


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

Jarkko S. Heiskanen MD¹  | Saku Ruohonen PhD^{1,2} | Suvi P. Rovio PhD¹ | Ville Kytö MD, PhD^{1,3} | Mika Kähönen MD, PhD⁴ | Terho Lehtimäki MD, PhD⁵ | Jorma S. A. Viikari MD, PhD^{6,7} | Markus Juonala MD, PhD^{6,7} | Tomi Laitinen MD, PhD⁸ | Päivi Tossavainen MD, PhD⁹ | Eero Jokinen MD, PhD¹⁰ | Nina Hutri-Kähönen MD, PhD¹¹ | Olli T. Raitakari MD, PhD^{1,12}

¹Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland

²Orion Pharma, Turku, Finland

³Heart Center, Turku University Hospital, Tyks T-Hospital, Turku, Finland

⁴Department of Clinical Physiology, Tampere University Hospital and Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

⁵Department of Clinical Chemistry, Fimlab Laboratories and Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

⁶Department of Medicine, University of Turku, Turku, Finland

⁷Division of Medicine, Turku University Hospital, Turku, Finland

⁸Department of Clinical Physiology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

⁹Department of Pediatrics, PEDEGO Research Unit and Medical Research Center Oulu, University of Oulu, Oulu, Finland

¹⁰Department of Paediatric Cardiology, Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

¹¹Department of Pediatrics, Faculty of Medicine and Life Sciences, University of Tampere and Tampere University Hospital, Tampere, Finland

¹²Department of Clinical Physiology and Nuclear Medicine, University of Turku, Turku, Finland

Correspondence

Jarkko S. Heiskanen, Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland.
Email: jsheis@utu.fi

Funding information

This work was supported by the Academy of Finland (grant numbers: 286284, 134309 [Eye], 126925, 121584, 124282, 129378 [Salve], 117787 [Gendi], and 41071 [Skidi]); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Aarne Koskelo Foundation and Diabetes Research Foundation of Finnish Diabetes Association.

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,

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 ComPACS 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 planimetric 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 ($BSA = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$).⁸

Left ventricular mass was calculated as $(0.8[1.04((LV \text{ end-diastolic diameter} + \text{end-diastolic posterior wall thickness} + \text{end-diastolic inter-ventricular septum thickness})^3 - LV \text{ end-diastolic diameter}^3)] + 0.6 \text{ g}$. Relative wall thickness was calculated as $(2 \times \text{end-diastolic posterior wall thickness})/LV \text{ end-diastolic diameter}$. 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

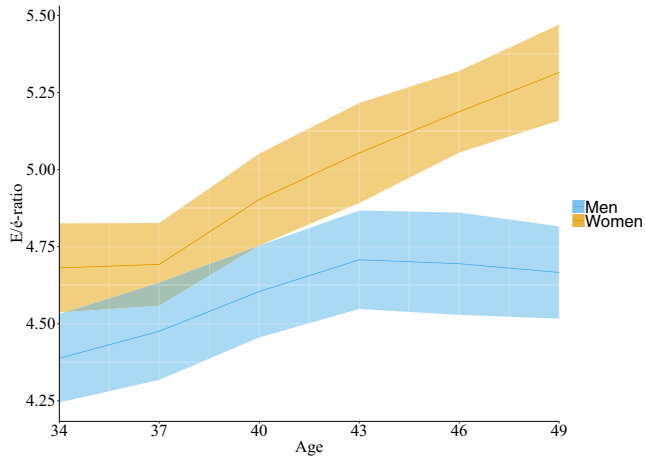


FIGURE 1 Mean E/é-ratio in different age groups in men and women. Ribbons denote 95% confidence intervals

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 \geq 102 cm in men and \geq 88 cm in women, (b) fasting serum glucose \geq 5.6 mmol/L or treatment for diabetes mellitus, (c) hypertriglyceridemia \geq 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 \geq 130/ \geq 85 mm Hg or treatment for hypertension. A diagnosis of the metabolic syndrome required having \geq 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 \times 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, $\beta = 0.020$; women; $\beta = 0.048$). 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 ($\beta = 0.78$, SE = 0.082 in women; $\beta = 0.38$, 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.

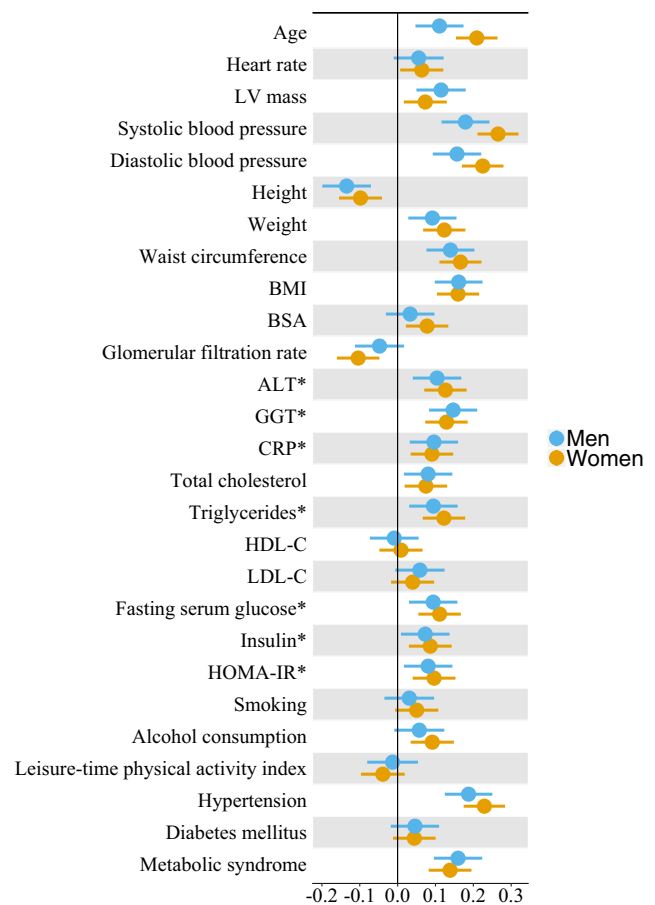


FIGURE 2 Sex-specific normalized β -estimates for the associations between E/é-ratio and each separate study variable. Sex-stratified univariate linear regression analyses were adjusted for study centers, and variables were standardized (0–1). Error bars denote 95% confidence intervals. *Variable log-transformed 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.

^aHeight and waist were not included in the model.

^bLog-transformed prior to modeling.

^cAlcohol consumption measured as drinks per day.

^dAn 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

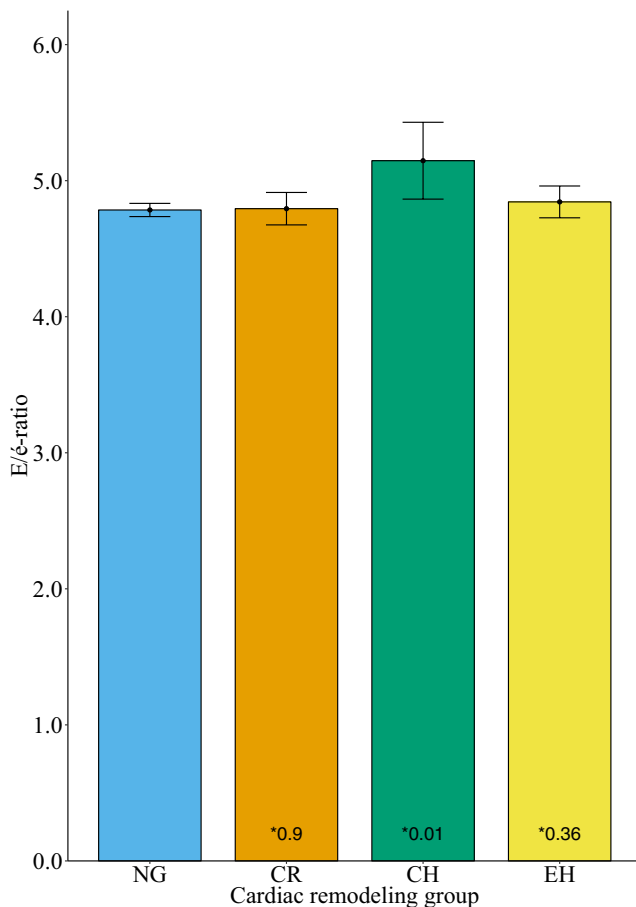


FIGURE 3 Least-squares means of E/é-ratio in different cardiac remodeling groups. Error bars denote 95% confidence intervals. CH = concentric hypertrophy (n = 40), CR = concentric remodeling (n = 229), EH = eccentric hypertrophy (n = 234), NG = normal cardiac geometry (n = 1353). P-values compared to 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 al²⁸ 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.

ACKNOWLEDGMENTS

Expert technical assistance in data management and statistical analyses by Irina Lisinen, Johanna Ikonen, and Noora Kartiosuo is gratefully acknowledged.

ORCID

Jarkko S. Heiskanen  <https://orcid.org/0000-0002-0564-7933>

REFERENCES

- Braunwald E. Heart failure. *J Am Coll Cardiol HF*. 2013;1(1):1–20.
- Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1321–1360.
- Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32(6):670–679. <https://doi.org/10.1093/eurheartj/ehq426>
- Kitzman DW, Little WC. Left ventricle diastolic dysfunction and prognosis. *Circulation*. 2012;125(6):743–745.
- Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: the cardiovascular risk in young Finns study. *Int J Epidemiol*. 2008;37(6):1220–1226.
- Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233–271.
- Ruohonen S, Koskenvuo JW, Wendelin-Saarenhovi M, et al. Reference values for echocardiography in middle-aged population: the cardiovascular risk in Young Finns Study. *Echocardiography*. 2016;33(2):193–206.
- Du Bois D, Du Bois E. Clinical calorimetry tenth paper: a formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med*. 1916;XVII(6_2):863–871.
- Huotari PRT, Mikkelsen L, Kujala UM, Laakso L, Nupponen H. Physical activity and fitness in adolescence as predictors of self-estimated fitness in adulthood. *J Sports Med Phys Fitness*. 2013;53(2):177–184.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159–2219.
- Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International. *Circulation*. 2009;120(16):1640–1645.
- Suomela E, Oikonen M, Virtanen J, et al. Prevalence and determinants of fatty liver in normal-weight and overweight young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med*. 2015;47(1):40–46.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499–502.
- Burgner DP, Sabin MA, Magnussen CG, et al. Early childhood hospitalisation with infection and subclinical atherosclerosis in adulthood: the Cardiovascular Risk in Young Finns Study. *Atherosclerosis*. 2015;239(2):496–502.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.
- Lenth RV. Least-squares means: the R Package lsmeans. *J Stat Softw*. 2016;69(1):1–33.
- Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population

- with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol*. 2012;59(11):998–1005.
19. Perkiömäki JS, Möttönen M, Lumme J, Kesäniemi YA, Ukkola O, Huikuri HV. Predictors of development of echocardiographic left ventricular diastolic dysfunction in the subjects aged 40 to 59 years (from the Oulu Project Elucidating Risk of Atherosclerosis Study). *Am J Cardiol*. 2015;116(9):1374–1378.
 20. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991;114(5):345–352.
 21. Fischer M, Baessler A, Hense HW, et al. Prevalence of left ventricular diastolic dysfunction in the community: results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J*. 2003;24(4):320–328.
 22. Peterson V, Norton GR, Raymond A, et al. Insulin resistance-associated decreases in left ventricular diastolic function are strongly modified by the extent of concentric remodeling in a community sample. *Int J Cardiol*. 2016;220:349–355.
 23. Okura H, Takada Y, Yamabe A, et al. Age- and gender-specific changes in the left ventricular relaxation: a Doppler Echocardiographic Study in Healthy Individuals. *Circ Cardiovasc Imaging*. 2009;2(1):41–46.
 24. Xu B, Daimon M. Cardiac aging phenomenon and its clinical features by echocardiography. *J Echocardiogr*. 2016;14(4):139–145.
 25. Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol*. 2011;26(6):562–568.
 26. Rigotti NA, Clair C. Managing tobacco use: the neglected cardiovascular disease risk factor. *Eur Heart J*. 2013;34(42):3259–3267.
 27. Nadruz W, Claggett B, Gonçalves A, et al. Smoking and cardiac structure and function in the elderly: the ARIC Study (Atherosclerosis Risk in Communities). *Circ Cardiovasc Imaging*. 2016;9(9):e004950.
 28. Bennet L, Larsson C, Söderström M, Råstam L, Lindblad U. Diastolic dysfunction is associated with sedentary leisure time physical activity and smoking in females only. *Scand J Prim Health Care*. 2010;28(3):172–178.
 29. Markus MRP, Stritzke J, Baumeister SE, et al. Effects of smoking on arterial distensibility, central aortic pressures and left ventricular mass. *Int J Cardiol*. 2013;168(3):2593–2601.
 30. Hwang YC, Jee JH, Kang M, Rhee EJ, Sung J, Lee MK. Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level. *Int J Cardiol*. 2012;159(2):107–111.
 31. Aijaz B, Ammar KA, Lopez-Jimenez F, Redfield MM, Jacobsen SJ, Rodeheffer RJ. Abnormal cardiac structure and function in the metabolic syndrome: a population-based study. *Mayo Clin Proc*. 2008;83(12):1350–1357.
 32. Ghouri N, Preiss D, Sattar N. Liver enzymes, nonalcoholic fatty liver disease, and incident cardiovascular disease: a narrative review and clinical perspective of prospective data. *Hepatology*. 2010;52(3):1156–1161.
 33. Fargion S, Porzio M, Fracanzani AL. Nonalcoholic fatty liver disease and vascular disease: state-of-the-art. *World J Gastroenterol*. 2014;20(37):13306–13324.
 34. Ballestri S, Lonardo A, Bonapace S, Byrne CD, Loria P, Targher G. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(7):1724–1745.
 35. Francque SM. The role of non-alcoholic fatty liver disease in cardiovascular disease. *Eur Cardiol*. 2014;9(1):10–15.
 36. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018;72(21):2625–2641.
 37. Peterson LR. Obesity and insulin resistance: effects on cardiac structure, function, and substrate metabolism. *Curr Hypertens Rep*. 2006;8(6):451–456.
 38. Utomi V, Oxborough D, Whyte GP, et al. Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. *Heart*. 2013;99(23):1727–1733.
 39. Andersson C, Lyass A, Larson MG, et al. Physical activity measured by accelerometry and its associations with cardiac structure and vascular function in young and middle-aged adults. *J Am Heart Assoc*. 2015;4(3):e001528.
 40. Hegde SM, Gonçalves A, Claggett B, et al. Cardiac structure and function and leisure-time physical activity in the elderly: the Atherosclerosis Risk in Communities Study. *Eur Heart J*. 2016;37(32):2544–2551.
 41. Juonala M, Viikari JSA, Raitakari OT. Main findings from the prospective Cardiovascular Risk in Young Finns Study. *Curr Opin Lipidol*. 2013;24:57–64.
 42. Mitter SS, Shah SJ, Thomas JD. E/A and E/é to assess diastolic dysfunction and LV filling pressure. *J Am Coll Cardiol*. 2017;69(11):1451–1464. <https://doi.org/10.1016/j.jacc.2016.12.037>
 43. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306(8):856–863.
 44. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289(2):194.
 45. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med*. 2011;171(12):1082–1087.
 46. Bella JN, Palmieri V, Roman MJ, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the strong heart study. *Circulation*. 2002;105(16):1928–1933.
 47. Russo C, Jin Z, Homma S, et al. Effect of diabetes and hypertension on left ventricular diastolic function in a high-risk population without evidence of heart disease. *Eur J Heart Fail*. 2010;12(5):454–461. <https://doi.org/10.1093/eurjhf/hfq022>

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.

How to cite this article: Heiskanen JS, Ruohonen S, Rovio SP, et al. Determinants of left ventricular diastolic function—The Cardiovascular Risk in Young Finns Study. *Echocardiography*. 2019;00:1–8. <https://doi.org/10.1111/echo.14321>