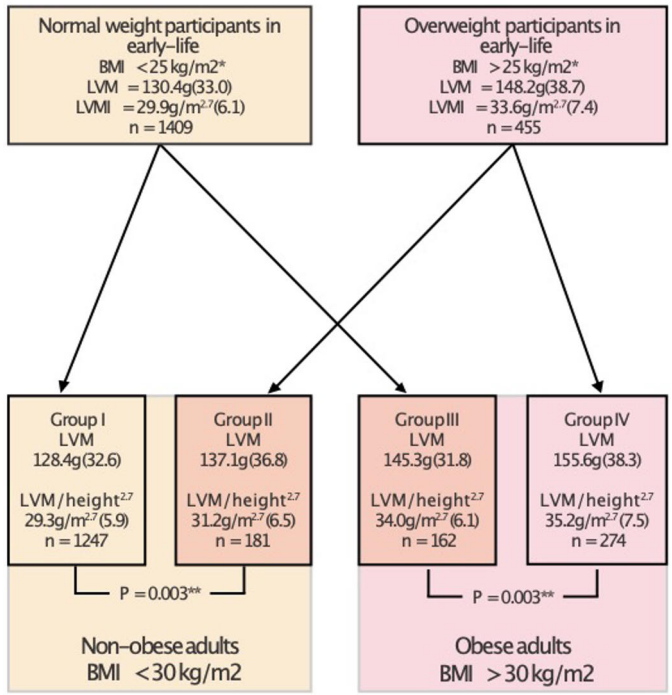

Figure 5.3 Numbers in parentheses correspond to SD values unless stated otherwise. *Participants were defined as overweight in early life if: (I) their age- and sex-specific BMI values exceeded the international BMI percentiles corresponding to adult BMI of 25 kg/m^2 in at least 50% of the measured values between ages 6 and 18 or (II) their BMI burden between years 6 and 18 calculated as AUC exceeded AUC value derived from the international BMI corresponding to adult BMI of 25kg/m2. Group I: non-overweight in early life and non-obese in adulthood, Group II: overweight in early life and non-obese in adulthood, Group III: non-overweight in early life and obese in adulthood, Group IV: overweight in early life and obese in adulthood. **Unadjusted p-value for comparison of LVM between the groups. Modified from the original publication II.

When assessing the long-term burden by utilizing the AUC parameters between the ages of 6-18 in a multivariable model, the burden of early-life BMI was associated significantly with increased LVM in adulthood. (Table 5.3) After adjusting for contemporary adult determinants of LVM, early-life BMI burden was associated significantly with LVM (3.61g/SD increase in early-life BMI; [1.94–5.28], p<0.001). The magnitude of this association is ~36% of the association between adult BMI and LVM. To analyze whether weight or height is a significant factor in BMI, we repeated the multivariable model, but with BMI replaced with weight and height separately. In this model, LVM was significantly associated with early-life weight, (4.18 g per one SD in weight; CI 2.02–6.34 g, p<0.001) but height was not (p = 0.14). Furthermore, the increased burden of elevated SBP in early life was associated with higher LVM in adulthood, but the association was diminished to insignificant when the analysis was adjusted for other risk factors. We calculated inverse probability weights to fit marginally structural models to study the magnitude of observed associations and correct for possible issues due to collinearity in regression analysis. The analysis gave similar estimates for both early-life BMI (5.23 g per one SD in BMI; CI 2.07–8.40 g, p < 0.001) and adult BMI (11.65 g per one SD in BMI; CI 9.41–13.89 g, p < 0.001).

Table 5.3 Results of multivariable models of adulthood and early life (age 6-18 years) factors associating with the left ventricular mass.

	Adulthood model ‡			Combined model ‡		
	β	CI	P-value	β	CI	P-value
Age (for year)	0.3516	0.11–0.60	0.005	0.4774	0.22–0.74	<0.001
Sex (for male sex)	39.9307	37.35–42.51	<0.001	38.6191	35.82–41.42	<0.001
Adult BMI, kg/m^2	11.7948	10.47–13.12	<0.001	9.83	8.25–11.41	<0.001
Adult SBP, mmHg	2.1246	0.77–3.48	0.002	2.1161	0.65–3.58	0.005
Early life BMI*	-	-	-	3.5456	1.87–5.21	<0.001
Early life SBP*	-	-	-	0.3708	-1.09–1.84	0.62
Variance Explained:	50.7 %			51.5 %		

*Both Early-life BMI and Early-life SBP were measured as AUC derived from longitudinal measurements between the ages 6 and 18. ‡Models were additionally adjusted for the study centre in the year 2011 adult alcohol consumption and physical activity. The β-coefficients indicate the change in the outcome variable (measured in grams) corresponding to one SD change in continuous exposure variables or for the difference between sexes. Reproduced from the original publication II.

The secondary analysis results showed that early-life BMI has an independent association with the risk of developing an eccentric hypertrophy remodeling pattern. The study population was divided into equal size quartiles by sex-specific early-life BMI values using the 1st quartile as the reference group. The odds ratio for having eccentric hypertrophy increased systematically between the early-life BMI quartiles, showing a significant difference between the 1st, 3rd, and 4th quartiles and for trend across the groups ($p < 0.001$). Inline, continuous exposure to high BMI from early life to adulthood was associated with a higher risk for eccentric hypertrophy in stratified analysis (adjusted odds ratio 2.04, CI 1.35–3.07, $p < 0.001$). Similar associations were not found with concentric remodeling, concentric hypertrophy, and early-life BMI quartiles. The independent association of early-life BMI with LV end-diastolic volume was highly significant and comparable to the effect of adult BMI (8.01 ml per one SD in early-life BMI; CI 6.43–9.60ml, $p<0.0001$ and 9.92 ml per one SD in adult BMI; CI 8.49–11.35 ml, $p<0.0001$). Early-life SBP did not associate with adulthood LVM or any remodeling patterns after adjusting for adulthood risk factors ($p > 0.05$ for all analyses).

5.4 Associations between childhood cardiovascular risk factor burden and left ventricular diastolic function in adulthood (Study III)

High cumulative childhood PA exposure was associated with a better adulthood LV diastolic function, whereas high cumulative exposure to childhood adiposity and SBP were associated with worse adulthood LV diastolic function (Figure 5.4A, Table 5.4). After adjusting the model with adulthood counterpart risk factors, the association between adulthood LV diastolic function and childhood adiposity and PA exposures stayed statistically significant (Table 5.4) The association between childhood SBP was insignificant when adulthood risk factors were taken into account.

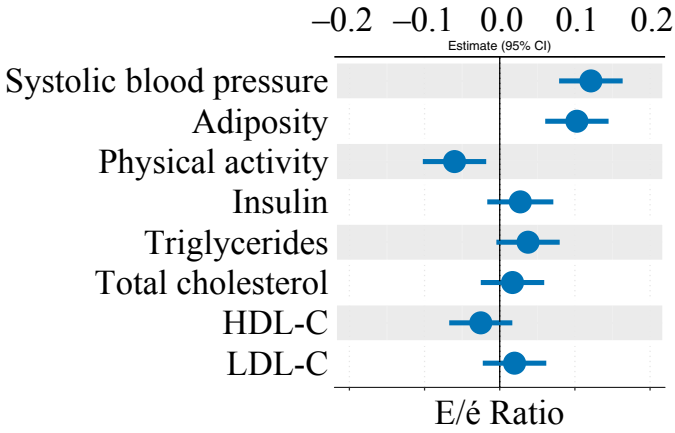

Figure 5.4A Standardized b-estimates for the associations between each separate childhood (age 6–18 years) cumulative cardiovascular risk factor and adulthood E/é-ratio. Linear regression analyses were conducted separately for each cardiovascular risk factor adjusting for age, sex, study center (in the year 2011), and adulthood height. Standardized cardiovascular risk factor variables (mean 0 and SD 1) are shown. Error bars denote 95% confidence intervals. Modified from the original publication III.

Table 5.4 Associations between LV diastolic function (E/é-ratio) and childhood risk factors.

	Childhood-model			Combined-model		
	β	SE	P-value	β	SE	P-value
Female sex	0.084	0.066	0.202	-0.217	0.072	0.003
Age (years)	0.093	0.022	<0.001	0.084	0.023	<0.001
Height in adulthood (cm)	-0.140	0.031	<0.001	-0.137	0.032	<0.001
SBP in childhood*	0.100	0.022	<0.001	0.015	0.025	0.557
PA in childhood*	-0.061	0.023	0.007	-0.053	0.024	0.029
Adiposity in childhood*	0.091	0.025	<0.001	0.075	0.028	0.007
SBP in adulthood (mmHg)				0.180	0.025	<0.001
PA in adulthood				0.018	0.022	0.410
Adiposity in adulthood (cm)				0.039	0.028	0.166

*Childhood cumulative parameters were calculated as AUC variables from estimated participant-specific curves (age window 6-18 years). Explanatory variables were standardized (mean 0 and SD 1). Both models were additionally adjusted for the study center. β = β-estimate. SE = Standard error. Reproduced from the original publication III.

Adjusted means between the childhood risk factor score (0–3) groups showed a significant trend between a higher number of childhood risk factors and a higher E/é-ratio in adulthood (p = 0.007). Compared with the participants with no childhood risk factors, the participants with 2 or 3 childhood risk factors had a higher E/é-ratio in adulthood. (Figure 5.4B)

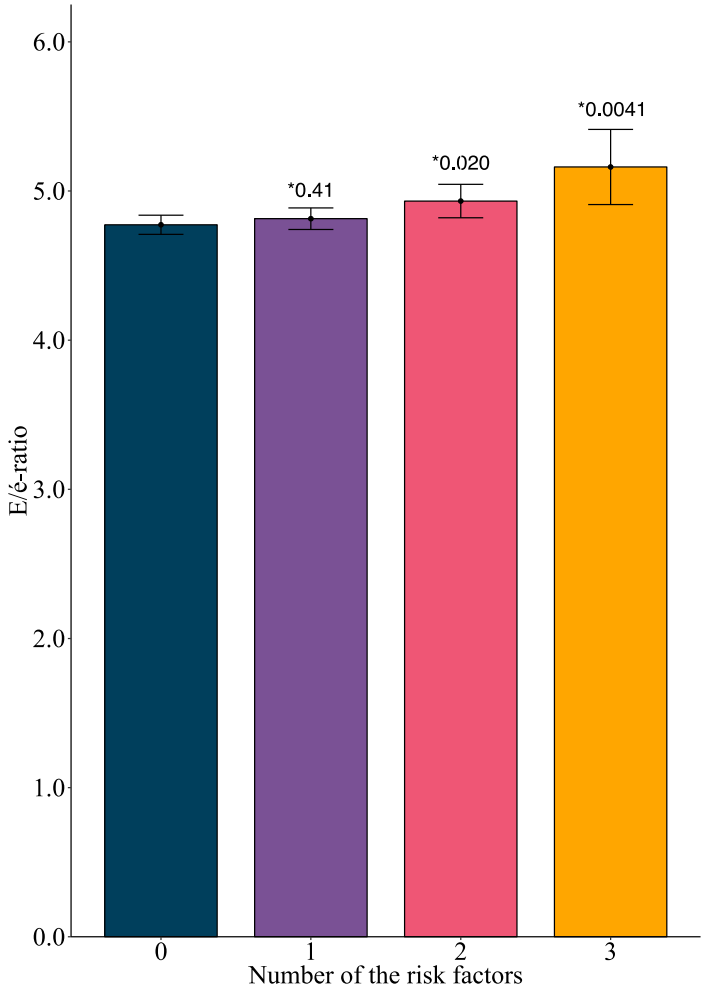

Figure 5.4B The associations between adjusted means for adulthood E/é ratio and childhood cardiovascular risk score. Study participants were divided into 4 groups based on the sum of the risk factors in childhood (n): 0 = 870, 1 = 652, 2 = 296, and 3 = 53. *P values compared with the group with 0 risk factors. The analyses were adjusted for age, sex, research center, adulthood height, systolic blood pressure, physical activity, and waist circumference. Modified from original publication III.

6 Discussion

This study identified several factors associated with LV diastolic function. SBP, waist circumference, and smoking were identified as modifiable adulthood risk factors associated with LV diastolic function. In contrast, height, age, and sex were identified as non-modifiable risk factors. The burden of early-life adiposity and physical activity was associated with adulthood LV diastolic function. In addition, SBP had an association with adulthood LV diastolic function; however, this association diminished when adulthood SBP levels were considered. The early-life burden of higher BMI was associated with higher LVM in adulthood and eccentric hypertrophy pattern. An overview of the main findings of this study is shown in Figure 6.

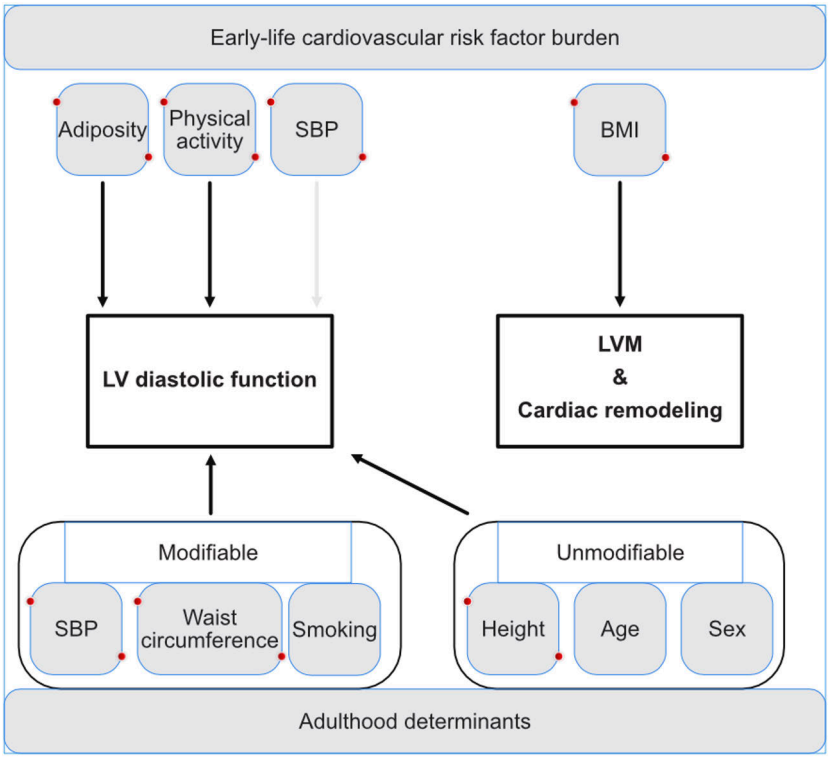

Figure 6. Overview of the main findings of the study.

6.1 Study population

YFS is an internationally unique longitudinal population-based study. The ongoing study started in 1980, and the final sample consisted of 3596 participants aged 3 to 18 years. Participants were randomly chosen from the national population register from five different university cities and their rural surroundings. An equal number of males and females living in eastern and western Finland were chosen. 83.2% of the invited population participated in the initial study, and no systematic reasons for not participating were found. The final sample was representative of the total random sample.

As in every longitudinal study, the possible selection of the study population must be addressed. In the year 2011, 2,063 (57.4%) individuals participated in the study follow-up.(Juonala et al., 2013) The participation in the follow-up visits has been dynamic, and many subjects lost to follow-up early in the study have returned to the study later. Comparisons between participants and those lost in follow-up have been studied previously; participants who were lost to follow-up were more often male and younger than those participating in the study. However, analyses have found no significant differences in either men or women in the major study variables. (Juonala et al., 2004b; Raitakari et al., 2008) The study population is racially homogeneous; therefore, our results are generalizable to white European subjects.

The study population was aged 34–49 at the time of the ultrasound study. Naturally, the amount of significant CVD is low, and the means of the studied LV diastolic parameters were in the normal range, and only sporadic measurements were outside the reference values. This enables more reliable associations with the childhood burden, as the associations are studied before the confounding caused by the onset of severe CVD endpoints, i.e., myocardial infarction, which may cause significant change to the movement of the myocardium and the studied parameters. In contrast, we are not able to tell which part of the study population will generate clinically significant heart disease, e.g., HF. However, disease processes are longitudinal, and as we show in these studies, the cardiovascular risk factor burden already affects clinically healthy hearts.

Third, the study population allows for studying the associations before the confounding caused by the onset of severe CVD endpoints,

6.2 Methodological considerations

6.2.1 Left ventricular diastolic function

The key methodological considerations in this thesis are related to the assessment of LV diastolic function and LVM. When assessing the LV diastolic function in a

clinical setting on an individual patient, the current guidelines recommend interpreting several echocardiographic markers in a wide context that includes clinical status and symptoms. However, this kind of evaluation is strongly based on clinicians' evaluation of an individual patient, and it is not a reliable method in a population-based study. In our studies, we chose to use E/é-ratio as the main study variable for LV diastolic function. E/é-ratio is a commonly used marker for LV diastolic function, but it is not recommended in specific clinical situations, i.e., arrhythmias and ischemic mitral regurgitation. (Yesildag et al., 2011) However, E/é-ratio has been shown to associate with an increased incidence of HF at a population level and has been used in multiple studies to predict all-cause mortality, cardiovascular death, and HF hospitalizations. (Halley et al., 2011; Redfield et al., 2003) Additionally, the E/é-ratio was found to be a predictive factor for worse LV diastolic dysfunction in the follow-up in a population-based follow-up study by Kane et al. (Kane et al., 2011) Furthermore, as our population is relatively young, it is preferable to use E/é-ratio as a continuous parameter as the study population does not reach the clinical cut-offs for LVDD. However, it is reasonable to use parameters in which the tissue Doppler measurements are used as the intracardiac pressure shifts happen when the LV relaxation is already significantly impaired. Thus E/A-ratio or tricuspid regurgitation peak velocity are not ideal parameters for this study population. Using LA volume as a study parameter is not ideal as it is strongly associated with body size.(Maceira et al., 2010) Therefore, it is commonly used as LAVi. However, this causes multicollinearity problems when studying anthropometric cardiovascular risk factors such as obesity. In addition, it has been shown that in healthy individuals, LAVi correlates strongly with cardiorespiratory fitness, and using LAVi as LVDD marker should be done in relation to age relative to cardiorespiratory fitness.(Letnes et al., 2020)

6.2.2 Left ventricular mass and remodeling

LVM was calculated using the 2DE guided M-mode approach as the current guideline by the American Society of Echocardiography and the European Association of Cardiovascular Imaging suggests. Echocardiography is the preferred method to assess LVM in clinical practice due to its low cost, accuracy, and accessibility. (Lang et al., 2015) Furthermore, the M-mode measurement offers less measurement variability when studying large populations. In the YFS study population, the reproducibility of the measurement has been excellent (coefficient of variance 8.4%, interclass correlation 0.9) as described by Ruohonen et al. (Ruohonen et al., 2016) The limitations of this method include that the measurements need to be truly perpendicular to the LV long axis. In addition, the methodology assumes that the thickness of the myocardium is consistent with a ventricle shaped like an

ellipsoid. The formula includes a correction for the 20% overestimation found during the original validation studies of the M-mode technique, and the results are not interchangeable with 2D measurements. (Lang et al., 2015) However, there is a large body of evidence to support the accuracy of this method, and most studies that relate LVM to prognosis are based on this method. (Armstrong et al., 2012) In addition, LVM measurements using different methods have been published earlier in YFS, and only minor differences are found. (Ruohonen et al., 2016)

LVM is strongly associated with lean body mass and is commonly indexed to BSA or raising the height to the power of 2.7. (Bella et al., 1998; Toemen et al., 2020) Current recommendations use indexing with BSA for the calculation of the LV remodeling patterns. (Lang et al., 2015) Most of the large population studies have indexed LVM to BSA. However, as BSA depends strongly on weight, it may underestimate LVM in overweight individuals, especially in children. (Krysztofiak et al., 2019) Indexing of LVM is still under active investigation. In study II, we use absolute LVM, and LVM indexed to height$^{2.7}$, and LVM indexed to BSA when calculating the LV remodeling patterns, and the results are consistent with each other.

LV remodeling patterns were defined according to current recommendations. (Lang et al., 2015) However, as our study population is a relatively young general population thus, only single individuals reach the cut-off for clinical diagnosis of LV hypertrophy. Therefore, we used 85% of the population cut-off for LV remodeling pattern definition and used LVM as a continuous parameter.

6.2.3 Cardiovascular risk factors

Self-reported physical activity was assessed with a questionnaire that included questions on leisure-time physical activity duration, intensity, and frequency. As in every questionnaire-based assessment, there are limitations to discuss. The question on the frequency of physical activity had options with a wide range, i.e., one option included a frequency of 2–6 times a week, and the question on intensity had only three options. However, the reliability of the questionnaire in the YFS has been evaluated repeatedly, and the physical activity levels tracks from childhood to adulthood; furthermore, the participants who are constantly inactive express a less beneficial coronary risk profile compared with those who are constantly active. (Raitakari et al., 1994; Telama et al., 2005)

The used laboratory methods are reliably standardized; thus, the results can be generalized from study to study.(Juonala et al., 2013; Porkka et al., 1997; Raitakari et al., 2008) Due to changes in methodology between the follow-ups, correction equations were used for total cholesterol, HDL-C, triglycerides, and glucose (Table 4.3.3). The stability of laboratory methods is strengthened by the absence of

systematic changes in lipid and glucose levels. Blood pressure was measured in 1980 and 1983 with a standard mercury sphygmomanometer and from 1986 with a random-zero sphygmomanometer. Only SBP was measured using an ultrasound device at baseline in the youngest age group. The use of random-zero sphygmomanometers may have resulted in a downward bias in blood pressure levels. (Yang et al., 2008)

The measurement of BMI has remained constant during the study and can reliably be compared between the follow-ups. In 1980, 1983, and 1986, adiposity was measured using skinfold measurements, and in the follow-up studies conducted in 2001, 2007, and 2011, waist circumference was used to indicate adiposity. A combination AUC-parameter from skinfold measurements and waist circumference measurements was used in Study III. This is because; 1. diastolic function measurements are strongly correlated with height, and parameter describing excess body mass without using height in the formula was required 2. During early-life growth, the changes in BMI are strongly associated with differences in height. (Tryggestad & Chernausek, 2020) The relationship between skinfold measurements and body fat percent has been studied in children and adolescents earlier, and the skinfold measurements have been shown to correlate well with total body dual-energy X-ray absorptiometry and compare in predicting adverse cardiovascular risk profile. (Steinberger et al., 2005) Waist circumference is a commonly used parameter to determine excess body fat and is associated with mortality in adults. (Bigaard et al., 2005) Furthermore, the strength of waist circumference as a cardiovascular risk factor is the measurement of abdominal adiposity, which contributes significantly to the individual's cardiovascular risk. (Misra & Vikram, 2003)

6.2.4 Statistical methods

We used standard statistical methods for the analyses. AUC variables were used to assess the cumulative burden of cardiovascular risk factors in early life. This methodology allows us to analyze longitudinal data from individuals who haven't been in each of the follow-up visits. AUC is calculated from the individual trajectory for each participant by using mixed model regression splines. Therefore, the number of statistical assumptions increases compared to data where all participants have measurements from all time points. However, this methodology reduces the effects of within-participant variability and increases tracking correlations leading to improved estimates of correlation and risk prediction. (Cook et al., 2004)

6.3 Results

6.3.1 Associations between cardiovascular risk factors and LV diastolic function

In previous studies, aging, higher SBP, female sex, higher BMI, sedentary lifestyle, and ventricular remodeling have been shown to associate with worse LV diastolic function. (Bhella et al., 2014; B. J. Borlaug & Paulus, 2011; Kitzman & Little, 2012; Kuznetsova et al., 2014) In contrast, higher physical activity has been associated with higher LV diastolic function. (Bhella et al., 2014) However, most of these associations have been studied in middle-aged or elderly populations.

In study I, we identified the determinants of LV diastolic function in the YFS study population aged 34-49. SBP and age had a strong association with all studied LV diastolic function parameters. In addition, E/é-ratio was associated significantly with female sex, age, waist circumference, smoking, ALT, height, and concentric hypertrophy. These associations with cardiovascular risk factors are in line with the previous studies in more aged populations, suggesting that individuals with these cardiovascular risk factors may be at risk for developing LV diastolic dysfunction.

Study III studied associations between early life cardiovascular risk factor burden and LV diastolic function. This was the first study to show independent associations between early life cardiovascular risk factor burden and adulthood LV diastolic function. The study demonstrated that lower LV diastolic function in adulthood is associated with an increased burden of adiposity and decreased physical activity in childhood. Furthermore, an increasing number of cardiovascular risk factors in childhood are associated with lower LV diastolic function in adulthood. Even though CVD manifestations occur in middle age or later in life, most of the CVD's are longitudinal processes already from childhood, i.e., coronary heart disease, in which longitudinal pathophysiology is well established. (Libby & Theroux, 2005) Similarly, LV remodeling and carotid intima-media thickness in young adulthood has been associated with childhood cardiovascular risk factors. (Li et al., 2003; Raitakari et al., 2003; Tadic & Cuspidi, 2015) Whereas LV remodeling and carotid intima-media thickness have been shown to associate with LV diastolic function. (Nakanishi et al., 2020) Thus, it is logical to hypothesize that decrease of LV diastolic function is a similar longitudinal process acquired across the lifetime. Our results support this hypothesis by showing the associations between the longitudinal burden of early-life cardiovascular risk factors and LV diastolic function. Furthermore, similar findings have been made in a population of young adults in which worse cardiorespiratory fitness was found to associate with higher LV diastolic filling pressures independent of cardiovascular risk factor burden in middle age. (Pandey et al., 2017) If these links are causal, then these data would

support active preventive methods for obesity and sedentary lifestyle during the life course, especially in individuals with cardiovascular risk factor clustering. Furthermore, elevated SBP and smoking should be actively intervened in adults. However, studies on active interventional prevention are needed.

6.3.2 Associations between the early-life burden of BMI and SBP with LVM in adulthood

In adults, higher BMI and SBP are shown to be strongly associated with higher LVM. (Cuspidi et al., 2014; Levy et al., 1988) The findings in children and adolescents are in line with associations found in adults. (Friberg et al., 2004) Furthermore, in children and adolescents, obese individuals have been shown to have higher LVM independent of blood pressure. (Brady, 2016; Friedemann et al., 2012) A review article by Ghosh et al. showed results of high BMI during follow-up resulting in abnormalities in cardiac structure, including higher LVM, but concluded that there is a lack of studies investigating the cumulative effect of life-course exposure to cardiovascular risk factors on the cardiac structure. (Ghosh et al., 2014) Understanding the associations between childhood risk factors and adulthood LVM is important, as higher LVM in adulthood is associated with a higher risk for HF. Thus, it is plausible that early-life high BMI could be an independent risk factor for HF later in life.

In Study II we showed that higher BMI in early life had an independent effect on LVM and the risk of developing eccentric hypertrophy regardless of overweight status in adulthood. SBP levels in early life did not have an independent effect on LVM or LV remodeling. These results suggest that in the general population, early life BMI is a more important predictor of adulthood LVM. It has been previously demonstrated in the YFS cohort that consistently high BMI from childhood to adulthood is associated with a higher risk of type 2 diabetes, hypertension, adverse lipid status, and increased carotid intima-media thickness. (Juonala et al., 2013) However, high BMI did not seem to confer substantial risk for most of the outcomes among participants who became non-obese in adulthood. (Juonala et al., 2013) Study II suggests that LVM is sensitive to early-life high BMI, and the effects last to adulthood. Similar associations have been shown before; in a study by Lai et al., childhood BMI and SBP were associated with higher LVM and with the risk of eccentric and concentric hypertrophy in adulthood. (Lai et al., 2014) The partly different findings may be explained by their study population being overweight and because participants on antihypertensive therapy were excluded from their study population. The implication of these findings is that primary prevention of high BMI in early life may prevent the development of high LVM and eccentric hypertrophy in adulthood.

6.4 Strengths and Limitations

The strengths of this study include the YFS study population, which is well-phenotyped from childhood to adulthood. This kind of longitudinal data is unique worldwide, especially as the data has been reinforced with data from Finnish healthcare databases with updated information on the diagnoses and medications of the participants. Physical, laboratory, and ultrasound examinations of the participants were determined with established and guideline-recommended methods.

There are limitations to discuss. First, as echocardiography is performed by sonographers by manually finding the optimal views, the limitation of the method is that naturally there is small variations between views on each study subject. However, the measurements were made from the standard views by a single observer to avoid variation between observers. Second, the study population is relatively young, and therefore, there was no possibility to study associations with clinical endpoints. Third, as in all longitudinal studies, a loss of follow-up is inevitable. However, as discussed previously, the study population is representative of the original study population. Fourth, The YFS population is racially homogeneous; therefore, our results are generalizable to white European subjects. Overall, it would be ideal to replicate these studies in different study populations. The fifth limitation to discuss is the lack of echocardiographic strain imaging, which could give more information on the LA and LV function. In addition, as we have no longitudinal echocardiographic data, we cannot study the changes in LV diastolic function between two time points. However, as YFS is an ongoing study, there is a possibility for another echocardiography in future follow-ups.

6.5 Clinical implications

The clinical implications of these studies focus on prevention. To underline the importance of prevention, the increasing prevalence of HFpEF and the burden of hospitalizations for patients and the healthcare system must be mentioned. HFpEF is a disease characterized by repeated hospitalizations as the disease progresses, and the quality of life is already reduced in younger patients. (Reddy et al., 2020) In a review study of hospitalization costs associated with HFpEF in U.S the average cost of initial hospitalization per admission was ~8000$ and increased up to ~31 000$ for those with comorbidities. (Clark et al., 2021) Prevention of HFpEF is the main way to suppress the burden it causes because, at the time of the diagnosis, the LV diastolic function is already considerably decreased.

Results of these studies further strengthen the strong evidence supporting active interventions on childhood obesity. Active interventions are crucial as childhood obesity is a constantly growing problem globally. (NCD Risk Factor Collaboration (NCD-RisC), 2017) In the United States, over half of young adults are overweight.

(Ellison-Barnes et al., 2021) WHO considers obesity as today's most blatantly visible – yet most neglected – public health problem. Additionally, these results reinforce the promotion of a physically active lifestyle. The levels of a sedentary lifestyle are rising; according to WHO, the prevalence of physical inactivity was 28% in 2016. (Guthold et al., 2016) The most worrying aspect of the inactivity epidemic is that only 19% percent of adolescents achieve the recommended levels of physical activity in their daily life. (World Health Organization, 2013)

Overall, these results underline the importance of primordial prevention already from childhood. As longitudinal interventional cardiovascular risk prevention studies from childhood to adulthood most likely will not be implemented in the future, the data from observational studies is the base for guidelines. In line with our results, the American Academy of Pediatrics guideline suggests focusing preventive efforts on children with cardiovascular risk factor clustering. (Magge et al., 2017) However, as seen worldwide, the application of preventive data to the form that will make people change their lifestyles is complicated. However, if positive lifestyle habits are already introduced in early life, the effect persists, as continuing these habits is easier than modifying an unhealthy lifestyle. (Niinikoski et al., 2012; Raitakari et al., 2005) Healthcare providers have a central role in educating and reaching parents, children, and young adults at risk. These growing epidemics are beyond individuals' choices and require the use of international and national level preventive methods, including supportive environments and communities, which are fundamental in shaping people's choices. Eventually, making the choice of healthier foods and regular physical activity the easiest choice available.

6.6 Future research prospects

As the YFS study population ages, the CVD events will accumulate. The regular follow-ups will allow studying of the CVD risk factor burden throughout life until the onset of the cardiac disease or CVD event. This enables us to use clinical endpoints instead of surrogate markers of cardiac diseases leading to a better understanding of the cardiovascular risk factor burden. With clinical endpoints, it would be of interest to study cardiovascular risk factor trajectories to get a better understanding of how the risk factor levels in different timepoints affect CVD onset. For example, this would give us a better insight into how obesity status during life course affects the onset of HF.

As these studies are done in a single population-based study, it would be ideal to replicate these studies in different study populations or use data from the i3C Consortium. Which is an international collaboration of longitudinal cohort studies with data from multiple follow-up studies combined that YFS is also part of.

The future follow-ups of YFS make follow-up echocardiography possible. This will allow the studying of longitudinal changes in used echocardiographic parameters and further expand the scope with LV strain measurements. Through recent advances in artificial intelligence, the analyses could be partly automated to reduce the risk of human error.(Alsharqi et al., 2018; Howard et al., 2021; Salte et al., 2021) Furthermore, this enables the possibility of verifying whether the early changes in LV diastolic function and LV remodeling will lead to clinically significant disease. As the usefulness of LV diastolic function measurement in apparently healthy individuals is still under debate, future studies could confirm the usefulness of these measurements by showing the predictive value of the earlier LV diastolic function measurements.

7 Summary and conclusions

1. In the YFS population, representing the general Finnish population, SBP, waist circumference, and smoking were identified as modifiable adulthood risk factors associated with LV diastolic function. In contrast, height, age, and sex were determinants that individuals cannot affect.
2. LV diastolic function in adulthood is associated with early-life cardiovascular risk factor burden. Early-life higher adiposity was associated with lower LV diastolic function, whereas high levels of physical activity in early life were associated with higher LV diastolic function. Furthermore, clustering of early-life cardiovascular risk factors was associated with lower LV diastolic function.
3. The long-term burden of increased BMI in early life was associated with increased LVM and the risk of developing eccentric type hypertrophy in adulthood regardless of adult BMI. The association remained strong even after accounting for adult determinants of LVM and was mainly attributable to higher absolute body weight.

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Original Publications

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ORIGINAL INVESTIGATION

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Determinants of left ventricular diastolic function—The Cardiovascular Risk in Young Finns Study

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Decreased left ventricular (LV) diastolic function is associated with increased all-cause mortality and risk for a heart failure. The determinants of LV diastolic function have been mainly studied in elderly populations; however, the origin of LV heart failure may relate to the lifestyle factors acquired during the life course. Therefore, we examined biochemical, physiological, and lifestyle determinants of LV diastolic function in 34–49-year-old participants of the Cardiovascular Risk in Young Finns Study (Young Finns Study). In 2011, clinical examination and echocardiography were performed for 1928 participants (880 men and 1048 women; aged 34–49 years). LV diastolic function was primarily defined using E/é-ratio (population mean 4.8, range 2.1–9.0). In a multivariate model, systolic blood pressure ($P < 0.005$), female sex ($P < 0.005$), age ($P < 0.005$), waist circumference ($P = 0.024$), smoking ($P = 0.028$), serum alanine aminotransferase ($P = 0.032$) were directly associated with E/é-ratio, while an inverse association was found for height ($P < 0.005$). Additionally, a higher E/é-ratio was found in participants with concentric hypertrophy compared to normal cardiac geometry ($P < 0.005$). Other indicators of the LV diastolic function including E/A-ratio and left atrial volume index showed similarly strong associations with systolic blood pressure and age. In conclusion, we identified systolic blood pressure,

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waist circumference and smoking as modifiable determinants of the LV diastolic function in the 34–49-year-old participants of the Young Finns Study.

KEYWORDS
echocardiography, left ventricular function, left ventricular remodeling

1 | INTRODUCTION

Heart failure with preserved ejection fraction is one of the main cardiac disorders with rising prevalence in developed countries.[1] This condition is a clinical syndrome characterized by symptoms of heart failure with preserved LV systolic function but decreased LV diastolic function, including prolonged isovolumic LV relaxation, slow LV filling, and increased diastolic LV stiffness.[2,3] As LV diastolic function is already considerably decreased when the symptoms of heart failure appear, it is of interest to characterize the determinants of LV diastolic function in healthy populations. With improved knowledge on the determinants of LV diastolic function, targeted lifestyle intervention could be focused earlier on individuals with increased risk of LV diastolic dysfunction.

In previous studies among elderly populations, hypertension, obesity, diabetes, ventricular remodeling, and high age have been found to associate with worse LV diastolic dysfunction.[3,4] Even though the origins of decreased LV diastolic function in later life are suggested to stem from lifestyle factors exerting their influence during the whole life course, the links between these factors and LV diastolic function in clinically healthy adult population have remained obscure. To address this paucity of knowledge, we identified the determinants of LV diastolic function leveraging the echocardiographic, biochemical, physiological, and lifestyle data collected from the 34- to 49-year-old participants of the Cardiovascular Risk in Young Finns Study (YFS).

2 | METHODS

Young Finns Study is an ongoing longitudinal population-based study on cardiovascular risk factors from childhood to adulthood.[5] The study population is representative of the general Finnish population. The baseline study including 3596 children and adolescents (boys and girls; aged 3, 6, 9, 12, 15 and 18 years) was conducted in 1980. Extensive data on cardiovascular risk factors were recorded at baseline and in all follow-up studies performed regularly in 1983, 1986, 1989, 2001, 2007, and 2011. The study protocol was approved by the ethics committee of the University of Turku, and informed consent was obtained from all participants. Detailed information on the YFS population and the study protocol has been reported earlier.[5] All authors had full access to the data.

Echocardiography was performed in 2011 for N = 1994 participants according to the joint American and European guidelines.[2,6] After excluding the participants with missing LV diastolic function measurements, severe cardiovascular diseases (including stroke, myocardial infarction, atrial fibrillation, unstable angina pectoris, cardiomyopathies, and regurgitation or stenosis of mitral or aortic valve), the study population of the present study consisted of N = 1928 participants (880 men and 1048 women, mean age 41.9 ± 5.0 years, range 34–49 years). Population characteristics are shown in detail in Table S1.

Trained sonographers performed the echocardiographic examinations at five YFS study centers in Finland. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Acuson, Mountain View, CA) ultrasonography, using 3.5 MHz scanning frequency phased-array transducer. All sonographers were trained by a single cardiac imaging specialist. Analysis of the echo images was performed by one observer blinded to the clinical details with the CommPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program.[7] We included the study center as a technical covariate in the statistical models to ensure that the results are not driven by differences between the centers.

E/é-ratio, a noninvasive measurement representing LV filling pressure in early diastole, was used as an indicator of LV diastolic function in the present study. Pulsed-wave Doppler imaging was used to measure E and pulsed-wave tissue Doppler imaging to measure é; E wave describes the mitral blood flow during the early filling of the LV, and é measures mitral annular early diastolic velocity toward left atrium (LA). In the present study, E/é-ratio was calculated using the average of lateral and septal values of é velocity.[2] High E/é-ratio reflects lower LV diastolic function, due to deterioration of LV relaxation. Moreover, E/A-ratio, as well as left atrial volume index (LAVi) were defined as additional indicators of LV diastolic function. In E/A-ratio, A wave describes the mitral blood flow during the late filling of the LV at the time of LA contraction. LA volume was planimetered from the apical four chamber view. LAVi was calculated as "LA volume/body surface area (BSA)," for which BSA was calculated using Du Bois formula ($BSA = 0.007184 \times weight^{0.425} \times height^{0.725}$).[8]

Left ventricular mass was calculated as $(0.8[1.04((\text{LV end-diastolic diameter} + \text{end-diastolic posterior wall thickness} + \text{end-diastolic inter-ventricular septum thickness})^3 - \text{LV end-diastolic diameter})^3] + 0.6$ g. Relative wall thickness was calculated as (2× end-diastolic posterior wall thickness)/LV end-diastolic diameter. The LV geometry groups were defined by the population 85th percentile cut-offs values for LV hypertrophy (indexed LV mass/BSA) and relative wall thickness. Concentric remodeling is defined as high relative wall thickness without LV hypertrophy. Eccentric hypertrophy is defined as LV hypertrophy without high relative wall thickness. Concentric hypertrophy is defined as LV hypertrophy with high

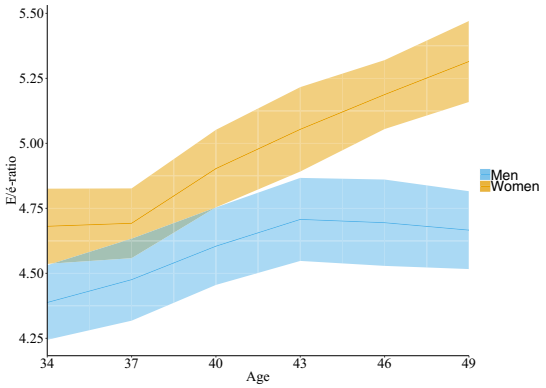

FIGURE 1 Mean E/é-ratio in different age groups in men and women. Ribbons denote 95% confidence intervals

relative wall thickness. The intra-class correlation coefficients with 5th and 95th percentile confidence intervals and coefficient of variance have been reported earlier together with the complete methodology of the cardiac imaging, and the offline analysis of the cardiac measurements conducted in the YFS.[7]

Data on daily smoking (no/yes), leisure-time physical activity (an index ranging between 5–15), and alcohol consumption (standard drinks/day) were collected using questionnaires.[9] Using the data from the follow-up studies in 2001, 2007 and 2011, diabetes mellitus was defined as (a) fasting serum glucose over 7.0 mmol/L, (b) hemoglobin A1c over 6.5%, (c) use of insulin or per oral antidiabetic agents, or (d) a previous diagnosis of diabetes mellitus.

Heart rate was reported directly from the electrocardiography readings. Blood pressure was measured using a random zero sphygmomanometer. Hypertension was defined as (a) systolic blood pressure > 140 mm Hg, or (b) diastolic blood pressure > 90 mm Hg, or (c) using antihypertensive medication.[10] Harmonized definition was used for the metabolic syndrome: (a) waist ≥ 102 cm in men and ≥ 88 cm in women, (b) fasting serum glucose ≥ 5.6 mmol/L or treatment for diabetes mellitus, (c) hypertriglyceridemia ≥ 1.7 mmol/L and high-density lipoprotein cholesterol (HDL-C) levels < 1.0 mmol/L in men and < 1.3 in women and (d) blood pressure ≥ 130/≥85 mm Hg or treatment for hypertension. A diagnosis of the metabolic syndrome required having ≥3 of the 5 criteria.[11] The use of prescription medications was queried from the participants and confirmed from the electronic Patient Data Repository of Social Insurance Institution of Finland.

Height, weight and waist circumference were measured during each study visit. Body mass index (BMI) was calculated as weight (kg)/height (m)^2. Venous blood samples were drawn after an overnight fast and serum was separated, aliquoted, and stored at −70°C until analysis. C-reactive protein (CRP) was determined immunoturbidimetrically.[12] The concentration of serum insulin was determined with an immunoassay.[12] Homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as (insulin × fasting serum glucose)/22.5.[13] Fasting serum glucose, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total cholesterol, HDL-C, and triglyceride concentrations were measured by enzymatic methods.[12] Low-density lipoprotein cholesterol (LDL-C) concentration was calculated using the Friedewald's formula in subjects with triglycerides < 4.0 mmol/L.[14] Serum creatinine was determined spectrophotometrically with the Jaffe' method.[15] Glomerular filtration rate was counted using the Chronic Kidney Disease Epidemiology Collaboration equation.[16] The detailed descriptions of the determinants and biochemical analyses have been published earlier.[5,7,12]

2.1 | Statistical methods

Kolmogorov-Smirnov test and visual evaluation were used to confirm the distributions of the study variables. Due to skewed distributions, values for ALT, GGT, CRP, triglycerides, fasting serum glucose, insulin, and HOMA-IR were log-transformed. To study the differences between men and women, a Welch Two Sample *t* test was used for each continuous variable with a normal distribution, while an independent 2-group Mann-Whitney *U*-Test was used for continuous variables with skewed distribution. For categorical variables, a Pearson's chi-squared test with Yates' continuity correction was used. Age, sex and study center adjusted mean E/é-ratio was calculated for each cardiac remodeling group using least-squares means (The R Package lsmeans).[17] Pearson's correlation analysis was used to analyze correlations between E/é-ratio, conventional cardiac structure measurements, and systolic function measurements.

Linear regression analyses were conducted to study the associations between the biochemical, physiological, and lifestyle determinants and LV diastolic function. First, sex-stratified univariate linear regression analyses adjusted for study center (as a technical categorical variable 1–5) were conducted separately for each determinant to study their associations for E/é-ratio. Second, a multivariate linear regression model for E/é-ratio was conducted by additionally including sex, age, LV mass, systolic blood pressure, height, waist circumference, glomerular filtration rate, ALT, total cholesterol, fasting serum glucose, smoking, alcohol consumption, and physical activity as dependent variables.

The possible effect modification by sex was analyzed by adding interaction terms (sex * age and sex * systolic blood pressure) in the multivariate linear regression model. No significant interactions were found (interaction *P*-values always >0.05). Therefore, the interaction terms were excluded from the multivariate linear regression model. A similar multivariate model was conducted separately for E/A-ratio and LAVi (due to collinearity, height and waist were not included in the model for LAVi). The level of statistical significance was set at $P < 0.05$. We used all available data (Table S1) in the analyses. Therefore, the number of participants varies between the models. The data were analyzed using the R statistical package, version 3.3.2. (R Core Team 2016. R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

3 | RESULTS

The characteristics of the study population are described in Table S1. The prevalence of obesity (BMI > 30) in the study population was 20%. In the whole population, the E/é-ratio values ranged between 2.1 and 9.0, with a mean value of 4.8. Women had higher E/é-ratio than men (5.0 ± 1.0 vs 4.6 ± 0.9; $P < 0.005$). Age was directly associated with E/é-ratio in both sexes (men, β = 0.020; women; β = 0.048). A statistically significant interaction term (age * sex $P = 0.003$) indicated a more pronounced age effect in women than in men (Figure 1). In men, one SD increase in age (ie, 5 years) was found to be associated with ~0.1 SD increase in E/é-ratio while the increase was ~0.2 SD in women (Figure 2). Furthermore, similar results were found between age and systolic blood pressure: a more pronounced age effect was found in women than in men (β = 0.78, SE = 0.082 in women; β = 0.38, SE = 0.089 in men).

In univariate regression analyses in the whole study population, E/é-ratio was directly associated with age, LV mass, systolic blood pressure, diastolic blood pressure, weight, waist circumference, BMI, ALT, GGT, CRP, total cholesterol, triglycerides, fasting serum glucose, insulin, HOMA-IR, hypertension, and the metabolic syndrome, and inversely with height (Figure 2). Additionally, among women, E/é-ratio was directly associated with heart rate, BSA and alcohol consumption and inversely associated with glomerular filtration rate.

The results of multivariate linear regression analyses for E/é-ratio, E/A-ratio and LAVi are shown in Table 1, for septal é and lateral é the results are shown in Table S2. In the analyses for E/é-ratio, female sex, age, systolic blood pressure, waist circumference, ALT, and smoking were directly associated with E/é-ratio, whereas an inverse association was found for height. Additionally, LV mass tended to associate directly with E/é-ratio ($P = 0.08$). No statistically significant multivariable associations were found for other determinants. In the analyses for E/A-ratio, age, systolic blood pressure, and waist circumference were inversely associated with E/A-ratio, whereas female sex, LV mass, and physical activity were directly associated with E/A-ratio. LAVi was directly associated with age, systolic blood pressure, LV mass, glomerular filtration rate, and physical activity.

To gain further insights of associations between the indicators of glucose metabolism and LV diastolic function, we conducted multivariate analyses replacing fasting serum glucose by insulin. In such models, insulin was inversely associated with E/A-ratio and LAVi ($P < 0.005$ for both), whereas no association was found for E/é-ratio ($P = 0.6$). When systolic blood pressure, waist circumference, total cholesterol, and fasting serum glucose were replaced with the diagnosis of the metabolic syndrome in the multivariate model, the metabolic syndrome was found to have a significant association with higher E/é-ratio (unadjusted mean values between groups: 5.05 ± 1.02 vs 4.74 ± 1.02) and lower E/A-ratio (1.40 ± 0.32 vs 1.59 ± 0.41) (multivariate $P < 0.005$ for both), whereas no association was found for LAVi (22.79 ± 6.56 vs 22.49 ± 6.39) ($P = 0.2$).

The results from the analyses comparing each specific cardiac remodeling group (ie, concentric hypertrophy, eccentric hypertrophy and concentric remodeling) to the normal cardiac geometry group are shown in Figure 3. The study participants with concentric hypertrophy had the highest mean E/é-ratio values. Furthermore, compared to participants with normal cardiac geometry, participants with concentric hypertrophy had a higher mean systolic blood pressure (118 ± 13.8 vs 125 ± 16.3 mm Hg, $P = 0.016$). Additionally, E/é-ratio correlated significantly with the following cardiac measurements: deceleration time, LV diastolic volume, LA systolic volume, relative wall thickness, and diastolic posterior wall- and septum thickness. (Table S3). No statistically significant correlations were observed between E/é-ratio and LAVi, E/A-ratio, ejection fraction, LV diastolic diameter, LV mass/BSA or LV mass.

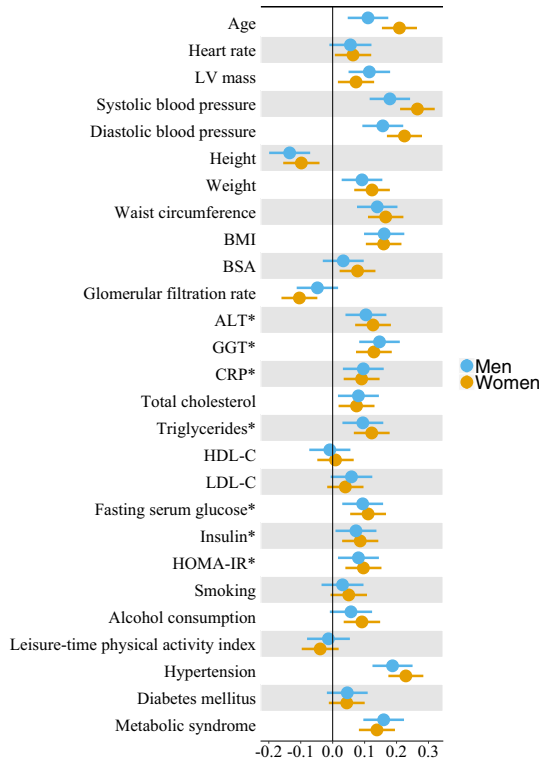

FIGURE 2 Sex-specific normalized β-estimates for the associations between E/é-ratio and each separate study variable. Sex-stratified univariate linear regression analyses were adjusted for study centers, and variables were standardized (0–1). Error bars denote 95% confidence intervals. *Variable log-transformed prior to modeling. ALT = alanine aminotransferase; BMI = body mass index; BSA = body surface area; CRP = C-reactive protein; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = Homeostasis model assessment-estimated insulin resistance; LDL-C = low-density lipoprotein cholesterol; LV = left ventricle

TABLE 1 Results of multivariate linear regression analyses

	E/é			E/A			LAVi[a]		
	β-estimate	SE	*P*-value	β-estimate	SE	*P*-value	β-estimate	SE	*P*-value
Female sex	0.443	0.081	<0.005	0.099	0.034	<0.005	−0.465	0.496	0.348
Age (years)	0.019	0.006	<0.005	−0.016	0.002	<0.005	0.121	0.041	<0.005
LV mass (g)	0.002	0.001	0.081	0.001	0.000	<0.005	0.050	0.006	<0.005
Systolic blood pressure (mm Hg)	0.011	0.002	<0.005	−0.004	0.001	<0.005	0.044	0.012	<0.005
Height (cm)	−0.018	0.004	<0.005	0.002	0.002	0.289			
Waist circumference (cm)	0.005	0.002	0.024	−0.006	0.001	<0.005			
Glomerular filtration rate (mL/min/1.73 m^2)	−0.004	0.005	0.443	−0.001	0.002	0.582	0.123	0.037	<0.005
ALT[b] (U/l)	0.100	0.047	0.032	−0.031	0.020	0.107	−0.471	0.313	0.133
Total cholesterol (mmol/L)	0.005	0.024	0.836	−0.015	0.010	0.128	−0.146	0.166	0.380
Fasting serum glucose[b] (mmol/L)	0.146	0.186	0.434	−0.065	0.078	0.406	−2.479	1.326	0.062
Smoking (yes/no)	0.140	0.064	0.028	−0.022	0.027	0.400	0.219	0.444	0.623
Alcohol consumption[c]	0.011	0.021	0.604	0.010	0.009	0.267	0.140	0.145	0.334
Leisure-time physical activity index[d]	0.002	0.012	0.888	0.014	0.005	<0.005	0.429	0.082	<0.005

ALT = alanine aminotransferase; LAVi = left atrial volume index; LV = left ventricle; SE = standard error.
[a]Height and waist were not included in the model.
[b]Log-transformed prior to modeling.
[c]Alcohol consumption measured as drinks per day.
[d]An index score ranging between 5–15.
Additionally, to the variables shown in the table, study center was included as an independent variable in the models.

4 | DISCUSSION

Our study revealed several potential determinants of impaired LV diastolic function in a population of 34–49-year-old individuals. In addition to aging, strong links were seen with metabolic markers, such as blood pressure and waist circumference. The results suggest that individuals with cardio-metabolic risk factors may be at risk for developing LV diastolic dysfunction. In addition to these metabolic markers, we identified female sex, shorter stature, liver enzyme ALT and smoking as risk factors for impaired diastolic LV function in this age group. Interestingly, the association between age and LV diastolic function was stronger in women than in men, suggesting that women's LV diastolic function may be more vulnerable to the adverse effects of aging than men's. In both sexes, the systolic blood pressure was inversely and strongly associated with LV function already within normal or mildly elevated systolic blood pressure levels. Our results are thus well in-line with the previous studies which have demonstrated that elevated blood pressure a risk factor for LV diastolic dysfunction.[4,18] As an example, a previous study by Perkiömäki et al,[19] identified elevated systolic blood pressure as the main determinant predicting LV diastolic dysfunction during 20-year follow-up in a middle-aged population.

Additionally, we observed higher E/é-ratios in participants with concentric hypertrophy than in participants with normal cardiac geometry. Compared to the participants with normal cardiac geometry, participants with concentric hypertrophy had higher mean systolic blood pressure. Higher E/é-ratio also tended to associate with higher LV mass. If ignored, these changes may lead to increased mortality or sudden death.[20] Our results are in-line with previous observations that have shown that LV hypertrophy is associated with lower LV diastolic function.[21,22] Previously, concentric hypertrophy, with reduced LV relaxation and worse LV volume-mass, associated with lower LV diastolic function in population study with a high prevalence of obesity (44%).[22] Our results suggest that concentric hypertrophy associates similarly with LV diastolic function in a population with a markedly lower prevalence of obesity.

In our study, higher age and female sex were important determinants of higher E/é-ratio. Previous studies in elderly populations have also indicated that diastolic LV function decreases with age.[19,23] Several mechanisms have been proposed to be implicated in the age-related LV diastolic function decrease. These may include an increase of myocardial fibrosis, an increase of myocyte stiffness, changes in intra-cellular calcium homeostasis, progressive thickening of LV walls during aging, and mitochondrial oxidative stress which plays a central role in cardiac aging.[24] Regarding the sex difference, previous investigations have reported that the prevalence of heart failure with preserved ejection fraction and LV diastolic dysfunction is higher in women than in men.[23,25] Previously, it has been suggested that the lack of estrogen may cause impaired LV function in postmenopausal women.[23] Our novel data suggest that the sex difference in diastolic LV function starts to emerge already during the 3rd and 4th decade of life, that is, before menopause, and that in women diastolic function declines faster by age than in men already after the age of 40. The underlying pathophysiological mechanisms

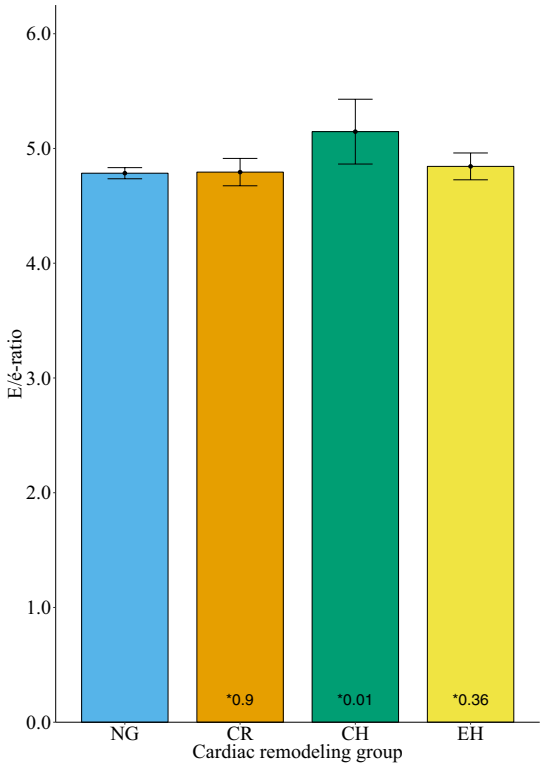

FIGURE 3 Least-squares means of E/é-ratio in different cardiac remodeling groups. Error bars denote 95% confidence intervals. CH = concentric hypertrophy (n = 40), CR = concentric remodeling (n = 229), EH = eccentric hypertrophy (n = 234), NG = normal cardiac geometry (n = 1353). *P*-values compared to NG group displayed at the bottom of each bar. Model adjusted with study center, sex, and age. Corresponding results were seen with unadjusted mean values. The LV geometry groups were defined by the population 85th percentile cut-offs values for LV hypertrophy (indexed LV mass/BSA) and relative wall thickness

creating the sex difference is most likely multifactorial, and not due only to the loss of the cardioprotective effects of estrogens.

Active smoking was associated with lower LV function independent of the other determinants. Previous studies have shown an association between smoking and a higher risk for the incidence of heart failure independent of coronary artery disease.[26] In the study by Nadruz et al,[27] active smoking and cumulative cigarette exposure were associated with subtle alterations in LV structure and function in a population aged 45–64 years. Additionally, Bennet et al[28] have reported an association between smoking and LV diastolic dysfunction in women. The adverse effects of tobacco on the myocardium could be driven by smoking-induced increases in arterial stiffness and increase of LV mass.[27,29] It has also been hypothesized that increased blood pressure or other coexisting risk factors, such as alcohol consumption or lower physical activity level, could confound smoking-associated decrease on LV diastolic function.[27,28] However, our results do not support confounding. We were able to take into account a wide array of potential confounders and still smoking remained independently associated with a lower diastolic function.

In the present study, metabolic syndrome was found to be associated with E/é- and E/A-ratios, as seen in previous studies.[30,31] In addition, E/é-ratio was directly associated with liver enzyme ALT, which may become elevated, for example, in the fatty liver disease.[32] The metabolic syndrome is a clustering of metabolic and cardiovascular risk factors, and fatty liver disease is considered to be the hepatic manifestation of the metabolic syndrome. Both the metabolic syndrome and fatty liver disease are associated with cardiovascular disease, as well as alterations in cardiac structure, function, and metabolism.[30,31,33] The precise mechanisms by which the metabolic syndrome and fatty liver disease cause abnormal of LV diastolic function are unknown, and the proposed mechanisms associate additionally to multiple other comorbidities.[34,35] Our population-based data demonstrating an independent association between elevated ALT and LV diastolic function suggest that hepatic manifestations may play a role or coincide with the development of LV diastolic function. Our data also indicated that the link between the metabolic syndrome and LV diastolic function was driven by elevated systolic blood pressure and waist circumference, as the other components, such as lipids and glucose, showed no associations with LV function.

The other indicators of LV function, including E/A-ratio and LAVi were inversely associated with insulin and directly with physical activity, whereas these associations were not detected for the E/é-ratio. In the study by Hwang et al,[30] insulin resistance was associated with impaired LV diastolic function in a Korean population, and stronger effects were seen for E/A-ratio than E/é-ratio. In several previous studies, insulin resistance and diabetes have been shown to be linked with alterations in cardiac structure and function.[36,37] Several factors may explain the structural and functional changes, including hyperglycemia, coronary microvascular disease, autonomic neuropathy, altered cardiac progenitor cell function, and renin-angiotensin-aldosterone system activation.[36] The precise pathophysiologic mechanisms behind these links, however, are not understood. Furthermore, both E/A-ratio and LAVi were significantly associated with physical activity, which is previously known to cause alterations in cardiac structure, and enlargement of LA.[38] Our results are in-line with varied results from previous studies where no association was found between E/é-ratio and physical activity in a middle-aged population, but in an elderly population ideal level of physical activity was associated favorably with LV diastolic function.[39,40]

There are some limitations in our study that need to be discussed. One potential limitation is a possible selection of the study population. As in every longitudinal study, there is a loss to follow-up in the YFS. However, detailed assessments of the representativeness have previously demonstrated that there are no significant differences between the participants and nonparticipants in the age and sex-adjusted analyses.[5,41] The YFS population is racially homogeneous, therefore our results are generalizable to white Caucasian

populations. Furthermore, since the LV function and LV structure measurements have been measured thus far only once in our cohort, we were not able to evaluate longitudinal changes in LV diastolic function or LV hypertrophy in our population. Future follow-ups is needed to provide insights on whether the LV function measured in asymptomatic individuals is of value in predicting which part of our study population will develop clinically relevant LV diastolic dysfunction or a heart failure. E/é-ratio is the best available non-invasive predictor for the evaluation of LV end-diastolic pressure, but it is not a consistent indicator of LV filling pressures in individual patients in specific clinical situations.[42] However, at a population level in healthy subjects E/é-ratio has been shown to associate with an increased incidence of heart failure and has been used in multiple studies to predict all-cause mortality, cardiovascular death, and heart failure hospitalizations in several disease states.[43–47] E/é-ratio includes the tissue Doppler measurement of mitral annular early diastolic velocity (é) and thus can be considered to reflect changes in the myocardial movement more directly than measurement of E/A-ratio or LAVi.[2] E/A-ratio and LAVi are being shown to be affected by physical activity and this was also shown to be confounding factor in our model as we studied healthy volunteers.[38] Notably, we failed to detect associations with insulin and physical activity for E/é-ratio. Finally, to study the associations of cardiac remodeling on diastolic function, we defined the remodeling phenotypes by using the population 85th cut-offs values for LV mass and relative wall thickness. Therefore, the number of individuals in the various remodeling categories is higher than it would have been by using the clinical criteria of LV remodeling phenotypes based on ASE and EACVI guideline.[6] For example, there were no individuals in our study population that fulfilled the clinical diagnoses of concentric hypertrophy. However, by using an arbitrary extreme cut-point based on population distribution, we are able to show significant differences on LV diastolic function between cardiac remodeling groups suggesting that the remodeling phenomenon is linked to diastolic function before reaching clinical diagnostic criteria.

In summary, all studied echocardiographic LV diastolic function indices were robustly associated with age and systolic blood pressure in the 34–49-year-old participants of the YFS. In addition, we found evidence that waist circumference, smoking and physical activity could be modifiable determinants of the LV function. Thus, our results support active and early on interventions focusing on the implementation of a healthy lifestyle during the whole lifespan in order to promote LV diastolic function.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics & study variables.

Table S2. Results of multivariate linear regression analyses for septal and lateral é.

Table S3. Correlation of E/é-ratio to conventional cardiac structure measurements and systolic function measurements.

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Influence of early-life body mass index and systolic blood pressure on left ventricle in adulthood – the Cardiovascular Risk in Young Finns Study

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ABSTRACT

Background: Increased left ventricular mass (LVM) predicts cardiovascular events and mortality. The objective of this study was to determine whether early-life exposures to body mass index (BMI) and systolic blood pressure (SPB) affects the left ventricular structure in adulthood.

Methods: We used longitudinal data from a 31-year follow-up to examine the associations between early-life (between ages 6–18) BMI and SPB on LVM in an adult population ($N = 1864$, aged 34–49). The burden of early-life BMI and SBP was defined as area under the curve.

Results: After accounting for contemporary adult determinants of LVM, early-life BMI burden associated significantly with LVM (3.61 g/SD increase in early-life BMI; [1.94 − 5.28], $p < 0.001$). Overweight in early-life (age- and sex-specific BMI values corresponding to adult BMI $> 25\ kg/m^2$) associated with 4.7% (2.5–6.9%, $p < 0.0001$) higher LVM regardless of BMI status in adulthood. Overweight in early-life combined with obesity in adulthood (BMI $> 30 kg/m^2$) resulted in a 21% (17.3–32.9%, $p < 0.0001$) increase in LVM. Higher early-life BMI was associated with a risk of developing eccentric hypertrophy. The burden of early-life SPB was not associated with adult LVM or left ventricular remodeling.

Conclusions: High BMI in early-life confers a sustained effect on LVM and the risk for eccentric hypertrophy independently of adulthood risk factors.

KEY MESSAGES

1. Excess in BMI in early-life has an independent effect on LVM and the risk of developing eccentric hypertrophy regardless of overweight status in adulthood.
2. Systolic blood pressure levels in early-life did not have an independent effect on LVM or LV remodeling.
3. The clinical implication of this study is that primary prevention of obesity in early-life may prevent the development of high LVM and eccentric hypertrophy.

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Left ventricular mass; body mass index; blood pressure; risk factor; epidemiology

Introduction

Obesity and hypertension are the major modifiable risk factors for increased left ventricular (LV) remodeling and LV mass (LVM) in adults [1]. In addition, age, male sex, diabetes, metabolic syndrome, alcohol consumption, and intense athletic training are associated with higher LVM [2–4]. Increased LVM is manifested by different LV remodeling patterns defined as eccentric

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hypertrophy, concentric hypertrophy, and concentric remodeling [5]. Increased LVM and LV remodeling are associated with an increased risk of heart failure and mortality in adults [6–8].

It is well established that excess body weight in childhood is associated with higher LVM in children, and it predicts increased LVM in young adulthood [9,10]. Furthermore, children with elevated blood pressure have higher LVM compared to normotensive children [11]. These often co-existing factors, excessive childhood adiposity, and elevated blood pressure are also associated with LV remodeling already in childhood in obese and hypertensive populations [10,12]. Previously, in a study by Lai et al., childhood body mass index (BMI) and systolic blood pressure (SBP) were associated with higher LVM and with the risk of eccentric and concentric hypertrophy in adulthood [13]. However, this study was done in an overweight population with participants on antihypertensive therapy excluded. In addition, other known risk factors, e.g. alcohol usage and physical activity, were not assessed. It is unclear if increased BMI or elevated SBP in childhood and adolescence can have long-lasting effects on LVM or LV remodeling in a general Caucasian population independent of adulthood risk-factors.

Childhood obesity is a growing global problem; therefore, it is of interest to examine its long-term health effects. Possible adverse effects on adult health would warrant more emphasis on primary prevention already from childhood. Thus, this study aimed to determine whether early-life exposures to BMI and SBP affect the LVM and LV remodeling in adulthood, independently of adulthood risk factors of LVM.

Materials and methods

We used the data of cardiac ultrasound measurements of the on-going multicenter study – the Cardiovascular Risk in Young Finns Study [14]. The Cardiovascular Risk in Young Finns Study was initiated in 1980 when participants were randomly recruited to six age cohorts of (3, 6, 9, 12, 15, and 18 years) from the national registry. Data on cardiovascular risk factors (anthropometric data, including BMI, physiological measurements such as blood pressure, biochemical measurements) were recorded. Physical activity and alcohol consumption (standard drinks/day) were collected using validated questionnaires. For additional information on the physical activity questionnaire, please see the online supplement. Follow-ups were performed in 3-year intervals until 1992 (1980, 1983, 986, 1989, and 1992), and additional follow-ups with more extensive measurements were organised in 2001 and 2007 (Figure 1) [15]. In the year 2011, echocardiography was performed for 1994 participants (914 men and 1080 women, mean age 41.9 ± 5.0 years). After excluding 11 women due to pregnancy at the time of cardiac ultrasound, participants with insufficient longitudinal data for BMI, SBP, and cardiac ultrasound measurements, the study population of the present study consisted of $n = 1864$ participants. Participants who were lost to follow-up between 1980 and 2011 were more often men (51% vs. 43%, $p < 0.001$), but there were no statistically significant ($p > 0.05$) differences between participants and non-participants in baseline age, BMI, or blood pressure values among men or women. By 2011, 93 of the original participants had died, with only 14.0% ($n = 13$) of the deaths attributable to cardiovascular causes. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and is approved by the ethics committee of the University of Turku. Informed consent was obtained from all participants. Specific details of the methodology have been described earlier [14,15].

The examinations were conducted according to American and European guidelines [5]. Trained ultrasound technicians performed the echocardiographic examinations at five study centres in Finland. All ultrasound technicians were trained by a cardiac imaging specialist. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Acuson, Mountain View, CA) ultrasonography, using a 3.5 MHz scanning frequency phased-array transducer. Analysis of the echo images was done by one observer blinded to the clinical details with CommPACS 10.7.8 (MediMatic Solutions, Italy) analysis program. The methodology for imaging has been described earlier in more detail [16]. LVM and relative wall thickness were calculated from M-mode parasternal long-axis views based on diastolic values. LVM was indexed to body height ($m^{2.7}$) as the LVM index expressed in $g/m^{2.7}$ [17]. LV end-diastolic volume was measured from apical four-chamber view images with Simpson's rule in a single plane.

To evaluate the possible association of the long-term burden of BMI and systolic blood pressure in early-life (between ages 6 and 18) on LVM in adulthood, area under the curve values (AUC) were calculated for each participant by using the results from repeated measurements of BMI and SBP and used as main exposure variables. Participant-specific curves for BMI and blood pressure were estimated by mixed model regression splines [18]. For more detailed information on the methodology, please see Online

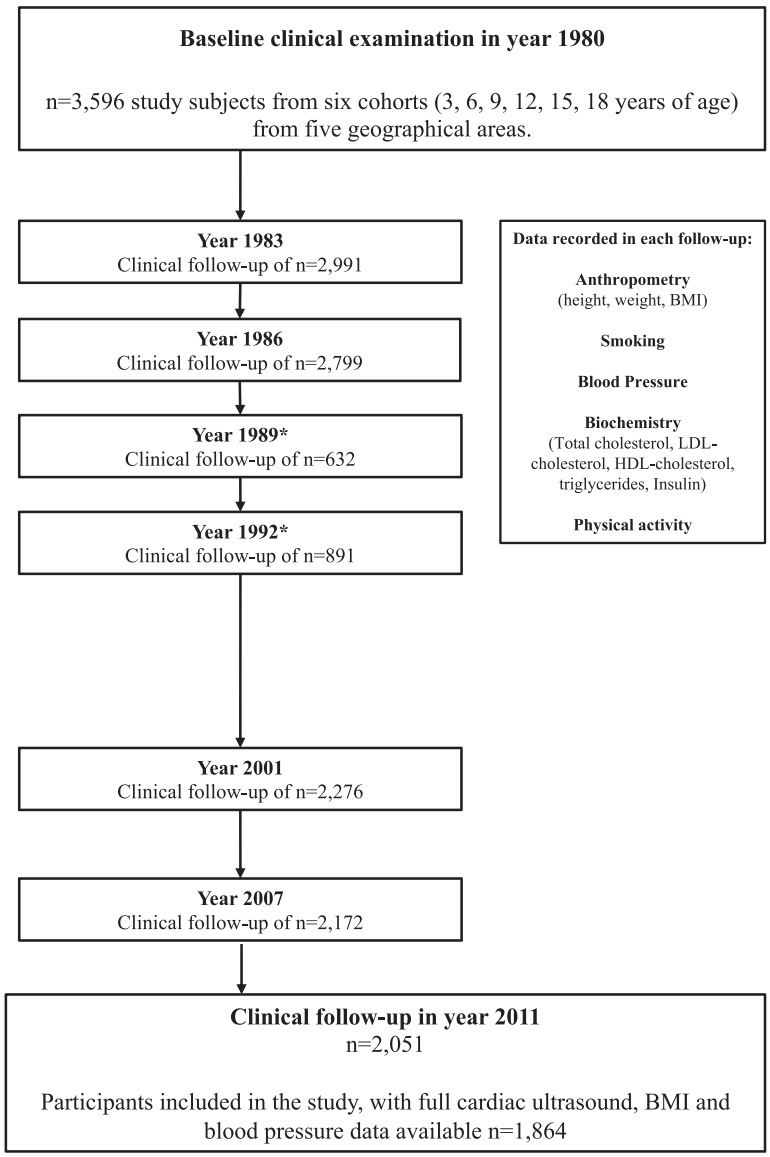

Figure 1. Flowchart of the on-going Cardiovascular Risk in Young Finns Study *Participants invited from only one of the five geographical areas.

supplement 1. Similar to the approach of Lai et al. [13], we then evaluated the AUC as a measure of a long-term burden of each of the measured attributes. The most extensive set of measurements was available between ages 6 and 18 years, after which the proportion of measurements decline significantly. The AUC values were standardised for analysis (z-transformed with mean = 0 and standard deviation (SD)=1). All the effect sizes are reported as an absolute change in the response variable (in grams) corresponding to one SD increase in exposure variables with continuous distribution unless stated otherwise.

The main outcome variable was LVM, and secondary endpoints were LV volume and LV remodeling patterns: eccentric hypertrophy (LV hypertrophy with low relative wall thickness), concentric hypertrophy (LV hypertrophy with high relative wall thickness), and concentric remodeling (high relative thickness without LV hypertrophy). The remodeling phenotypes were defined by using the population 85th cut-off values

for LVM and relative wall thickness. We used multivariable linear adjusted regression analysis to analyse the association between main exposure variables and outcome variables. All the analyses were adjusted for age, sex, adult BMI, and adult SBP. We also included the study centre as a technical covariate in the statistical models to ensure that the results are not driven by differences between the study centres. Alcohol consumption and physical activity in adulthood were significantly associated with LVM ($p < 0.05$ for both) and were used as covariates in the multivariable models. To verify the magnitude of observed associations and correct for possible issues due to collinearity and multicollinearity in regression analysis, we calculated inverse probability weights to fit marginally structural models. These models are used to estimate causal effects from observational data by correcting for confounding with minimal risk for adjusting away part of the effect [19]. R-package ipw was applied in the analysis (http://CRAN.R-project.org/package=ipw).

For stratified analysis, the study population was stratified into four groups by overweight status in early-life and obesity in adulthood at follow-up in 2011 (Figure 2). Participants were defined as having excess early-life overweight if (I) their age- and sex-specific BMI values exceeded the international cut off points for BMI (defined by Cole et al.) corresponding to adult BMI of 25 kg/m^2 in at least 50% of the measured values between ages 6 and 18 or (II) their BMI burden between years 6 and 18 calculated as AUC exceeded AUC value derived from the international cut off points for BMI corresponding to adult BMI of 25 kg/m^2 [20]. Adult participants were stratified by obesity status using a cut-off of 30 kg/m^2.

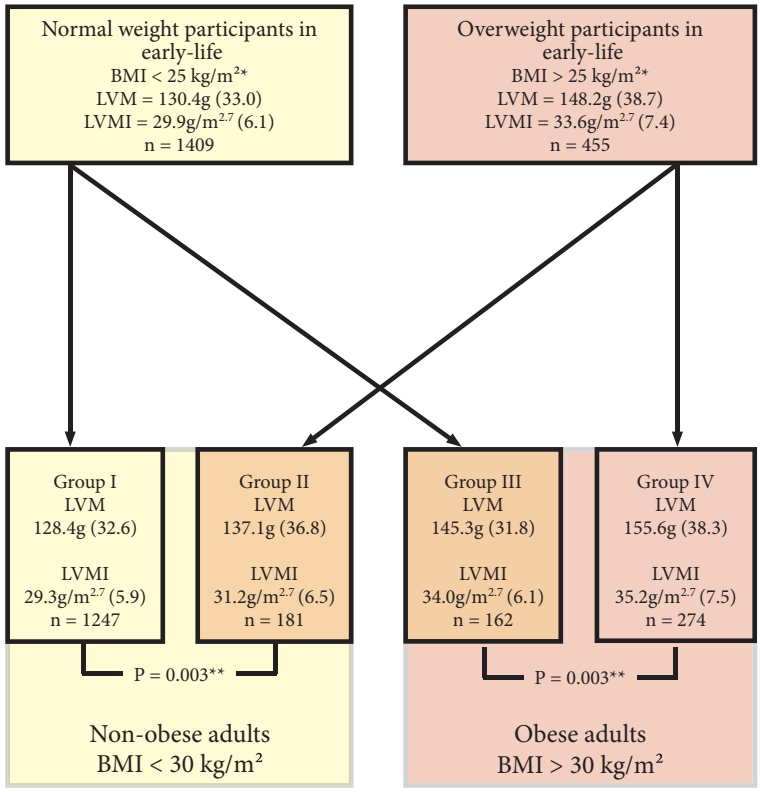

Figure 2. Adulthood LVM by BMI development from early-life to adulthood. Numbers in parentheses correspond to standard deviation values unless stated otherwise. *Participants were defined as overweight in early-life if: (I) their age- and sex-specific BMI values exceeded the international BMI percentiles corresponding to adult BMI of 25 kg/m^2 in at least 50% of the measured values between ages 6 and 18 or (II) their BMI burden between years 6 and 18 calculated as AUC exceeded AUC value derived from the international BMI corresponding to adult BMI of 25 kg/m^2. Group I: non-overweight in early-life and non-obese in adulthood, Group II: overweight in early-life and non-obese in adulthood, Group III: non-overweight in early-life and obese in adulthood, Group IV: overweight in early-life and obese in adulthood. **Unadjusted *p*-value for comparison of LVM between the groups. Abbreviations: AUC: area under curve; BMI: body mass index; LVM: left ventricular mass; LVMI: left ventricular mass indexed for height$^{2.7}$.

Confidence intervals (CI) are reported as 95% CI. We used all available data in the analyses. Therefore, the number of participants varies between the models. Data were analysed with the R statistical package, version 4.0.2 (R Core Team (2016). R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/).

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Study population characteristics at the end of the follow-up (in 2011) are presented in Table 1. The study population represents the general Caucasian population. At the baseline of the study, the prevalence of the participants exceeding the international BMI percentiles corresponding to adult BMI of 25 kg/m^2 was 7.3%. The overall prevalence of obesity (BMI $\geq$ 30 kg/m^2) in adulthood was 19.4%. Mean LVM was significantly higher in men (158.2 g) than in women (115.2 g). We did not find evidence for sex-specific differences in the associations between early-life body mass index and systolic blood pressure with adult LVMI (data not shown). LVM in adulthood was significantly associated with BMI, SBP, and age (Table 2). Diabetes, daily smoking, diastolic blood pressure, use of blood pressure-lowering medication, and metabolic syndrome did not associate significantly with LVM ($p > 0.05$ for all) when the analysis was adjusted for BMI and sex.

In multivariable models, after accounting for adult risk factors, early-life BMI associated significantly with LVM (3.61 g per one SD in BMI; CI 1.94 − 5.28, $p < 0.001$). This association's magnitude is ∼36% of the association between adult BMI and LVM (Table 2). No statistically significant changes were observed in the multivariate model when adjusting either with cumulative childhood physical activity, a blood pressure-lowering medication, having diabetes in adulthood, or birth weight (data not shown).

The Marginal Structural Model analysis gave similar estimates for both early-life BMI (5.23 g per one SD in BMI; CI 2.07–8.40g, $p = 0.001$) and adult BMI (11.65 g per one SD in BMI; CI 9.41–13.89g, $p < 0.001$). To analyse weight and height separately, we repeated the analysis by replacing early-life BMI with early-life weight and height (similar AUC estimates) and adjusted the analyses with adult height and weight. The independent association of early-life weight with LVM was substantial (4.18 g per one SD in weight; CI 2.02–6.34g, $p < 0.001$), whereas the early-life height was not associated with adulthood LVM ($p = 0.14$).

In the secondary analysis, early-life BMI was associated independently with the risk of developing an eccentric hypertrophy remodeling pattern. The increased risk for eccentric hypertrophy attributable

Table 1. Characteristics of the study participants in adulthood (measured in 2011) with full cardiac ultrasound data.

	Men ($n = 846$)	Women ($n = 1018$)
Age, years (range 34–49 years)	41.7 (5.0)	42.1 (4.9)
Diabetic (%) ($n = 10$ with Type I)	31 (3.7)	35 (3.4)
Daily Smokers (%)	134 (15.8)	130 (12.8)‡
Body-Mass Index, kg/m^2	26.7 (4.0)	26.0 (5.4)‡
Overweight* (%)	537 (63.4)	506 (49.7)‡
Obese† (%)	165 (19.5)	197 (19.4)
Systolic blood pressure, mmHg	122.9 (13.4)	115.5 (13.6)‡
Diastolic blood pressure, mmHg	77.5 (10.8)	72.3 (9.5)‡
Physical activity (index score ranging 5–15)§	9.0 (1.9)	9.15 (1.9)
Alcohol consumption (drinks/day)§	1.2 (1.5)	0.51 (0.73)‡
Use of blood pressure lowering medication (*n*)	72 (8.5)	87 (8.5)‡
Metabolic disorder (%)	199 (23.5%)	177 (17.4%)‡
Left Ventricle Mass, g	158.2 (32.8)	115.2 (23.5)‡
Left Ventricle Mass Index, g/m$^{2.7}$	32.5 (6.8)	29.4 (6.1)‡
Relative Wall Thickness	0.286 (0.038)	0.278 (0.037)‡

*Overweight: adult body mass index $\geq$ 25kg/m^2 †Obese: adult body mass index $\geq$ 30 kg/m^2 ‡$p < 0.05$ for the comparison between men and women. §men ($n = 747$), women ($n = 935$).
Values are presented as mean ± SD for the continuous variable and n (%) for categorical variables.

Table 2. Regression analyses of factors associating with the left ventricular mass in the study population.

	Adulthood model 1†			Combined model†		
	Coefficients	CI	*p*-value	Coefficients	CI	*p*-value
Age (years)	0.35	0.11 − 0.60	0.005	0.42	0.17 − 0.68	0.001
Male sex	39.93	37.35 − 42.51	<0.001	39.99	37.41 − 42.57	<0.001
Adult BMI, kg/m^2	12.04	10.69 − 13.39	<0.001	10.01	8.39 − 11.62	<0.001
Adult SBP, mmHg	2.16	0.78– 3.54	0.002	2.08	0.59–3.57	0.006
Early-life BMI*	–		–	3.61	1.94 − 5.28	<0.001
Early-life SBP*	–		–	0.42	−1.04 − 1.89	0.570
Variance Explained:	50.7 %			51.5 %		

*Both Early-life BMI and Early-life SBP were measured as the area under the curve derived from longitudinal measurements between the ages 6 and 18.
†Models were additionally adjusted for study centre in the year 2011 adult alcohol consumption and physical activity.
The coefficients indicate the change in the outcome variable (measured in grams) corresponding to one standard deviation change in continuous exposure variables or for the difference between sexes.
Abbreviations: BMI: body mass index; CI: Confidence interval; SBP: systolic blood pressure.

Table 3. Odds ratio between early-life BMI quartiles and the risk for eccentric hypertrophy in adulthood.

	2nd Quartile	3rd Quartile	4th Quartile
Odds ratio	1.00	1.8	2.24
Confidence interval	0.63–1.59	1.19–2.75	1.49–3.42
p-value	0.99	0.006	0.001

The population was divided into equal size quartiles by sex-specific early-life BMI. 1st quartile was used as the reference group. $p < 0.001$ for trend across groups.

independently to early-life BMI can be demonstrated by dividing the population into equal size quartiles by sex-specific early-life BMI values using the 1st quartile as the reference group. The odds ratio increased systematically between the early-life BMI quartiles, showing a significant difference between 1st and 3rd ($p = 0.006$), 1st and 4th ($p = 0.001$), and for trend ($p < 0.001$) across the groups (Table 3.). A similar analysis was conducted for concentric remodeling and concentric hypertrophy odds ratio between early-life BMI quartiles and the risk for eccentric hypertrophy. However, early-life BMI was not associated independently with the risk of developing concentric remodeling ($p = 0.26$ for trend across groups) or concentric hypertrophy ($p = 0.057$ for trend across groups). The independent association of early-life BMI on LV end-diastolic volume was highly significant and comparable to the effect of adult BMI (8.01 ml per one SD in early-life BMI; CI 6.43–9.60 ml, $p < 0.0001$ and 9.92 ml per one SD in adult BMI; CI 8.49–11.35.ml, $p < 0.0001$). Early-life SBP did not associate with adulthood LVM or any remodeling patterns after adjusting for adult risk factors ($p > 0.05$ for all analyses).

To illustrate the independent association of early-life high BMI and the combined effects of high BMI in early-life and adulthood, we stratified the study population into four groups by overweight status in early-life and obesity in adulthood at follow-up in 2011 (Figure 2).

Before adjusting for other factors, participants who had been overweight in early-life had ~14% higher LVM in adulthood among non-obese and obese adults (Figure 2). After accounting for adult BMI and other adult determinants, early overweight was associated with 4.7% (CI 2.5–6.9%, $p < 0.0001$) higher LVM in the whole study population.

The additive effect of high BMI from early-life to adulthood can be demonstrated by comparing participants who were continuously exposed to high BMI from early-life to adulthood (Group IV) to participants without the exposure to high BMI (Group I) The unadjusted difference of 27.2 g in mean LVM values between these two groups is substantial (an increase of 21.2%, CI 17.3–32.9%) comparing Group I and Group IV, $p < 0.0001$). When the analysis was adjusted with all other adult determinants of LVM (as described earlier), the difference was slightly attenuated but remained highly significant (17.5%, 14.9–20.1%, $p < 0.0001$). Inline, continuous exposure to high BMI from early-life to adulthood associated with a higher risk for eccentric hypertrophy (adjusted odds ratio 2.04, CI 1.35–3.07, $p < 0.001$).

Discussion

We found that the long-term burden of increased BMI in early-life is associated with increased LVM and the risk of developing eccentric type hypertrophy in adulthood regardless of adult BMI in the Young Finns Study cohort. This association remained strong even after accounting for adult SBP and BMI and other known adult determinants of LVM and was mainly attributable to higher absolute body weight.

Previously, a review article by Ghosh et al. [21] showed results of early-life high BMI resulting in worse cardiac structure but concluded that there is a lack of studies investigating the cumulative effect of life-course exposure to risk factors for cardiac structure. Our recent study addresses this gap in knowledge and demonstrates a strong association between the cumulative burden of early-life exposure to BMI on adult LVM and LV remodeling. To clarify the relevance of early-life exposure, we accounted for separately adult risk factors and other confounding factors related to excess body weight. Normal weight participants in early-life, who were non-obese in adulthood, had the lowest LVM. In contrast, participants with consistently high adiposity status (overweight or obese in early-life and obese in adulthood) had over 21% higher LVM. After accounting for adult BMI and other contemporary factors associated with LVM, being overweight in early-life resulted in 4.7% higher LVM in adulthood in the total study population. These observations are clinically relevant as increased LVM is an independent predictor of heart failure even in the absence of ischemic heart disease [22].

YFS has previously demonstrated that consistently high BMI from childhood to adulthood associated with a higher risk of type 2 diabetes, hypertension, adverse lipid status, and increased carotid intima-media thickness [23]. However, excess childhood adiposity did not seem to confer substantial risk for most of the outcomes among participants who became non-obese in adulthood [23]. Our recent study suggests that LVM is sensitive to early-life high BMI, and the effects last to adulthood. In addition, the results suggest that high

BMI in early-life leads to a higher risk of eccentric hypertrophy regardless of BMI status in adulthood. Eccentric hypertrophy of the LV has been associated with obesity in adulthood, and a study by Lai et al. suggested that life course excessive adiposity affects the LV remodeling [13][24]. Although lifestyle changes in adulthood have also been shown to have a positive impact on LV geometry, our results support active intervention already in early-life overweight and obesity [26].

As an observational study, we lack a direct functional link between the burden of early-life BMI and LVM measured in adulthood. However, as high BMI increases total blood volume and cardiac output, the increased workload causes dilatation and stress leading to cardiac remodeling [25,26]. Supporting this, we observed that absolute body weight in early-life, which increases workload, has a strong and significant effect on LVM. The contributing pathophysiological mechanisms associated with increased workload may act through various pathways in the heart, including metabolic, endocrine, and inflammatory factors, ultimately leading to sarcomere replication and parallel growth of non-muscular myocardial components.[27] Our recent results suggest that the independent association of early-life BMI and LVM is shown mainly by the increased overall size of the ventricle by adapting its volume with a corresponding increase in LVM. Previous studies have associated obesity with concentric remodeling, but in their study populations, the study subjects have been morbidly obese with related comorbidities [28,29]. In our study, early-life BMI was associated with eccentric remodeling, in a study population comprising of a random sample of the general population with a low prevalence of extreme obesity (5.4% of participants with BMI $\geq$ 35 kg/m^2 and 1.5% with BMI $\geq$40 kg/m^2).

In this study, the increased burden of elevated SBP in early-life predicted higher LVM in adulthood, but the association was no longer significant when the analysis was adjusted for present risk factors, including adult SBP and BMI and early-life BMI. In the Beijing Blood Pressure Cohort Study, elevated blood pressure in childhood was seen to associate with the LVM index regardless of adult risk factor status [30]. However, childhood blood pressure and BMI were measured only on one occasion; thus, the variability of the parameters in childhood was not assessed. In addition, arbitrary criteria were used for childhood hypertension and adulthood obesity. In our study, we use cut-off values from international guidelines for categorised variables. Furthermore, cumulative childhood parameters are used, which captures the long-term effect of childhood risk factors more efficiently than a single measure. Thus, a direct comparison between these results cannot be made. Similar to our results, previous studies have shown that adulthood obesity may be a stronger risk factor for LV hypertrophy than elevated blood pressure or hypertension [24].

There are some limitations to our study that need to be discussed. One potential limitation is a possible selection of the study population. As in every longitudinal study, there is a loss to follow-up in the Young Finns Study. However, detailed assessments of the representativeness have previously demonstrated no significant differences between the participants and non-participants in the age and sex-adjusted analyses [14]. Comparisons between participants and those lost-to-follow-up using age-adjusted analysis have found no significant differences in either men or women in the major study variables, including anthropometrics, blood pressure, and serum lipoproteins. The Young Finns Study population is racially homogeneous; therefore, our results are generalisable to white Caucasian populations. Furthermore, since the echocardiography measurements have been measured thus far only once in our cohort, we could note evaluate longitudinal changes in LV hypertrophy in our population. Finally, to study the associations of cardiac remodeling and the burden of early-life BMI, we defined the remodeling phenotypes by using the population 85th cut-off values for LVM and relative wall thickness. Therefore, the number of participants in the various remodeling categories is higher than it would have been by using the clinical criteria of LV remodeling phenotypes based on the joint guideline by the American society of echocardiography and the European association of cardiovascular imaging [5]. The major strengths of this study include the longitudinal study design and the long follow-up of participants who were well phenotyped in childhood and adulthood.

In conclusion, we found that exposure to excess in BMI in early-life confers a sustained effect on LVM and the risk of developing eccentric hypertrophy in adulthood regardless of adulthood overweight status. The clinical implication of these findings is that primary prevention of obesity in early-life may prevent the development of high LVM and eccentric hypertrophy. As these traits are associated with a higher risk for heart failure even without the presence of ischemic heart disease, it is plausible that early-life high BMI could be an independent risk factor for heart failure.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data used is declared confidential. Enquires from the corresponding author.

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Cardiovascular Risk Factors in Childhood and Left Ventricular Diastolic Function in Adulthood.
Pediatrics

III

Cardiovascular Risk Factors in Childhood and Left Ventricular Diastolic Function in Adulthood

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abstract

BACKGROUND AND OBJECTIVES: Cardiovascular risk factors, such as obesity, blood pressure, and physical inactivity, have been identified as modifiable determinants of left ventricular (LV) diastolic function in adulthood. However, the links between childhood cardiovascular risk factor burden and adulthood LV diastolic function are unknown. To address this lack of knowledge, we aimed to identify childhood risk factors associated with LV diastolic function in the participants of the Cardiovascular Risk in Young Finns Study.

METHODS: Study participants (N = 1871; 45.9% men; aged 34–49 years) were examined repeatedly between the years 1980 and 2011. We determined the cumulative risk exposure in childhood (age 6–18 years) as the area under the curve for systolic blood pressure, adiposity (defined by using skinfold and waist circumference measurements), physical activity, serum insulin, triglycerides, total cholesterol, and high- and low-density lipoprotein cholesterols. Adulthood LV diastolic function was defined by using E/é ratio.

RESULTS: Elevated systolic blood pressure and increased adiposity in childhood were associated with worse adulthood LV diastolic function, whereas higher physical activity level in childhood was associated with better adulthood LV diastolic function ($P < .001$ for all). The associations of childhood adiposity and physical activity with adulthood LV diastolic function remained significant (both $P < .05$) but were diluted when the analyses were adjusted for adulthood systolic blood pressure, adiposity, and physical activity. The association between childhood systolic blood pressure and adult LV diastolic function was diluted to nonsignificant ($P = .56$).

CONCLUSIONS: Adiposity status and the level of physical activity in childhood are independently associated with LV diastolic function in adulthood.

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WHAT'S KNOWN ON THIS SUBJECT: In adults, decreased left ventricular (LV) diastolic function is associated with several known cardiovascular risk factors such as overweight, hypertension, and physical inactivity. However, the link between childhood cardiovascular risk factor burden and adulthood LV diastolic function is unknown.

WHAT THIS STUDY ADDS: This study reveals that lower LV diastolic function in adulthood is associated with an increased burden of adiposity and decreased physical activity in childhood, supporting the benefits of avoiding high adiposity and adopting a physically active lifestyle from childhood.

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The prevalence of overweight and low levels of physical activity are rising across Western countries, with an increased need for active prevention.[1,2] Cardiovascular risk burden accumulated across the lifetime contributes to cardiovascular disease outcomes that are the leading causes of death globally.[3] The decrease in left ventricular (LV) diastolic function is an early functional alteration of the heart. We have previously shown that higher waist circumference, systolic blood pressure, and smoking are associated with lower LV diastolic function in adults.[4] Adverse effects of childhood obesity on adulthood LV mass has been previously shown in the Bogalusa Heart Study.[5] Additionally, obese children have been reported to have worse LV diastolic function compared with normal-weight children.[6] Conversely, achieving ideal cardiovascular health, defined by the American Heart Association, in childhood has been associated with better LV diastolic function in adulthood.[7]

Heart failure with preserved ejection fraction is a clinical syndrome characterized by symptoms of heart failure without a decrease of LV systolic function.[8] Instead, LV diastolic function is decreased, including slow LV filling and increased diastolic LV stiffness.[9] Currently, there is no evidence-based medicine that improves the prognosis of the condition. Moreover, LV diastolic function is already considerably decreased when the symptoms of heart failure appear. Therefore, it is important to understand the role of risk burden acquired during the life course to be able to provide effective prevention. In adult populations, overweight, insulin resistance, and elevated systolic blood pressure are well-known modifiable risk factors for heart failure with preserved ejection fraction.[10] However, the links between childhood cardiovascular risk factor burden and adulthood LV diastolic function are unknown. To address this lack of knowledge, we aimed to identify childhood risk factors associated with LV diastolic function in the 34- to 49-year-old participants of the Cardiovascular Risk in Young Finns Study (YFS). The longitudinal study design with repeated risk factor measurements beginning from childhood allows us the unique assessment of cumulative risk factor burden from childhood.

METHODS

Study Population

The YFS is an ongoing multicenter, longitudinal, population-based study on cardiovascular risk factors from childhood to adulthood, representing the general Finnish population. The baseline study was conducted in 1980 and included 3596 children and adolescents (49.0% males aged 3, 6, 9, 12, 15, and 18 years). Extensive data on cardiovascular risk factors were recorded at the baseline in 1980, and all follow-up studies were conducted in 1983, 1986, 1989, 2001, 2007, and 2011.[11] Population characteristics from the year 2011 are presented in Table 1. Detailed information on the YFS population and study protocol has been reported earlier.[11] The study protocol has been approved by the ethics committee of the University of Turku and Turku University Central Hospital, and informed consent was obtained from all participants. All authors had full access to the data.

Echocardiographic Measurements

Echocardiography was performed in 2011 for 1994 participants according to the joint American and European guidelines.[9,12] After excluding the participants with severe cardiovascular diseases (including stroke, myocardial infarction, atrial fibrillation, unstable angina pectoris, cardiomyopathies, and regurgitation or stenosis of the mitral or aortic valve), type 1 diabetes, or missing echocardiographic measurements, the study population of the current study consisted of 1871 participants (859 men and 1012 women; mean age 41.8 $\pm$ 5.0 years).

Trained ultrasound technicians performed the echocardiographic examinations at 5 YFS study centers. All ultrasound technicians were trained by a cardiac imaging specialist. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Mountain

TABLE 1 Population Characteristics (the Follow-up Year 2011)

	Women (n = 1012)		Men (n = 859)	
	Mean[a]	SD	Mean[a]	SD
E/é ratio	5.0	1.0	4.6	0.9
Age, y	41.9	5.0	41.7	5.0
Systolic blood pressure, mm Hg	115.3	13.6	122.9	13.4
Height, cm	166.1	6.0	179.8	6.6
Waist circumference, cm	87.0	13.5	96.4	12.0
Weight, kg	71.4	14.8	86.9	15.2
BMI	25.9	5.2	26.8	4.2
Serum total cholesterol, mmol/L	5.1	0.9	5.3	1.0
Triglycerides, mmol/L	1.1	1.2	1.6	1.1
HDL-C, mmol/L	1.4	0.3	1.2	0.3
LDL-C, mmol/L	3.1	0.8	3.4	0.9
Insulin, mU/l	8.8	10.8	10.1	9.6
Physical activity (index score 5–15)	9.2	1.9	8.9	1.9
Overweight, %	30.5	—	44.4	—
Obese, %	18.8	—	19.9	—
Overweight or obese, %	49.3	—	64.3	—

Overweight defined as BMI between 25 and 30; obese defined as BMI ≥30. —, not applicable.
[a] Parameters with "%" indicate percentage rather than mean.

View, CA) ultrasonography by using a 3.5-MHz scanning frequency phased-array transducer. Analysis of the echo images was done by one observer blinded to the clinical details with the CommPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program.[13]

E/é ratio is a noninvasive measurement representing LV filling pressure in early diastole.[9] Pulsed-wave Doppler imaging was used to measure E. Pulsed-wave tissue Doppler imaging was used to measure é; E wave describes the mitral blood flow during the early filling of the LV, and é measures mitral annular early diastolic velocity. In this study, E/é ratio (mean 4.8; range 2.2–9.0) was calculated by using the average of lateral and septal values of é velocity.[9] High E/é ratio reflects low LV diastolic function and has been associated with all-cause mortality in several disease states.[14,15] The complete methodology of the cardiac imaging and the off-line analysis of the cardiac measurements in the YFS have been published earlier.[13]

Clinical Measurements and Questionnaires

Standard methods were used to measure blood pressure, fasting serum glucose, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) concentrations throughout the study.[16] Low-density lipoprotein cholesterol (LDL-C) was calculated according to Friedewald et al.[17] In 1980, 1983, and 1986, serum insulin was measured with a modification of the immunoassay method of Herbert et al.[18] The concentration of serum insulin was determined with an immunoassay in years 2001, 2007, and 2011.[19] At all follow-ups, the participants' weight (kilograms) and height (centimeters) were measured. In the follow-up studies conducted in 1980, 1983, and 1986, childhood adiposity was measured by using subscapular, biceps, and triceps skinfold measurements in triplicate from the nondominant arm by using a Harpenden skinfold caliper.[20] Using these adiposity measures, an area under the curve (AUC) variable was created for childhood adiposity (standardized mean = 100; SD = 15). In the adulthood follow-up studies in 2001, 2007, and 2011, waist circumference (centimeters) was used to indicate adiposity. Data on leisure-time physical activity were collected by using a validated self-report questionnaire from participants aged 9 to 18 years (Supplemental Information).[21] The questionnaire was administered in connection with the medical examination. For participants aged 6 years, physical activity was collected by using parents' ratings (Supplemental Information).[21]

To describe the long-term burden of the risk factors, we estimated participant-specific curves for age window between 6 and 18 years, systolic blood pressure, adiposity, physical activity, insulin, triglycerides, total cholesterol, HDL-C, and LDL-C by mixed-model regression splines.[22] For more detailed information on the methodology, please see the Supplemental Information.

Statistical Analysis

The distributions of the study variables were confirmed by visual evaluation and the Kolmogorov-Smirnov test. Unmodifiable parameters with a strong association with LV diastolic function, namely, age, sex, and adulthood height,[4] as well as the study site, were used as covariates in all statistical models. First, multivariable linear models were conducted separately for each childhood cardiovascular risk factor. Variables were standardized (mean 0 and SD 1) to ensure the comparability of the point estimates among the studied risk factors and to visualize the results as a forest plot. Second, all childhood variables revealing significant associations with adulthood LV diastolic function in the previous model (ie, adiposity, physical activity, and systolic blood pressure) were entered into the same statistical model (childhood model). Third, a multivariable linear model (combined model) was created adjusting the childhood model additionally for corresponding adulthood parameters (ie, adulthood adiposity, physical activity, and systolic blood pressure).

To study the associations of childhood cardiovascular risk factor clustering on adulthood LV diastolic function, we calculated a childhood risk score using those childhood risk factors that associated significantly with LV diastolic function in the multivariable models. The factors included in the score were (1) childhood adiposity, (2) physical activity, and (3) systolic blood pressure. First, for all 3 risk factors, the participants were categorized into those having the risk factor (1 point) and those without the risk factor (0 points). Having a risk factor was defined as having the AUC value within the highest quartile for adiposity and systolic blood pressure and in the lowest quartile for physical activity. The risk score was then calculated by summing all 3 risk factors (range 0–3), resulting in 4 groups: 0 risk factors (n = 870), 1 risk factor (n = 652), 2 risk factors (n = 296), and 3 risk factors (n = 53). Finally, the mean E/é ratio was calculated for each group by using least-squares means (The R Package lsmeans)[23] adjusting the analyses according to the combined model.

We used all available data in the analyses; therefore, the number of participants varies between the models. Variance inflation factors were used to detect multicollinearity in multivariable models (no significant multicollinearities were found). P values $\leq .05$ were considered statistically significant in all analyses. Data were analyzed by using the R statistical package,

version 3.3.2. (R Foundation for Statistical Computing, Vienna, Austria) (http://www.R-project.org/).

RESULTS

Childhood Risk Factors and Adulthood LV Diastolic Function

The high cumulative burden of childhood adiposity and systolic blood pressure were associated with worse adulthood LV diastolic function. The high cumulative childhood physical activity exposure was associated with a better adulthood LV diastolic function (Fig 1). The results remained similar when all 3 childhood risk factors were entered simultaneously in a multivariable linear model (Table 2, childhood model). No significant associations were found for the cumulative childhood burden of serum insulin, triglycerides, total cholesterol, HDL-C, or LDL-C with adult LV diastolic function (Fig 1).

To study whether the associations of childhood risk factors remained significant after controlling for the counterpart adulthood risk factors, we conducted a multivariable model including systolic blood pressure, physical activity, and adiposity measurements from both childhood and adulthood (Table 2, combined model). Childhood adiposity was found to have an association with worse adulthood LV diastolic function independent of adulthood adiposity. The adjustment with the counterpart

TABLE 2 Associations Between LV Diastolic Function (E/é Ratio) and Childhood Risk Factors

	Childhood Model			Combined Model		
	Estimate	SE	*P*	Estimate	SE	*P*
Female sex	0.084	0.066	.202	−0.217	0.072	.003
Age, y	0.093	0.022	<.001	0.084	0.023	<.001
Height in adulthood, cm	−0.140	0.031	<.001	−0.137	0.032	<.001
Cumulative systolic blood pressure in childhood	0.100	0.022	<.001	0.015	0.025	.557
Cumulative physical activity in childhood	−0.061	0.023	.007	−0.053	0.024	.029
Cumulative adiposity in childhood	0.091	0.025	<.001	0.075	0.028	.007
Systolic blood pressure in adulthood, mm Hg	—	—	—	0.180	0.025	<.001
Physical activity in adulthood (index score 5–15)	—	—	—	0.018	0.022	.410
Adiposity in adulthood, cm	—	—	—	0.039	0.028	.166

Both models were additionally adjusted for study center. Childhood cumulative parameters were calculated as AUC variables from estimated participant-specific curves (age window 6–18 y). Explanatory variables were standardized (mean 0 and SD 1). —, not applicable.

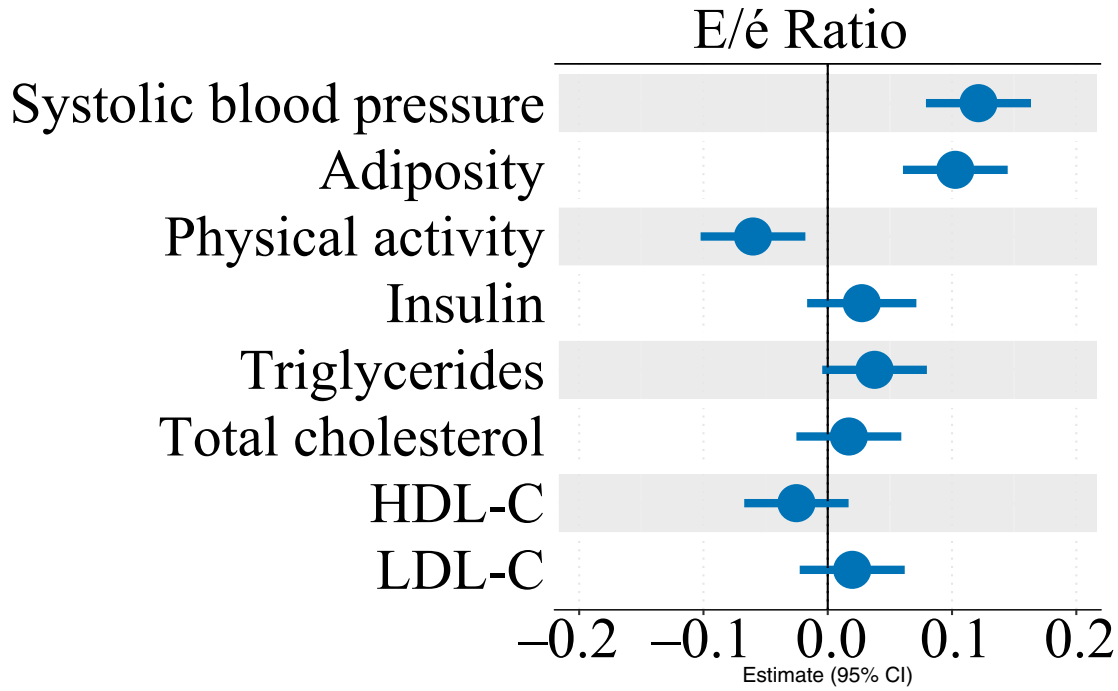

FIGURE 1
Standardized β-estimates for the associations between each separate childhood (age 6–18 years) cumulative cardiovascular risk factor and adulthood E/é ratio. Linear regression analyses were conducted separately for each cardiovascular risk factor adjusting for age, sex, study center (in the year 2011), and adulthood height. Standardized cardiovascular risk factor variables (mean 0 and SD 1) are shown. Error bars denote 95% confidence intervals (CIs).

adulthood risk factors diluted the effect estimate by ~18%. Childhood physical activity had an association with better adulthood LV diastolic function independent of adulthood physical activity. After further adjustment with the counterpart adulthood risk factors, the effect estimate of childhood physical activity was diluted by ~13%. The association of childhood systolic blood pressure with adulthood LV diastolic function was no longer significant when the adulthood risk factors were taken into account (the effect estimate was diluted by 85%).

Clustering of the Childhood Risk Factors

The results from the analyses for the childhood risk factor score, indicating the number of childhood risk factors, are shown in Fig 2. A significant trend was found between a higher number of childhood cardiovascular risk factors and worse LV diastolic function (P = .007). Compared with the participants with no childhood risk factors, the participants with 2 or 3 childhood risk factors had a higher E/é ratio denoting worse LV diastolic function (P = .047 and P = .0066, respectively).

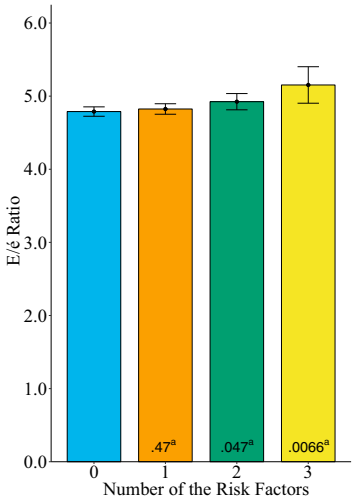

FIGURE 2

Association between childhood cardiovascular risk score and adjusted means for adulthood E/é ratio. The analyses were adjusted for age, sex, research center, adulthood height, systolic blood pressure, physical activity, and waist circumference. Study participants were divided into 4 groups on the basis of the sum of the risk factors in childhood (n): 0 = 870, 1 = 652, 2 = 296, and 3 = 53. [a] P values compared with the group with 0 risk factors.

Finally, all multivariable models were further adjusted for left atrial and ventricular volume, ejection fraction, and LV mass in separate models. The results of these analyses were similar to those of the main analyses reported in Table 2 and Fig 2 (data not shown), suggesting that the results are not driven by changes in LV volume, LV mass, or LV systolic function.

Sensitivity Analyses

Sensitivity analyses were conducted by using (1) arithmetic means instead of least-squares means or (2) cutoff limits of 80th/20th for the risk factors to calculate the childhood cardiovascular risk score indicating the childhood risk factor accumulation. The results from the sensitivity analyses were similar to the main analyses (data not shown).

DISCUSSION

This study reveals that the cumulative burden of adiposity, physical activity, and systolic blood pressure in childhood is associated with LV diastolic function at ages 34 to 49. Importantly, the associations of childhood adiposity and physical activity with adulthood LV diastolic function were independent of the adulthood levels of the same risk factor. This is the first study to indicate that the cumulative cardiovascular risk factor exposure already in childhood may independently contribute to diastolic LV function in adulthood.

Childhood obesity is known to associate with adverse changes in cardiovascular risk factors, such as serum lipoproteins, systolic and diastolic blood pressure, and glucose metabolism.[24] Moreover, both childhood and adulthood obesity are associated with myocardium remodeling and alteration of LV systolic and diastolic function.[25,26] This deterioration in LV diastolic function has been suggested to affect the elastic properties of the myocardium through multifactorial mechanisms.[25,27,28] Our present results indicate that increased childhood adiposity has an inverse association with LV diastolic function in adulthood and that this link remains significant after controlling for adulthood risk factor profile. This suggests that excess childhood adiposity may have long-term adverse influences on LV diastolic function. Importantly, although childhood adiposity was associated independently with adulthood LV diastolic function, the cardiometabolic markers closely linked to adiposity, including childhood insulin, triglycerides, total cholesterol, HDL-C, and LDL-C, were not. Therefore, our results suggest that the association between childhood adiposity and adulthood LV diastolic function is not driven by these cardiometabolic markers.

Previous studies have revealed that physical activity has numerous beneficial effects on cardiovascular health.[29,30] Physically active individuals have fewer cardiovascular comorbidities, including diabetes mellitus, hypertension, and dyslipidemia, than those with low physical activity levels.[31] Previous studies have revealed that lower cardiorespiratory fitness is a risk factor for worse LV diastolic function and heart failure with preserved ejection fraction and may contribute to the prognosis of the disease.[32–35] Furthermore, worse cardiorespiratory fitness in young adulthood was found to associate with higher LV diastolic filling pressures independent of cardiovascular risk factor burden in a middle-aged population.[36] Our

findings, revealing that the childhood cumulative physical activity is associated with better adulthood LV diastolic function, extend these previous observations by demonstrating that the beneficial effects of childhood physical activity may carry on to adulthood.

Hypertension is considered a key risk factor for LV diastolic dysfunction in adults, deterring it through several potential mechanistic pathways, including pressure overload causing LV hypertrophy and alterations in the neurohumoral activity and inflammation.[14,37] In contrast, childhood systolic blood pressure has not been previously linked with adulthood LV diastolic function. In our study, a higher cumulative burden of systolic pressure in childhood was associated with worse LV diastolic function in adulthood. However, the association diluted when adulthood systolic blood pressure was taken into account, suggesting that adulthood systolic blood pressure level is a more powerful determinant for the adulthood LV diastolic function compared to childhood systolic blood pressure.

Cardiovascular risk factors tend to cluster already in childhood, and the clustering of risk factors is thought to be a useful measure of cardiovascular health in children.[38] Our present study extends current knowledge by revealing that the cardiovascular risk factor clustering (ie, an increasing number of risk factors) already in childhood associates with lower LV diastolic function in adulthood. Noteworthy, by broadening the outlook to the long-term effects of childhood risk factor clustering on cardiovascular health and by highlighting the role of lifestyle-related childhood risk factors, the findings from our study underline the need for guideline-recommended active prevention strategies targeted to the individuals with several cardiovascular risk factors beginning from childhood.[39]

The major strengths of this study include the longitudinal study design and the long follow-up of participants who were well phenotyped in both childhood and adulthood. A potential limitation of the study is a possible selection of the study population. As in every longitudinal study, there is a loss in the follow-up. However, detailed assessments of the representativeness have previously revealed no significant differences between the participants and nonparticipants in the age- and sex-adjusted analyses.[11,16] The YFS population is racially homogeneous, therefore our results are generalizable to white European subjects. E/é ratio is a generally used marker for LV diastolic function, but it is not a consistent indicator of LV filling pressures in individual patients in specific clinical situations.[15] However, at a population level, E/é ratio has been shown to associate with an increased incidence of heart failure and has been used in multiple studies to predict all-cause mortality, cardiovascular death, and heart failure hospitalizations in several diseases states.[14,40] Additionally, in a population-based follow-up study by Kane et al,[41] baseline E/é ratio was found to be a predictive factor for worse LV diastolic dysfunction in the follow-up examination. Our study population with no significant cardiac diseases strengthens the significance of these results because the possibility for bias caused by cardiac diseases is low.

CONCLUSIONS

This study reveals that lower levels of adiposity and higher levels of physical activity in childhood are beneficially associated with LV diastolic function in adulthood. Importantly, the clustering of cardiovascular risk factors in childhood is associated with worse LV diastolic function in adulthood. These findings provide novel evidence on the childhood risk factors of adulthood LV diastolic function, supporting the benefits of avoiding high adiposity and adopting a physically active lifestyle already from childhood.

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ABBREVIATIONS

AUC: area under the curve
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
LV: left ventricular
YFS: Cardiovascular Risk in Young Finns Study

Deidentified individual participant data will not be made available.

Dr Heiskanen contributed to the conception and design of the work, contributed to acquisition, analysis, and interpretation of the data, and drafted the manuscript; Drs Ruohonen and Raitakari contributed to the conception and design of the work, contributed to acquisition, analysis, and interpretation of the data, and critically revised the manuscript; Drs Rovio, Pahkala, Kytö, Kähönen, Lehtimäki, Viikari, Juonala, Laitinen, Tossavainen, Jokinen, and Hutri-Kähönen contributed to the acquisition, analysis, and interpretation of data for the work and critically revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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