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ORIGINAL ARTICLE

Geographic origin as a determinant of left ventricular mass and diastolic function – the Cardiovascular Risk in Young Finns Study

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Abstract

Aims: Eastern Finns have higher risk of coronary heart disease (CHD) and carotid intima-media thickness than western Finns although current differences in CHD risk factors are minimal. Left ventricular (LV) mass and diastolic function predict future cardiovascular events but their east–west differences are unknown. We examined the association of eastern/ western baseline origin with LV mass and diastolic function. **Methods :** The study population included 2045 subjects of the Cardiovascular Risk in Young Finns Study with data from the baseline survey (1980) and the latest follow-up (2011) when echocardiography was performed at the age of 34–49 years. **Results:** Subjects with eastern baseline origin had in 2011 higher LV mass (139±1.0 vs. 135±1.0 g, p=0.006) and E/e′-ratio indicating weaker LV diastolic function (4.86±0.03 vs. 4.74±0.03, p=0.02) than western subjects. Results were independent of age, sex, area of examination and CHD risk factors such as blood pressure and BMI (LV mass indexed with height: p<0.0001; E/e′-ratio: p=0.01). LV end-diastolic volume was higher among subjects with eastern baseline origin (135±0.9 vs. 131±0.9 ml, p=0.0011) but left atrial end-systolic volume, also indicating LV diastolic function, was not different between eastern and western subjects (43.4±0.5 vs. 44.0±0.5 ml, p=0.45). Most of the subjects were well within the normal limits of these echocardiographic measurements. ***Conclusions:*** **In our healthy middle-aged population, geographic origin in eastern Finland associated with higher LV mass compared to western Finland. Higher E/e′-ratio suggests that subjects with eastern baseline origin might have higher prevalence of diastolic dysfunction in the future than western subjects.**

Introduction

Coronary heart disease (CHD) is one of the main cardiovascular diseases and a major cause of death globally. In international comparison CHD mortality has been very high in Finland, especially among men born in Eastern Finland who had globally the highest CHD mortality in the 1960s [1] through 1980s [2]. A national program – the North Karelia Project – was launched in the 1970s to tackle this problem and decrease the CHD risk factor levels and mortality rate [3].

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The Cardiovascular Risk in Young Finns Study (Young Finns Study) is a nationwide on-going study that has investigated Finnish children and adolescents since 1980 for atherosclerosis precursors (*n*=3596). One of the key purposes of the Young Finns Study has been to study differences in CHD risk between eastern and western Finns. In the follow-up conducted in 2007, subjects residing in eastern Finland had higher blood pressure and intima-media thickness (IMT) than western subjects [4]. In spite of east–west differences in CHD risk factors disappearing, 35–64 years old eastern Finns still have 20% higher CHD mortality than western Finns of the same age (National Institute for Health and Welfare; data from year 2012).

Left ventricular (LV) mass and LV hypertrophy are important indicators of future cardiovascular events [5–7]. LV diastolic dysfunction is thought to be a prominent part of the heart failure presenting insufficient diastolic suction, impaired relaxation, as well as disturbed compliance and stiffness properties of the left ventricle [8,9]. E/e′-ratio describing LV flow velocity compared to myocardial tissue velocity is a marker for LV diastolic function [10] and possibly an earlier indicator of decrease in diastolic function than the volume of left atrium (LA) [11,12].

In this study we investigated the previously unexplored association of eastern/western baseline origin with LV mass and diastolic function later in life among the Young Finns Study subjects. We also investigated east–west differences in these measures according eastern/western current residency and family origin. We hypothesized subjects with geographic origin in the east present higher LV mass and weaker diastolic function than their western counterparts, partly explaining their higher CHD mortality.

Material and methods

Subjects

The Young Finns Study was launched in 1980 to examine risk factors underlying cardiovascular diseases [13]. In total, 3596 subjects 3–18 years of age were randomly chosen from the national population register to be the first cross-sectional survey. In the baseline study and every follow-up, the subjects have been examined at five study centers in Finland (university hospital cities Turku, Helsinki, Tampere, Kuopio and Oulu, and their rural vicinities). We used data from the baseline survey in 1980 and the latest 31-year follow-up survey in 2011, where 2045 of the original subjects aged 34–49 years took part. Echocardiography was conducted in the 2011 follow-up for 1994 participants [14].

The ethics committees of each study center have approved the study and all subjects/their parents have given their written informed consents.

Definition of geographic origin

Subjects of this Caucasian population were compared according to their baseline origin (1980), current residency (2011) or family origin. Subjects were determined according to their study center either as eastern (Oulu and Kuopio) or western (Turku, Helsinki and Tampere) [15]. Geographically more correct terms would be northeastern and southwestern Finns, but the terms eastern and western are commonly used due to historical and simplicity reasons. Family origin was assessed by the subjects' grandparents' place of birth and was considered eastern if all four grandparents were born in eastern Finland (37%) and western if three or four grandparents were born in western Finland (20%). Data of grandparents' birthplace was incomplete in 26% of subjects and they were excluded from family origin categorization. Proportions of men and women were similar between eastern or western participants. The study population consists of white Caucasians.

Echocardiography

Echocardiography was introduced to the Young Finns Study in the latest follow-up in 2011. Echocardiographic measurements and analysis were performed according to EAE/ASE guidelines [10,14,16]. The sonographers in all study locations were trained by a cardiac imaging specialist. 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 using the ComPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program. Both the sonographer and the observer were blind to the subjects' details.

Echocardiographic examinations were produced from the standardized image planes and modes: parasternal long and short axis in 2D and M mode and apical four chamber view as described earlier [14]. Briefly, the LV end-diastolic and end-systolic volumes were measured from the apical 4-chamber view based on the recommendations to assess ejection fraction [10, 16], which was calculated as follows: Ejection fraction = 100 × (LV end-diastolic volume – LV end-systolic volume) / LV end-diastolic volume.

LV mass was calculated as follows: (0.8 × [1.04 × (LV end-diastolic diameter + posterior wall thickness + interventricular septum thickness)^3 – LV end-diastolic

diameter)^3] + 0.6 g (see [16]). LV mass was indexed according to subject's height using the allometric power of 2.7 (indexed LV mass=LV mass/height$^{2.7}$) since this indexation has been shown to perform better for obese subjects [17].

To calculate LV diastolic performance index, E/e′-ratio, continuous and pulse-wave Doppler were used to measure transmitral flow and tissue velocities as described earlier [14]. E/e′-ratio is calculated from transmitral flow and myocardial tissue velocities, lower E/e′ indicating more favourable LV diastolic function [10,14]. For e′, the mean of lateral e′ and medial e′ was used. A single outlying value of E/e′-ratio (over 11) was excluded from the analyses.

Cardiovascular risk factors

Weight and height were measured and body mass index (BMI) was calculated (kg/m^2). Blood pressure in 1980 and 2011 was measured with a random zero sphygmomanometer except for 3-year-old subjects (1980) for whom an ultrasonic device was used (Arteriosonde, Roche). An average of three measurements was used. Venous blood samples were drawn after an overnight fast and analyzed with standard enzymatic methods to determine serum lipids and glucose [13]. Information on parental socioeconomic status (SES; annual income index ranging from 1 to 8, higher indicating higher income) in 1980, subject's birth weight, and physical activity in childhood and in adulthood were obtained with questionnaires. A physical activity index was calculated, lower scores indicating lower activity level [18]. Since the physical activity index was different for children and adolescents/adults at baseline, these index values were *Z*-scored by age and sex.

Statistical analyses

Differences in characteristics of the study subjects at baseline were analyzed with an independent samples *t*-test. Association of LV mass, E/e′-ratio, EF, LV end-diastolic volume and LA end-systolic volume with eastern/western baseline origin (also with current residency and family origin for LV mass and E/e′) were analyzed with an age- and sex-adjusted analysis of covariance (ANCOVA). There were no significant sex★geographic origin interactions. Mean, SE and *p*-values were calculated with adjustment for age, sex and area of examination in 2011, and for LVM and E/e′ additionally baseline and current CHD risk factors were used as covariates. Birthweight, BMI, systolic blood pressure, total cholesterol, parental SES and physical activity at baseline and BMI, systolic blood pressure, total cholesterol, plasma glucose, prevalence of smoking, own SES and physical activity

at the time of the echocardiography (2011) were chosen as the covariates since these risk factors are known to associate with LV mass and in the data we have previously found an east–west difference in these risk factors [4,19]. The analyses were performed with SAS version 9.3 (SAS institute, Inc, Cary, NC). Values of *p*<0.05 were considered significant.

Results

Characteristics at baseline and in 2011

Baseline (1980) and current characteristics of the study subjects according to eastern or western place of residency are shown in Table I. There was no east–west difference in sex distribution (east 54.8% women vs. west 54.2% women, *p*=0.78) or age. Subjects living in the east had a higher systolic and diastolic blood pressure and low-density lipoprotein (LDL) cholesterol concentration than subjects living in the west. At baseline, parental SES (income index) was higher in western than among eastern subjects. In 2011, subjects who lived in eastern Finland at baseline were shorter than subjects who lived in western Finland at baseline. No other east–west differences in characteristics were found in 2011.

Echocardiographic measurements

Echocardiographic measurements according to baseline (1980) origin are shown in Table II (adjusted for age, sex and area of examination in 2011). Subjects with eastern baseline origin had higher LV mass, indexed LV mass and lower ejection fraction than subjects with western origin. Concerning diastolic function, subjects with baseline origin in east had higher E/e′-ratio and LV end-diastolic volume but no difference in left atrial end-systolic volume.

Left ventricular mass

The mean±SD for LV mass in men was 158±33 g and with allometric index 32.5±6.9 g/m$^{2.7}$ (*N*=862). In women the mean±SD for LV mass and indexed LV mass were 115±33 g and 29.4±6.1 g/m$^{2.7}$, respectively (*N*=1045). Indexed LV mass according to eastern/western baseline origin, current residency and family origin is shown in Figure 1a (adjusted for age, sex and area of examination in 2011). In all comparisons, the eastern subjects had higher indexed LV mass compared to their western peers. The most pronounced east–west difference in LV mass was found when the subjects were studied according their current place of residency. There was no sex★geographic origin interaction, indicating that the results were

Table I. Characteristics of the study subjects at baseline (1980) and in 2011, mean ± SE.

	Men				Women				p total * (East/West)
	East		West		East		West		
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	
Baseline									
Age, y	434	10.8±5.0	496	10.8±5.1	527	11.2±4.9	588	10.75.0	**0.20**
Height, cm	429	145±27	491	146±28	524	143±24	588	141±24	**0.001**
BMI, kg/m²	429	17.9±2.8	491	18.2±3.5	522	18.0±3.0	588	17.8±3.1	**0.93**
Systolic blood pressure, mmHg	428	114±13	490	113±13	522	114±11	588	111±11	**<0.0001**
Diastolic blood pressure, mmHg	369	71±9	417	67±10	460	70±8	507	67±10	**<0.0001**
LDL- cholesterol, mmol/l	431	3.41±0.84	490	3.34 ±0.79	520	3.56±0.95	581	3.41±0.79	**<0.0001**
Parental income (range 1 to 8)	419	4.7±2.0	478	5.1±1.8	513	4.7±2.1	564	5.1±1.8	**<0.0001**
2011									
Age, y	434	41.8±5.0	496	41.8±5.1	527	42.2±4.9	588	41.7±5.0	**0.94**
Height, cm	433	179±7	493	180±7	523	165±6	583	167±6	**0.001**
BMI, kg/m²	433	27.0±4.1	492	27.0±4.6	523	26.0±5.4	582	26.2±5.6	**0.76**
Systolic blood pressure, mmHg	428	123±13	492	123±14	520	115±13	583	116±15	**0.61**
Diastolic blood pressure, mmHg	428	78±10	492	77±11	520	72±9	583	72±10	**0.73**
Total cholesterol, mmol/L	434	5.31±0.99	496	5.33±1.03	527	5.11±0.89	588	5.04±0.88	**0.47**
HDL-cholesterol, mmol/L	415	1.19±0.28	477	1.21±0.31	524	1.43±0.32	582	1.43±0.33	**0.71**
LDL-cholesterol, mmol/L	434	3.45±0.91	494	3.42±0.89	527	3.17±0.74	588	3.12±0.76	**0.29**
Smokers (%)	407	19.4	457	15.3	509	13.4	560	12.5	**0.16**

*For *p*-value, men and women were analyzed together.

Table II. Echocardiography measurements according to baseline (1980) origin. Mean ± SE and *p*-value; adjusted for age, sex and area of examination in 2011.

	East (N range 902–941)	West (N range 1005–1022)	p-value
	Mean ± SE	Mean ± SE	
LV mass, g	139± 1.0	135± 1.0	0.006
LV mass, indexed, g/m²·⁷	31.5± 0.2	30.4± 0.2	0.001
Ejection fraction, %	58.1± 0.1	58.4± 0.1	0.04
Left atrium end-systolic volume, ml	43.4± 0.5	44.0± 0.5	0.45
LV end-diastolic volume, ml	135± 0.9	131± 0.9	0.001
E/e′- ratio	4.86± 0.03	4.74± 0.03	0.02

similar for men and women. We further analyzed east–west differences in indexed LV mass by additionally adjusting for CHD risk factors at baseline (birthweight, BMI, systolic blood pressure, total cholesterol, parental SES, physical activity) and current risk factors (BMI, systolic blood pressure, total cholesterol, plasma glucose, smoking, own SES and physical activity) (Figure 1b). With these adjustments, the east–west differences persisted between subjects according to their family origin, baseline origin and current place of residency.

Diastolic function (E/e′)

Among all subjects the average E/e′-ratio was 4.6±1.0 in men (N=887) and 5.0±1.0 in women (N=1051).

The E/e′-ratio according to eastern/western baseline origin, current residency or family origin is shown in Figure 2a. The western subjects had more effective diastolic function than their eastern peers according to baseline origin, current residency and family origin. There was no sex*geographic origin interaction indicating that the results were similar for men and women. To examine the independent association between geographic origin and E/e′-ratio, we included CHD risk factors at baseline (birthweight, BMI, systolic blood pressure, total cholesterol, parental SES, physical activity) and currently (BMI, systolic blood pressure, total cholesterol, plasma glucose, smoking, own SES and physical activity) into the analyses (Figure 2b). With this model, the east–west difference in E/e′-ratio according to family origin was no longer significant.
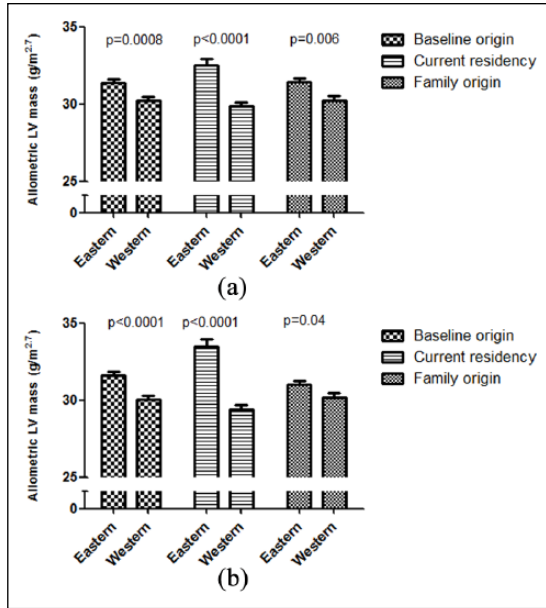
Figure 1. LV mass (allometric index, mean and SE).
(a) for subjects with baseline origin in east ($N=902$) / west ($N=1005$), current residency in east ($N=653$) / west ($N=1254$), family origin in east ($N=672$) / west ($N=401$); adjusted for age, sex and area of examination in 2011.
(b) for subjects with baseline origin in east ($N=645$) / west ($N=745$), current residency in east ($N=465$) / west ($N=925$), family origin in east ($N=499$) / west ($N=309$); adjusted for age, sex, examination area in 2011, risk factors at baseline (BMI, systolic blood pressure, total cholesterol, birthweight, parental SES, physical activity) and currently (BMI, systolic blood pressure, total cholesterol, plasma glucose, prevalence of smoking, own SES and physical activity).

Figure 2. E/e′ - ratio (mean and SE).
(a) for subjects with baseline origin in east ($N=920$) / west ($N=1017$), current residency in east ($N=680$)/ west ($N=1257$), family origin in east ($N=684$) / west ($N=407$), adjusted for age, sex and area of examination in 2011.
(b) for subjects with baseline origin in east ($N=655$) / west ($N=752$), current residency in east ($N=484$) / west ($N=923$), family origin in east ($N=505$) / west ($N=312$), adjusted for age, sex, examination area in 2011, risk factors at baseline (BMI, systolic blood pressure, total cholesterol, birthweight, parental SES, physical activity) and currently (BMI, systolic blood pressure, total cholesterol, plasma glucose, prevalence of smoking, own SES and physical activity).

Discussion

We found that 34–49-year-old subjects with baseline origin or current residency in east Finland had a higher LV mass and higher E/e′- ratio, indicating more adverse diastolic function, than subjects with baseline origin or current residency in western Finland. These associations were independent of childhood and adulthood CHD risk factors. Of note, most of our middle-aged population was well within the normal limits for LV mass and E/e′.

LV hypertrophy is an indicator of future cardiovascular events [7, 20]. The Framingham Heart Study was a groundbreaking study to show a continuous relation between LV mass and CV event rate in the general population [21]. The pathogenesis of LV hypertrophy initiates usually with essential arterial hypertension and reduction in blood pressure is marked with regression of LV hypertrophy [22].

Historically, eastern Finns have had higher CHD mortality rates than western Finns in the 1960s [1]. The excessive risk was associated with higher CHD risk factor levels in the east. A national intervention called the Nor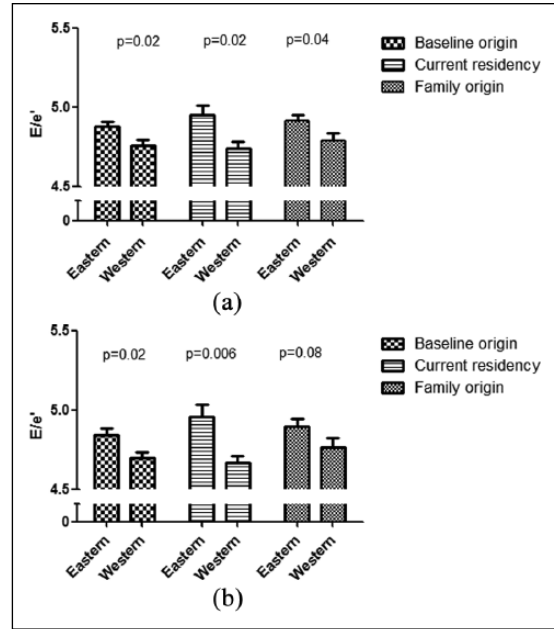th Karelia project was launched in the 1970s to lower CHD risk factors by targeting diet and other lifestyle factors especially in eastern Finland [3]. The CHD mortality in eastern Finland has declined significantly over decades, and the decline has been explained with the decrease in risk factors [23]. In our previous study [4] and other studies [24], the east–west difference in CHD risk factors had almost disappeared.

In spite the changes in CHD risk factors, eastern Finns have had higher carotid IMT compared to western Finns [25], as reported also in our recent study [4]. The results of the present study showing higher LV mass among eastern Finns are logical with earlier findings of higher IMT in the east as both are dependent on cardiovascular risk factors. Together these results suggest there might be a persisting increased risk for cardiovascular diseases in eastern Finns compared with western Finns also in the future despite the risk factor levels are evening out.

Elevated LV mass may contribute to the development of diastolic dysfunction [26] although LV mass may also be normal in patients with poor diastolic function [27]. LV diastolic dysfunction often occurs with normal systolic function, and this condition is

referred to as heart failure with preserved ejection fraction. It is a common clinical syndrome with high morbidity and mortality [28]. E/e′ is an appropriate noninvasive indicator of increased LV end-diastolic pressure in patients with heart failure with preserved ejection fraction [10]. In a study with hypertensive DOCA-salt treated porcine, especially e′ was shown to increase experimentally in rest and during dobutamine-induced stress [29]. Furthermore, E/e′-ratio indicates LV end-diastolic pressure regarding diastolic dysfunction [30,31], and in a hypertensive population it may predict primary cardiac events even better than LV mass [32].

In addition to E/e′-ratio, LV diastolic function is related to LV end-diastolic volume [8]. In this study both E/e′- ratio and LV end-diastolic volume were higher among subjects with eastern baseline origin compared to western subjects, thus indicating less effective diastolic function among eastern Finns. Another marker of LV diastolic dysfunction, the volume of LA remained unchanged. This is probably explained by the young age of the study group when considering cardiovascular events. The volume change of the LA needs longer exposure time to develop then change in the E/e′-ratio [11] [12].

Genetic differences have been suggested to explain part of the difference in CHD risk between eastern and western Finns [33]. We found eastern family origin associating with higher LV mass and diastolic function, in line with previously reported higher carotid IMT and lower brachial flow-mediated dilation in subjects with eastern family origin compared to western family origin [19]. The effect of family origin might also be due to inherited health behavior differences or epigenetics. In this study, the subject's current residency was not controlled in the analyses of family origin and may thus affect the association of the family origin with LV mass and diastolic function. Further investigation is needed to better understand the underlying factors in CHD risk related to family origin.

The east–west differences in LV mass and E/e′ were greater according to current place of residency than according to baseline origin. This finding suggests that migration has contributed to east–west differences in LV mass and diastolic function. Our previous study showed that 27% of subjects who lived in eastern Finland in 1980 had moved to west by 2007 whereas only 2% moved of those who lived in western Finland in in 1980 had moved to east by 2007 [4]. The subjects who migrated east-to-west had lower carotid IMT than subjects who continuously lived in eastern Finland [4]. Our current study lends support to prior results that migration influences east–west differences in surrogate markers of

cardiovascular diseases, likely increasing the observed differences.

To the best of the authors' knowledge, similar reports to this study from other countries are scarce. In addition to Finland, geographic difference in LV mass has been found earlier in Germany, where subjects from the northeast had higher LV mass than subjects from the southwestern part of the country [34]. A systematic review of 33 studies from different countries showed that normal values for LV mass differ largely between different nations and ethnicities worldwide [35].

The study has some limitations. Cardiac ultrasonography has been performed only at one time point, thus longitudinal estimation of change in cardiac shape cannot be made. LV mass can be measured more precisely with cardiac magnetic resonance than with transthoracic echocardiography as applied in this study [36]. To model diastolic function, a strain-analysis would have been even more accurate than the measurements available in this study [37]. Ejection fraction was calculated from measurements made in a single plane. Despite the east–west differences in LV mass and E/e′-ratio, the majority of our study population is well within the normal values of these echocardiographic measurements. Thus, it is too early to say whether east–west differences in the prevalence of actual LV hypertrophy and diastolic dysfunction will be seen. Furthermore, it is unknown whether any baseline differences in left ventricular structure and function existed. Adjustment for baseline and current CHD risk factors did not attenuate the differences in LV mass and E/e′- ratio between subjects with eastern and western baseline origin. Our model with adjustment for risk factors at two time-points might not be robust enough to dilute these differences, especially as current east–west differences in risk factors are nearly non-existent. In longitudinal studies, it is inevitable that loss to follow-up occurs. However, we have found that risk factor levels are essentially similar among participants and non-participants at baseline [13]. Long follow-up extending 30 years, detailed phenotyping of the participants and the prospective study design are the evident strengths of this study.

In conclusion, we found higher LV mass and E/e′-ratio indicating weaker diastolic function in eastern Finns compared to western Finns, independently of baseline and current risk factors. Most of the subjects were still well within normal limits, but the findings suggest we might observe higher prevalence of LV hypertrophy and diastolic dysfunction in subjects with eastern geographic origin compared to subjects with western geographic origin.

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Declaration of Conflicting Interest

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