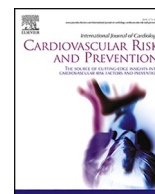




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Association of number of siblings with preclinical markers of cardiovascular disease. The cardiovascular risk in Young Finns study

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ABSTRACT

To investigate the association of number of siblings with preclinical cardiovascular disease (CVD) markers in adulthood.

The sample comprised 2776 participants (54 % female) from the Cardiovascular Risk in Young Finns Study who had CVD risk factor data measured in childhood in 1980 (aged 3–18 years) and markers of preclinical CVD measured in adulthood. Echocardiography was performed in 2011, and carotid intima-media thickness, carotid distensibility, brachial flow-mediated dilatation, and arterial pulse wave velocity were measured in 2001 or 2007. The association between the number of siblings and preclinical CVD was assessed using generalized linear and logistic regression models. Analyses were stratified by sex as associations differed between sexes.

Women with 1 sibling had lower E/e'-ratio (4.9, [95%CI 4.8–5.0]) in echocardiography compared with those without siblings (5.1[4.9–5.2]) and those with ≥ 2 more siblings (5.1[5.0–5.2]) (P for trend 0.01). Men without siblings had the lowest E/A-ratio (1.4[1.3–1.5]) compared with those with 1 sibling (1.5[1.5–1.5]), or ≥ 2 siblings (1.5[1.5–1.5]) (P for trend 0.01). Women without siblings had highest left ventricular ejection fraction (59.2 % [58.6–59.7 %]) compared with those with 1 sibling (59.1 % [58.8–59.4 %]), or ≥ 2 siblings (58.4 % [58.1–58.8 %]) (P for trend 0.01). In women, brachial flow-mediated dilatation, a measure of endothelial function, was the lowest among participants with ≥ 2 siblings (9.4 % [9.0–9.8 %]) compared with those with 1 sibling (10.0 % [9.6–10.3 %]) and those without siblings (10.4 % [9.7–11.0 %]) (P for trend 0.03).

We observed that number of siblings may be associated with increased risk of heart failure in women. As the associations were somewhat inconsistent in males and females, further research is warranted.

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1. Introduction

Cardiovascular disease (CVD) develops throughout the lifespan, although clinical manifestations typically become evident at middle age or later [1]. Early life is an important period for the initiation and progression of CVD, but it remains an overlooked window of opportunity for prevention. Progression of cardiovascular disease in asymptomatic individuals can be evaluated using known precursors of CVD, which can be assessed non-invasively by examining structural and functional changes of the heart with echocardiography, or structural (including carotid intima-media thickness (IMT) [2]) and functional changes (i.e. pulse wave velocity (PWV) [3], flow-mediated dilatation (FMD) [4], and distensibility [5]) in the arteries. These preclinical markers of CVD have been shown to associate with future CVD events [2–5].

Although there are number of well-known risk factors for CVD, more than 15 % of patients exhibiting life-threatening acute coronary syndrome have no history of traditional modifiable cardiovascular risk factors [6–8]. This emphasizes the necessity to explore potential novel risk factors. Despite this, the relationship of family size with cardiovascular health has not been well established. For example, the number of siblings has been shown to directly associate with CVD mortality among Scottish men [9], whereas the number of inhabitants in the household was not associated with coronary heart disease mortality [10]. Furthermore, we have earlier shown that children without siblings had poorer cardiovascular risk factor levels in childhood and in adulthood [11].

Therefore, using data from a population-based sample of individuals followed from childhood to adulthood for up to 31 years in the Cardiovascular Risk in Young Finns Study (YFS), we investigated the association between number of siblings with markers of preclinical CVD.

2. Methods

The prospective YFS has followed a population-based cohort from childhood to adulthood that were sampled from five cities with university hospitals in Finland (Helsinki, Kuopio, Oulu, Tampere, and Turku) and their rural surrounds. The baseline study was conducted in 1980 when 3596 randomly selected children and adolescents aged 3, 6, 9, 12, 15 and 18 years participated. Since 1980, the cohort has been regularly followed-up. A detailed description of the cohort has been published previously [12]. Participants or their parents provided written informed consent and the study was approved by local ethics committees. Participants included in this study had data available from baseline and echocardiography (in 2011) and/or vascular ultrasound data in adulthood (in 2001 or 2007) ($n = 2766$).

Information on the number of children in the family was collected from parents' in self-report questionnaires administered at baseline in 1980. Participants were categorized by the number of children in the family as: 1) no siblings (only child) ($n = 412$); 2) 1 sibling ($n = 1220$); and 3) 2 or more siblings ($n = 1134$). In addition, we utilized data gathered on the number of siblings in childhood follow-ups (1983 and 1986) and the latest adulthood follow-up in 2018–2020.

Brachial artery blood pressure was measured at baseline using an ultrasound device (Arteriosonde 1020, Roche) among participants aged 3 years, and using a standard mercury sphygmomanometer for participants aged ≥ 6 years at baseline. In case of missing information, data from the 1983 follow-up were used. Adult blood pressure measurements were collected in the 2011 follow-up using a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK). All measurements were taken using a standardized method repeating 3 times on the right arm after the participant had been seated for 5 min with the average of 3 measures used.

At baseline and all follow-up visits, weight was measured without shoes in light clothes with a digital Seca weighing scale. A Seca stadiometer was used for height measurements and body mass index (BMI)

was calculated as weight (kg) divided by height in meters squared (m^2). Baseline (1980) measurements of childhood/adolescent BMI were primarily used but in case of missing information, data from the 1983 follow-up were used. For adulthood BMI, data was derived from the latest follow-up study (2011) and in case of missing information, data from the latest adult follow-up (2007 or 2001) was used.

Fasting serum lipid and lipoprotein concentrations of total cholesterol, HDL-cholesterol, and triglycerides were measured in the same laboratory at each follow-up using standard methods [13,14]. LDL-cholesterol was calculated using the Friedewald equation [15]. Serum glucose concentration was determined by the enzymatic hexokinase method (Glucose reagent, Beckman Coulter Biomedical).

Echocardiographic examinations were performed in 2011 ($n = 1990$) according to American and European guidelines [16,17]. Transthoracic echocardiography was performed using a 3.5 MHz scanning frequency phased-array transducer (Sequoia 512, Acuson, CA, USA). Studies were saved in digital images which were all analysed using the ComPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program by one reader blinded to participant details [18].

LV (left ventricular) mass was calculated as previously described [19] and indexed LV mass was attained according to the individual'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 especially among obese individuals [20]. LV diameter, interventricular septal wall thickness, and LV posterior wall thickness were measured from parasternal long-axis view in M-mode at end-diastole. LV ejection fraction (LVEF) and ratios of E/e' and EA were calculated according to American and European guidelines [16,17]. Left atrium volume index (LAVI) was calculated in four-chamber apical view at end-systole and divided by body surface area using Du Bois formula ($BSA = 0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$).

Questionnaire data gathered at baseline included parents self-report of their family's annual income, which was considered as an indicator of socio-economic status (SES) and categorized as: 1) very low ($<17,840$ euros/year), 2) low (17,840–28,040 euros/year), 3) intermediate (28,041–38,230 euros/year), and 4) high ($>38,230$ euros/year) income groups. In case of missing information in 1980, data from the first follow-up in 1983 were used. Participants' household annual income in the year 2011 was considered as an indicator of adulthood SES and was categorized as: 1) very low ($<21,780$ euros/year), 2) low (21,780–32,670 euros/year), 3) intermediate (32,671–54,440 euros/year), and 3) high ($>54,440$ euros/year) income groups. In case of missing information in 2011, data from the latest adulthood follow-up (in 2007 or 2001) were used. Participant's smoking status was queried at all time-points among those aged 12 years and older. Those who indicated smoking daily between the ages 12–18 years were designated as smokers. Participants younger than 12 years were considered non-smokers. Adulthood smoking status was queried and defined from the data in the latest follow-up (2011, 2007 or 2001). Those who indicated that they smoked daily were designated as smokers.

Data on arterial PWV ($n = 1863$) was collected in the 2007 follow-up using a whole-body impedance cardiography device (Circomon, JR Medical Ltd, Tallinn, Estonia) as previously described [21]. Data on carotid distensibility (CDist) and IMT, and brachial FMD was collected in the 2007 follow-up (sample sizes from 2178–2190) or for those that did not attend the 2007 follow-up data, data from the 2001 follow-up (additional sample from 437 to 463) were used.

Ultrasound studies were performed using ultrasound mainframes (Sequoia 512, Acuson, Mountain View, Calif) with 13.0-MHz linear array transducers according to standardised protocols [2,22–25]. CDist was calculated using a formula: $CDist = ([Ds - Dd]/Dd)/(Ps - Pd)$, where Dd is the diastolic diameter, Ds the systolic diameter, Ps systolic blood pressure, and Pd diastolic blood pressure. Maximum carotid IMT was determined by taking six measurements of the common carotid far wall ~ 10 mm before the border of the carotid bulb [26]. Brachial FMD was assessed from B-mode ultrasound images at rest and during reactive

hyperemia [27].

Baseline characteristics of the study population are reported as mean (standard deviation, SD) or median (25th and 75th percentiles, if skewed distribution) for continuous variables or as proportions for categorical variables. The relationship between the number of siblings and continuous outcome variables was assessed using generalized linear models adjusted with Tukey-Kramer approximation and logistic regression models were used for categorical outcome variables.

Sex × outcome interactions were studied to investigate if the associations were similar in males and females. The association of number of siblings with E/e'-ratio, E/A-ratio, and FMD differed between sexes (P for interaction <0.05). Therefore, all analyses were sex-stratified and adjusted for age.

Sensitivity analyses were conducted for both the cardiac and the vascular outcomes to study the robustness of our findings. First, to consider for the possible misclassification of participants if the number of children in the family increased after the baseline survey, we combined data on the number of siblings from the parents of the participants when they contributed data to the latest YFS field study in 2018–2020. Second, we combined data on the number of siblings from baseline and the 1983 and 1986 follow-up surveys. adult.

To assess the degree of multicollinearity in the multivariable analyses, we investigated variance inflation factors and found no highly collinear relationships affecting the models (variance inflation factor always <3.1).

All statistical analyses were performed using SAS version 9.4 and statistical significance was inferred at a two-tailed P-value <0.05.

3. Results

Characteristics of the participants are shown in Table 1. Total number of participants with data on the number of siblings and outcomes was 2766 (54 % female). Of these, 1990 participants had data on the echocardiography outcomes and 2197 participants on the vascular measures. The mean age of the participants was 41.9 ± 5 years for the echocardiography outcomes (2011) and 37.6 ± 5 years for the vascular outcomes (2001 and 2007). Median number of children in the family was 2.0 (interquartile range 2.0–3.0, range 0–18). Mean values of adult echocardiography and vascular outcomes according to the number of siblings are shown in Supplemental Table 1.

In women, the number of siblings was statistically significantly associated with LV mass, E/e'-ratio, and LVEF (Table 2). Participants with ≥2 siblings had the highest LV mass in age-adjusted analyses. The association diluted after adjustment for risk factors. Women with 1 sibling had the lowest E/e'-ratio. The association persisted after further adjustment for risk factors. LVEF was the lowest among participants with ≥2 siblings. The association persisted after further adjustment for risk factors. Of the echocardiography outcomes in men, participants with no siblings had lower E/A compared to participants with 1 or ≥2 siblings (Table 3). The association remained after adjustment for risk factors.

The number of siblings associated with FMD in women (Table 4). FMD was the lowest in participants with ≥2 siblings. The association remained statistically significant after adjustment for risk factors (p for trend 0.03). For men, there were no associations between the number of siblings and adult vascular outcomes (Table 5).

In sensitivity analyses, we first used data collected on the number of siblings from the parents of the participants when they contributed data to the latest YFS field study in 2018–2020. In women, the results for echocardiography were similar (data not shown) to the main results. In men, in addition to the association between the number of siblings and E/A-ratio observed in the main results, an association between the number of siblings and interventricular septal wall diameter, and also LV posterior wall diameter was observed, but the association diluted after adjusting for childhood and adulthood risk factors (data not shown). In both sexes, there were no associations between the number of

Table 1
Characteristics of the participants in childhood and adulthood according to the number of siblings.

Number of siblings	Childhood			Adulthood		
	0	1	≥2	0	1	≥2
N (% of total participants)	412 (15)	1220 (44)	1134 (41)	314 (14)	971 (44)	921 (42)
Female sex (%)	52	53	54	54	56	56
Age (y)	8.8 (4.9)	9.7 (4.8)	12.2 (4.7)	40 (4.9)	40.8 (4.8)	43.3 (4.7)
Family income (%) ^a						
Low	27	19	35	18	16	17
Lower middle class	31	30	28	29	27	33
Upper middle class	29	24	16	37	37	35
High	13	27	20	16	20	16
HDL-cholesterol (mmol/l)	1.57 (0.31)	1.57 (0.31)	1.55 (0.30)	1.31 (0.33)	1.32 (0.33)	1.34 (0.32)
LDL-cholesterol (mmol/l)	3.46 (0.82)	3.43 (0.83)	3.45 (0.80)	3.21 (0.88)	3.21 (0.81)	3.35 (0.83)
Triglycerides (mmol/l)	0.59 (0.45, 0.78)	0.58 (0.45, 0.75)	0.61 (0.46, 0.82)	1.15 (0.85, 1.56)	1.05 (0.75, 1.56)	1.05 (0.75, 1.56)
Systolic blood pressure (mmHg)	111 (13)	111 (12)	114 (12)	118 (14)	118 (14)	120 (14)
Body mass index (kg/m ²)	17.4 (3)	17.5 (2.9)	18.4 (3.1)	26.5 (4.8)	26.4 (5.1)	26.7 (5.2)
Daily smoking (%) ^b	18	22	24	27	24	24
Fasting plasma glucose (mmol/l)				5.4 (0.8)	5.4 (1.0)	5.4 (0.9)

a. Low <17,840€/year, lower middle class 17,840–28,040 €/year, upper middle class 28,041–38,230 €/year, high >38,230€/year. b. Data from 1980 to 1992 surveys was used, explains if the participant has smoked between 12 and 18 years of age. Data are mean (SD) or median (25th, 75th percentile) for continuous variables and percentages for categorical variables.

siblings and vascular outcomes (data not shown).

We also used combined data on the number of siblings from baseline and the 1983 and 1986 follow-up surveys. Results for the echocardiography measures were similar to the main results in women. In men, we observed that the number of siblings associated only with interventricular septal wall and LV posterior wall diameter when adjusted for age, but the associations diluted after additional adjustments for risk factors. We did not observe an association between the number of siblings and FMD in women, but an association for PWV was found. However, the association diluted after adjusting for risk factors. In these sensitivity analyses, the number of siblings associated with FMD in men. Participants without siblings had the lowest FMD (6.9 %, 95%CI 6.2–7.5 %) compared with those with 1 sibling (7.8 %, 95%CI 7.4–8.1 %) and those with ≥2 siblings (7.6 %, 95%CI 7.3–7.9 %). This association remained significant after further adjustment for risk factors (p for trend 0.03).

4. Discussion

We examined the associations of the number of siblings with cardiovascular structure and function. Since we observed that among women the number of siblings associated with higher E/e'-ratio, lower LVEF, and lower FMD in adulthood, having more siblings may be associated with an increased risk of heart failure. Among men, an association between the number of siblings and E/A-ratio was observed.

Previously, a higher number of siblings has been associated with elevated all-cause mortality [28]. However, being the only child has been shown to increase the odds for childhood obesity [29], a known

Table 2
Adjusted means and their 95 % confidence intervals (CI) for adult echocardiography outcomes in 2011 according to the number of siblings among females.

Outcome	Model 1				P for trend	Model 2				P for trend
	Number of siblings					Number of siblings				
	0		1			0		1		
	Adjusted means	95%CI	Adjusted means	95%CI		Adjusted means	95%CI	Adjusted means	95%CI	
LV Mass (g/ m ^{2.7}) _a	29.1	28.1–30.1	28.8	28.2–29.3	29.8	29.2	28.3–30.1	29.1	28.5–29.6	29.5
IV septal wall (mm) _a	6.9	6.8–7.0	6.9	6.8–7.0	6.9	6.9	6.8–7.1	6.9	6.9–7.0	6.9
LV posterior wall (mm) _a	6.8	6.7–6.9	6.8	6.8–6.9	6.9	6.8	6.7–6.9	6.8	6.8–6.9	6.9
E/e' _a	5.1	4.9–5.2	4.9	4.8–5.0	5.1	5.1	4.9–5.2	4.9	4.8–5.0	5.1
E/A _a	1.6	1.6–1.7	1.6	1.6–1.7	1.6	1.6	1.6–1.7	1.6	1.6–1.7	1.6
LAVI	21.5	20.6–22.5	21.6	21.0–22.1	21.9	21.1	20.1–22.2	21.7	21.1–22.3	21.9
LV diameter (mm)	49.3	48.6–50.0	49.3	48.9–49.7	49.8	49.3	48.6–49.9	49.3	48.9–49.7	49.5
LVEF (%)	59.2	58.6–59.7	59.1	58.8–59.4	58.4	59.1	58.4–59.7	59.0	58.6–59.3	58.2
Cardiac output (l/min) _a	4.3	4.1–4.4	4.2	4.06–4.4	4.2	4.2	4.1–4.4	4.2	4.1–4.3	4.2
N _b	153		461		451	135		429		415

a Data skewed; logarithmic transformation was used in statistical analyses. b In model 1, N varied between 136 and 141 in participants with no siblings, 416–442 in participants with one sibling, and 405–429 in participants with two or more siblings. In model 2, N varied between 130 and 135 in participants with no siblings, 406–429 in participants with one sibling, and 392–415 in participants with two or more siblings. Adjusted Model 1 included age. Adjusted model 2 age, childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, body mass index, serum glucose concentration, and smoking status).

Table 3
Adjusted means and their 95 % confidence intervals (CI) for adult echocardiography outcomes in 2011 according to the number of siblings among males.

Outcome	Model 1				P for trend	n	Model 2				P for trend	n
	Number of siblings						Number of siblings					
	0	1	Adjusted means	95%CI			Adjusted means	95%CI	Adjusted means	95%CI		

a Data skewed; logarithmic transformation was used in statistical analyses. b In model 1, N varied between 115 and 125 in participants with no siblings, 374–400 in participants with one sibling, and 348–369 in participants with two or more siblings. In model 2, N varied between 110 and 118 in participants with no siblings, 334–353 in participants with one sibling, and 315–332 in participants with two or more siblings. Adjusted Model 1 included age. Adjusted model 2 age, childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, body mass index, serum glucose concentration, and smoking status).

Table 4
Adjusted means and their 95 % confidence intervals (CI) for adult vascular outcomes in 2007 or 2001 according to the number of siblings among females.

Outcome	Model 1				P for trend	Model 2				P for trend	n		
	Number of siblings					Number of siblings							
	0	1	≥2			0	1	≥2					
	Adjusted means	95%CI	Adjusted means	95%CI		Adjusted means	95%CI	Adjusted means	95%CI				
Carotid distensibility (%/10 mmHg)	2.0	1.9–2.1	2.1	2.0–2.1	0.81	2.1	2.0–2.2	2.0	2.0–2.1	2.1	2.0–2.2	0.33	1192
Flow mediated dilation (%)	10.4	9.7–11.0	10.0	9.6–10.3	0.03	10.7	10.0–11.5	10.3	9.8–10.7	9.6	9.2–10.1	0.03	1186
Pulse wave velocity (m/s)	7.8	7.6–8.0	7.6	7.5–7.8	0.08	7.7	7.5–7.8	7.7	7.5–7.8	7.7	7.6–7.8	0.82	931
Intima-media thickness (µm)	641	627–656	635	627–644	0.60	613	601–625	607	600–614	609	601–616	0.66	1192
N _a	210	631	595			166		525		501			

b In model 1, N varied between 143 and 210 in participants with no siblings, 435–631 in participants with one sibling, and 436–595 in participants with two or more siblings. In model 2, N varied between 124 and 166 in participants with no siblings, 401–525 in participants with one sibling, and 406–501 in participants with two or more siblings. Adjusted Model 1 included age. Adjusted model 2 age, childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, body mass index, serum glucose concentration, and smoking status).

Table 5
Adjusted means and their 95 % confidence intervals (CI) for adult vascular outcomes in 2007 or 2001 according to the number of siblings among males.

Outcome	Model 1				P for trend	Model 2				P for trend	n		
	Number of siblings					Number of siblings							
	0	1	≥2	Adjusted means		95%CI	0	1	≥2			Adjusted means	95%CI
	Adjusted means	Adjusted means	Adjusted means	Adjusted means	95%CI	Adjusted means	Adjusted means	Adjusted means	Adjusted means	95%CI	Adjusted means	95%CI	
Carotid distensibility (%/10 mmHg)	1.8	1.7–1.9	1.8	1.7–1.8	1.8	1.7–1.8	1.8	1.7–1.9	1.7	1.7–1.8	1.8	1.7–1.8	
Flow mediated dilation (%)	7.1	6.5–7.6	7.6	7.3–8.0	7.7	7.3–8.0	7.7	6.5–7.7	7.9	7.5–8.3	7.8	7.4–8.2	
Pulse wave velocity (m/s)	8.8	8.5–9.0	8.7	8.5–8.8	8.6	8.4–8.7	8.6	8.5–9.0	8.7	8.6–8.9	8.6	8.5–8.8	
Intima-media thickness (µm)	641	627–656	635	627–644	633	623–642	633	617–650	645	635–655	641	630–651	
N _a	184	539	485			145	423	390					

b In model 1, N varied between 126 and 184 in participants with no siblings, 379–539 in participants with one sibling, and 344–485 in participants with two or more siblings. In model 2, N varied between 119 and 145 in participants with no siblings, 344–423 in participants with one sibling, and 317–390 in participants with two or more siblings. Adjusted Model 1 included age. Adjusted model 2 age, childhood SES (household annual income) and childhood risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, and body mass index), adult SES (annual income) and adult risk factors (LDL-cholesterol, HDL-cholesterol, triglycerides, systolic blood pressure, body mass index, serum glucose concentration, and smoking status).

risk factor of CVD. Although, in a cohort of 3641 Finnish males, no association between the number of inhabitants in childhood household and death from coronary heart disease was found [10]. In fact, in a recent Swedish study, participants with siblings had lower risk of mortality but higher risk of coronary heart disease. However, it is also reported that the number of siblings did not relate with all-cause mortality in adulthood except among children without siblings who experienced an elevated mortality risk in adulthood [30]. Also, we have demonstrated that individuals with no siblings have poorer cardiovascular risk factor levels in childhood and in adulthood compared to those with siblings [11]. Whereas smaller families may benefit from the lack of resource dilution in family, children with sibling might benefit from increased amount of shared physical activity between siblings. In addition, previously published study showed that positive childhood psychosocial factors associate with better cardiovascular health in adulthood [31] and children with siblings have better social skills [32]. Moreover, a recent study showed that each additional sibling reduces wealth in adulthood by 38 % [33] and lower SES is inversely related to risk factor levels and subclinical signs of CVD among young adults [34, 35]. In Young Finns study, we have previously shown that low family SES in childhood was associated with increased LV mass and impaired diastolic performance more than 3 decades later [36]. In addition, in a large study combining data from US and Finland, it was shown that low income is related with increased risk of nonfatal myocardial infarction and cardiovascular death [37].

We examined whether the number of siblings is associated with changes of the cardiac structure and function and found that in fully adjusted models the number of siblings associated with higher E/e'-ratio and lower LVEF in women and higher E/A-ratio in men. E/e'-ratio compares LV flow velocity and myocardial tissue velocity, and is used as a measurement of LV diastolic function (higher values of E/e'-ratio indicating a lower diastolic function) [17]. LV diastolic dysfunction has been found to predict cardiovascular death as well as all-cause mortality [38]. E/A-ratio is another measure of diastolic dysfunction, and higher ratio is considered better in our relatively young study population without pseudonormal mitral inflow patterns [39]. LVEF describes systolic function of the heart and is a significant predictor for multiple outcomes such as total mortality, cardiovascular death and hospitalizations, and heart failure hospitalizations [40]. Our results show that the number of siblings (i.e., women with 2 or more siblings) associated with lower LVEF in adulthood even after adjustment for childhood and adulthood risk factors. Endothelial dysfunction and alterations in function and structure of the arterial wall are considered the earliest changes in aging and atherosclerosis [41]. Brachial FMD can be used to measure endothelial dysfunction [42] and it has been associated with cardiovascular events [4]. In the present study, we observed an inverse association between the number of siblings and FMD among women.

The main strength of this study is the large study sample with comprehensive data on lifestyle, biochemistry, anthropometric, cardiac, and vascular measurements as well as on socioeconomic status starting from childhood and extending into adulthood with over 30 years follow-up. As in all observational studies, an apparent limitation of this study is that causality cannot be established based on our findings. However, our existing population-based follow-up study with extensive data from childhood to adulthood provides an opportunity to examine the life-course associations between possible cardiovascular risk factors and subsequent preclinical outcome measures. Admittedly, findings from longitudinal studies might suffer from bias if loss to follow-up is differential. However, the YFS study population has been dynamic as a portion of the participants lost to follow-up have re-joined the study at later phases [43]. In addition, we have shown that baseline risk factor data does not differ between adulthood participants and non-participants [44]. Thus, the cohort in the present study is likely representative of the original population [12]. Although we had covariates available from childhood and adulthood, we are unable to discount that residual or unmeasured confounding could in-part explain

our findings. Even though we observed some statistically significant associations, clinical relevance of these findings remains somewhat unclear as observed differences between groups were minor, measured values were within normal range in all participants, and no consistent link between number of siblings and surrogate markers of CVD in adulthood was found. We acknowledge that the differences between the groups are subtle and the clinical significance of our findings based on the effect sizes and their confidence intervals remains unclear. Finally, we recognize that study participants, especially those who were younger at baseline, might have had more siblings after the initial measurement time-point. However, our sensitivity analyses that used information collected from childhood follow-ups and also from the recently completed (2018–20) YFS follow-up were largely similar.

4.1. Conclusion

In conclusion, findings of this study suggest that number of siblings may associate with increased risk of heart failure in women, and with E/A-ratio in men. As the associations were somewhat inconsistent in males and females, further research is warranted in the area.

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Declaration of competing interest

The authors declared they do not have anything to disclose regarding no conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcrp.2023.200227>.

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