DETERMINANTS OF LEFT VENTRICULAR DIASTOLIC FUNCTION - THE CARDIOVASCULAR RISK IN YOUNG FINNS STUDY

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ABSTRACT

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 1,928 participants (880 men and 1,048 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: Left ventricular function; Left ventricular remodeling; Echocardiography

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).

METHODS

YFS 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 3,596 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 = 1,994 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 = 1,928 participants (880 men and 1,048 women, mean age 41.9 ± 5.0 years, range 34 - 49 years). Population characteristics are shown in detail in Supplementary Table 1.

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 non-invasive 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 towards 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]

LV mass was calculated as $(0.8[1.04((\text{LV end-diastolic diameter} + \text{end-diastolic posterior wall thickness} + \text{end-diastolic interventricular septum thickness})^3 - (\text{LV end-diastolic diameter})^3] + 0.6g$. Relative wall thickness was calculated as (2 x 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 relative wall thickness. The intraclass 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 1) fasting serum glucose over 7.0 mmol/l, 2) hemoglobin A1c over 6.5%, 3) use of insulin or per oral antidiabetic agents, or 4) 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 1) systolic blood pressure > 140 mmHg, or 2) diastolic blood pressure > 90 mmHg, or 3) using antihypertensive medication.[10] Harmonized definition was used for the metabolic syndrome: 1) waist ≥ 102 cm in men and ≥88 cm in women, 2) fasting serum glucose ≥ 5.6 mmol/l or treatment for diabetes mellitus, 3) 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 4) blood pressure ≥ 130 / ≥ 85 mmHg 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 x 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]

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 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 (Supplementary Table 1) 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/).

RESULTS

The characteristics of the study population are described in Supplementary Table 1. 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 (i.e., 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 analysis 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 analysis 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 Supplementary Table 2. 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 (i.e. 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 mmHg, 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. (Supplementary Table 3). 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.

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 intracellular 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, i.e. 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 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 to 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, e.g. 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 non-participants 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 remodelling on diastolic function, we defined the remodelling 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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TABLES

Tables are included in a separate WORD-document.

FIGURE LEGENDS

Figure 1.

Title - Mean E/é-ratio in different age groups in men and women.

Caption - Ribbons denote 95% confidence intervals.

Figure 2.

Title - Sex-specific normalized β-estimates for the associations between E/é-ratio and each separate study variable.

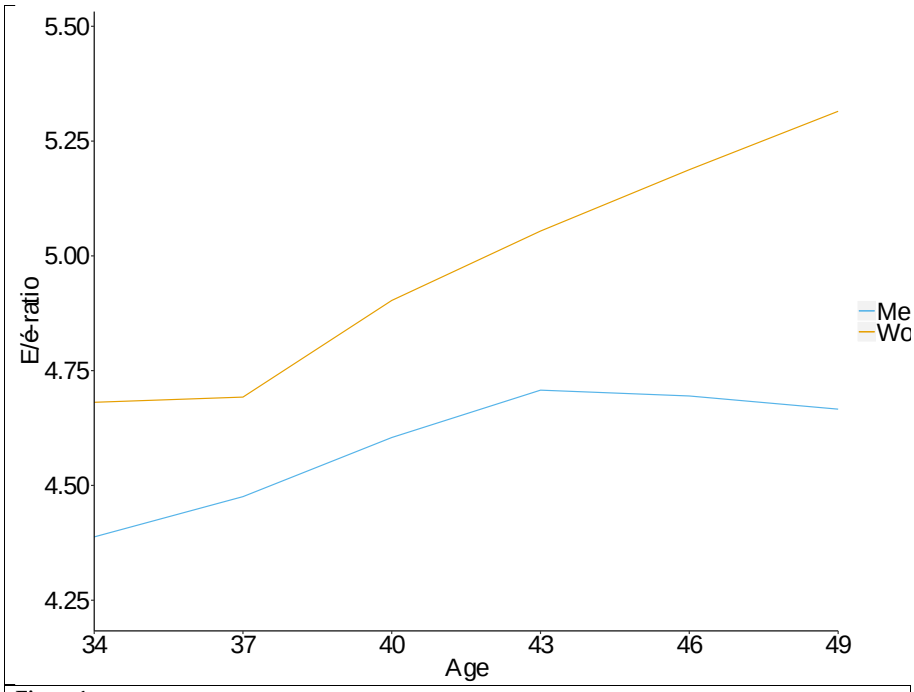
Caption - Sex-stratified univariate linear regression analyses were adjusted for study centers, and variables were standardized (0 to 1). Error bars denote 95% confidence intervals. *variable log-transformed prior to modeling. LV = left ventricle, BMI = body mass index, BSA = body surface area, ALT = Alanine aminotransferase, GGT = gamma-glutamyltransferase, CRP = C-reactive protein, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, HOMA-IR = Homeostasis model assessment-estimated insulin resistance.

Figure 3.

Title – Least-squares means of E/é-ratio in different cardiac remodeling groups.

Caption - 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.

FIGURES AND LEGENDS



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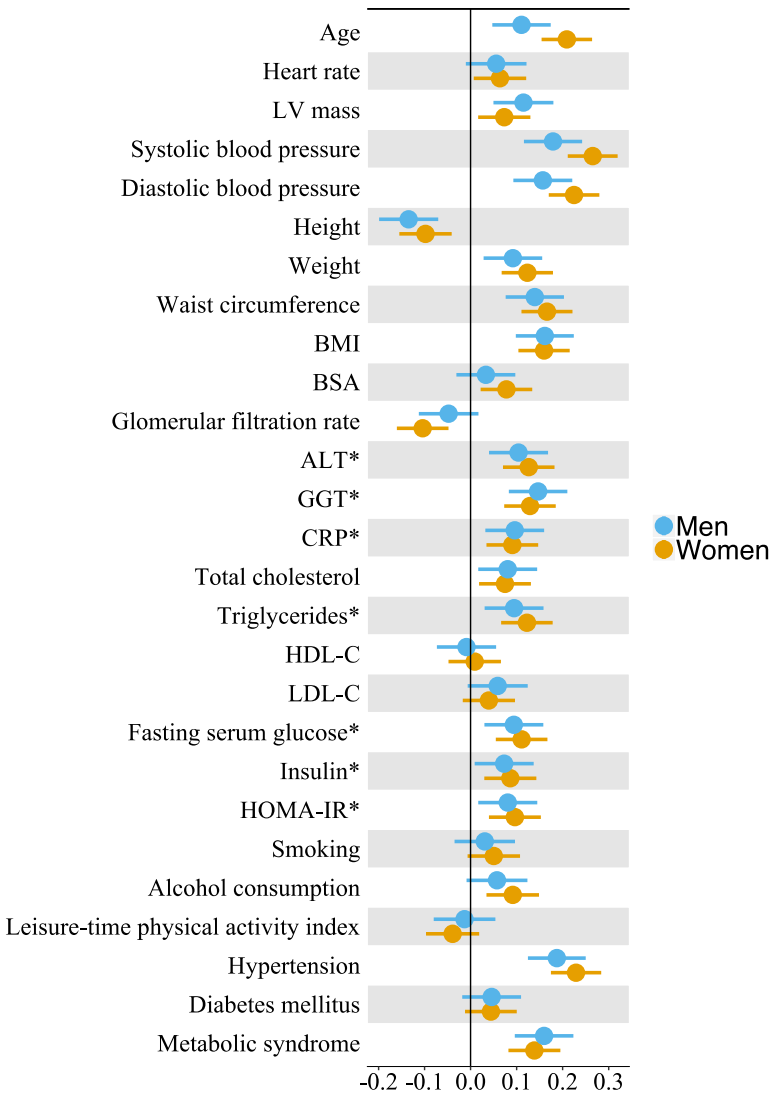

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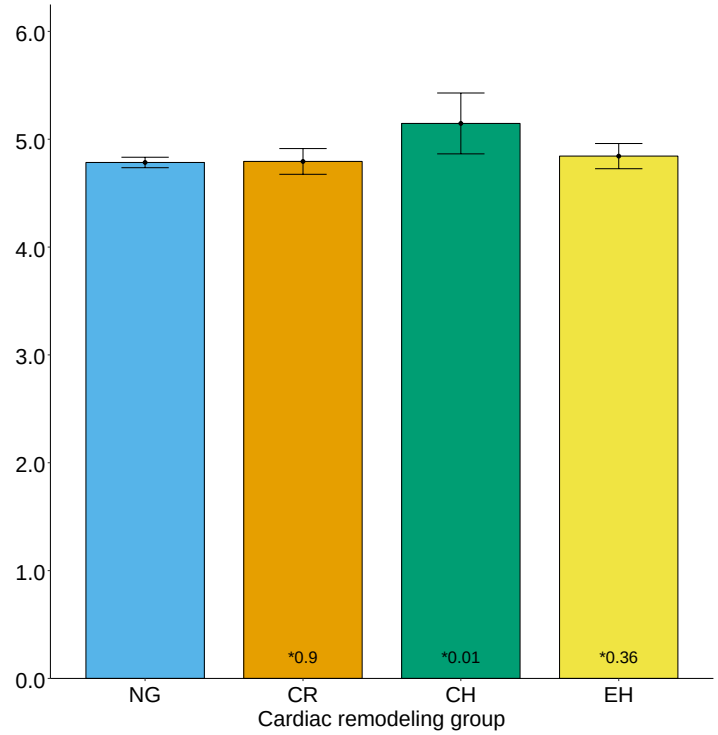

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TABLES

Table 1. Results of multivariate linear regression models

	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 (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/I)	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 modelling. [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 model. LAVi = Left atrial volume index, SE = standard error, LV = Left ventricle, ALT = Alanine aminotransferase.

Supplementary Table 1. Characteristics & study variables				
	Women		Men	
	n	Mean ± SD	n	Mean ± SD
E/é-ratio	1048	5.0 ± 1.0	880	4.6 ± 0.9
E/A-ratio	1046	1.6 ± 0.4	879	1.5 ± 0.4
LAVi	1019	21.8 ± 6.0	862	23.4 ± 6.8
Age (Years)	1048	42.0 ±5.0	880	41.7 ± 5.0
Heart rate (beats/min)	1012	63 ± 9.3	830	61.0 ± 10.1
LV mass (g)	1020	115.2 ±23.2	838	157.9 ± 32.7
Systolic blood pressure (mmHg)	1043	115.4 ± 13.6	876	122.9 ± 13.3
Diastolic blood pressure (mmHg)	1043	72.3 ± 9.4	876	77.6 ± 10.9
Height (cm)	1046	166.1 ± 6.0	880	179.8 ± 6.6
Weight (kg)	1048	71.8 ± 15.1	880	87.1 ± 15.4
Waist circumference (cm)	1047	87.4 ± 13.8	880	96.6 ± 12.2
BMI (kg/m2)	1046	26.0 ± 5.4	880	26.9 ± 4.2
Glomerular filtration rate (mL/min/1.73 m2)	1040	103.4 ± 5.8	875	97.2 ± 5.2
ALT (U/I)[a]	1040	13.2 ± 9.7	875	23.0 ± 15.2
GGT (U/I)[a]	1040	24.4 ± 28.8	875	44.8 ± 43.9
CRP (mg/l)[a]	1040	1.8 ± 2.6	875	1.5 ± 2.6
Total cholesterol (mmol/l)	1040	5.1 ± 0.9	875	5.3 ± 1.0
Triglycerides (mmol/l)[a]	1040	1.1 ± 1.2	875	1.6 ± 1.2
HDL-C (mmol/l)	1040	1.4 ± 0.3	873	1.2 ± 0.3
LDL-C (mmol/l)	1032	3.1 ± 0.8	838	3.4 ± 0.9
Fasting serum glucose (mmol/l)[a]	1040	5.2 ± 1.0	875	5.5 ± 0.8
Insulin (mU/I)[a]	1036	9.6 ± 16.0	873	10.4 ± 10.7
HOMA-IR[a]	1036	2.6 ± 8.6	873	2.8 ± 4.2
Alcohol consumption[b]	995	0.5 ± 0.7	808	1.2 ± 1.4
Leisure-time physical activity[c]	980	9.1 ± 1.9	786	8.9 ± 1.9
Smoking	1009	133 (13%)	821	137 (17%)
Diabetes mellitus	1048	36 (3%)	881	33 (4%)
Hypertension	1048	151 (14%)	881	206 (23%)
Metabolic syndrome	1025	180 (18%)	870	222 (26%)

The values are mean ± SD, number of patients and percentage of patients. [a]Log-transformed prior to modelling. [b]Alcohol consumption measured as drinks per day. [c]An index score ranging between 5-15. ALT = Alanine aminotransferase, BMI = Body-mass index, CRP = C-reactive protein, GGT = Gamma-glutamyltransferase, HDL-C = High density lipoprotein cholesterol, HOMA-IR = Homeostasis model assessment-estimated insulin resistance, LAVi = Left atrial volume index, LDL-C = Low density lipoprotein cholesterol, LV = Left ventricle

Supplementary Table 2. Results of multivariate linear regression models for septal and lateral é

	Septal é			Lateral é		
	β-estimate	SE	P-value	β-estimate	SE	P-value
Female sex	0.557	0.197	< 0.005	0.006	0.284	0.983
Age (Years)	-0.075	0.014	< 0.005	-0.184	0.021	< 0.005
LV mass (g)	-0.011	0.002	< 0.005	-0.001	0.003	0.654
Systolic blood pressure (mmHg)	-0.016	0.004	< 0.005	-0.030	0.006	< 0.005
Height (cm)	0.044	0.009	< 0.005	0.021	0.013	0.105
Waist circumference (cm)	-0.016	0.005	< 0.005	-0.030	0.008	< 0.005
Glomerural filtration rate (mL/min/1.73 m2)	0.042	0.013	< 0.005	0.026	0.018	0.153
ALT[b] (U/I)	-0.267	0.113	< 0.005	-0.429	0.163	< 0.005
Total cholesterol (mmol/l)	-0.099	0.058	0.086	-0.120	0.083	0.147
Fasting serum glucose[a] (mmol/l)	0.371	0.452	0.411	0.195	0.650	0.764
Smoking (yes/no)	-0.263	0.154	0.089	-0.237	0.222	0.286
Alcohol consumption[b]	0.045	0.051	0.376	-0.038	0.073	0.603
Leisure-time physical activity index[c]	0.005	0.029	0.852	0.002	0.041	0.965

[a]Height and waist were not included in the model [b]Log-transformed prior to modelling. [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 model. SE = standard error, LV = Left ventricle, ALT = Alanine aminotransferase.

Supplementary table 3. Correlation of E/é-ratio to conventional cardiac structure measurements and systolic function measurements.

	n	r	p-value
E/A-ratio	1925	0.037	0.10
Deceleration time	1922	0.085	<0.005
Ejection fraction (4ch)	1896	0.018	0.44
LV diastolic volume (4ch)	1898	-0.102	<0.005
LV diastolic diameter (plax)	1861	-0.013	0.58
LA systolic volume (4ch)	1883	-0.056	0.02
LAVi	1881	-0.025	0.29
LV posterior wall thickness diastolic (plax)	1859	-0.070	<0.005
Septum thickness diastole (plax)	1860	-0.053	<0.005
Relative wall thickness	1858	-0.053	0.02
LV mass/body surface area	1856	-0.003	0.91
LV mass	1858	-0.044	0.06

r = Pearson product-moment correlation coefficient, 4ch = four-chamber view, LV = left ventricle, plax = parasternal long axis view, LA =Left atrium, LAVi = left atrial volume index, Relative wall thickness calculated as follows: 2 times posterior wall thickness/LV diastolic diameter, LV mass calculated as follows: (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