CARDIOVASCULAR RISK FACTORS IN CHILDHOOD AND LEFT VENTRICULAR DIASTOLIC FUNCTION IN ADULTHOOD

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Short title: Childhood CV Risk Factors and LV Function in Adults

Conflict of Interest Disclosures (includes financial disclosures): The authors declare that there is no conflict of interest.

Funding: The Young Finns Study has been financially supported by the Academy of Finland: grants 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; and EU Horizon 2020 (grant 755320 for TAXINOMISIS); and European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation. Aarne Koskelo Foundation and Diabetes Research Foundation of Finnish Diabetes Association.

Role of Funder: The funders of this study had no role in the design and conduct of the study.

Data Sharing Statement: Deidentified individual participant data will not be made available.

Abbreviations:
AUC = Area under the curve
HDL-C = High-density lipoprotein cholesterol
LDL-C = Low-density lipoprotein cholesterol
LV = Left ventricle
SD = Standard deviation
YFS = the Cardiovascular Risk in Young Finns Study

Article Summary: Adiposity status and the level of physical activity in childhood are independently associated with LV diastolic function in a population representing Finnish adult population.

What's Known on This Subject:
In adults, decreased left ventricular diastolic function is associated with several known cardiovascular risk factors such as overweight, hypertension, and physical inactivity. However, the link between childhood cardiovascular risk factor burden and adulthood left ventricular diastolic function are unknown.

What This Study Adds:
This study shows that lower left ventricular diastolic function in adulthood is associated with an increased burden of adiposity and decreased physical activity in childhood, supporting the benefits of avoiding high adiposity and adopting a physically active lifestyle from childhood.

Contributors' Statement Page

Jarkko S. Heiskanen contributed to the conception or design of the work, acquisition, analysis, or interpretation of the data, and drafted the manuscript of the work.

Saku Ruohonen and Olli Raitakari contributed to the conception or design of the work, acquisition, analysis, or interpretation of the data, and critically revised the manuscript of the work.

Suvi Rovio, Katja Pahkala, Ville Kytö, Mika Kähönen, Terho Lehtimäki, Jorma Viikari, Markus Juonala, Tomi Laitinen, Päivi Tossavainen, Eero Jokinen, Nina Hutri-Kähönen contributed to the acquisition, analysis, or interpretation of data for the work, and critically revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Word Count: 2641

ABSTRACT

Background and Objectives

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

Methods

Study participants (N=1,871, 45.9% men, aged 34-49 years) have been examined repeatedly between the years 1980 and 2011. We determined the cumulative risk exposure in childhood (age 6-18 years) as the area under the curve for systolic blood pressure, adiposity (defined using skinfold and waist circumference measurements), physical activity, serum insulin, triglycerides, and total cholesterol, and high- and low-density lipoprotein cholesterols. Adulthood LV diastolic function was defined using E/é-ratio.

Results

Elevated systolic blood pressure and increased adiposity in childhood were associated with worse adulthood LV diastolic function, whereas higher physical activity level in childhood was associated with better adulthood LV diastolic function ($p<0.001$ for all). The associations of childhood adiposity and physical activity with adulthood LV diastolic function remained significant (both $p<0.05$) but were diluted when the analyses were adjusted for adulthood systolic blood pressure, adiposity, and physical activity. The association between childhood systolic blood pressure and adult LV diastolic function was diluted to non-significant ($p=0.56$).

Conclusions

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

Keywords

Cardiology, Epidemiology, Preventive medicine

INTRODUCTION

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

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

METHODS

Study population

YFS is an ongoing multicentre longitudinal population-based study on cardiovascular risk factors from childhood to adulthood, representing the general Finnish population. The baseline study was conducted in 1980 and included 3,596 children and adolescents (49.0% males; aged 3, 6, 9, 12, 15, and 18 years). Extensive data on cardiovascular risk factors were recorded at the baseline in 1980, and all follow-up studies conducted in 1983, 1986, 1989, 2001, 2007, and 2011.[11] Population characteristics from the year 2011 are presented in Table 1. Detailed information on the YFS population and study protocol has been reported earlier.[11] The study protocol has been approved by the ethics committee of the University of Turku and Turku University Central Hospital, and informed consent was obtained from all participants. All authors had full access to the data.

Echocardiographic measurements

Echocardiography was performed in 2011 for 1,994 participants according to the joint American and European guidelines.[9,12] After excluding the participants with severe cardiovascular diseases (including stroke, myocardial infarction, atrial fibrillation, unstable angina pectoris, cardiomyopathies, and regurgitation or stenosis of the mitral or aortic valve), type 1 diabetes, or missing echocardiographic measurements, the study population of the present study consisted of 1,871 participants (859 men/1,012 women; mean age 41.8 ± 5.0 years).

Trained ultrasound technicians performed the echocardiographic examinations at five YFS study centers. All ultrasound technicians were trained by a cardiac imaging specialist. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Acuson, Mountain View, CA) ultrasonography, using a 3.5 MHz scanning frequency phased-array transducer. Analysis of the echo

images was done by one observer blinded to the clinical details with the CommPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program.[13]

E/é-ratio is a non-invasive measurement representing LV filling pressure in early diastole.[9] 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. In this study, E/é-ratio (mean 4.8, range 2.2-9.0) was calculated using the average of lateral and septal values of é velocity.[9] High E/é-ratio reflects low LV diastolic function and has been associated with all-cause mortality in several disease states.[14,15] The complete methodology of the cardiac imaging and the offline analysis of the cardiac measurements in the YFS have been published earlier.[13]

Clinical measurements and questionnaires

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

participants aged 9 to 18 years (Online supplement 1).[21] The questionnaire was administered in connection with the medical examination. For participants aged 6-years, physical activity was collected using parents' ratings (Online supplement 1).[21]

To describe the long-term burden of the risk factors, we estimated participant-specific curves for age-window between 6-18 years, systolic blood pressure, adiposity, physical activity, insulin, triglycerides, total cholesterol, HDL-C, and LDL-C by mixed model regression splines.[22] For more detailed information on the methodology, please see Online supplement 1.

Statistical analysis

The distributions of the study variables were confirmed by visual evaluation and Kolmogorov–Smirnov test. Unmodifiable parameters with a strong association with LV diastolic function, namely age, sex, and adulthood height[23], as well as the study site, were used as covariates in all statistical models. First, multivariable linear models were conducted separately for each childhood cardiovascular risk factor. Variables were standardized (mean 0 and SD 1) to ensure the comparability of the point estimates between the studied risk factors and to visualize the results as a forest plot. Second, all childhood variables showing significant associations with adulthood LV diastolic function in the previous model (*i.e.*, adiposity, physical activity, and systolic blood pressure) were entered into the same statistical model (Childhood-model). Third, a multivariable linear model (Combined-model) was created adjusting the Childhood-model additionally for corresponding adulthood parameters (*i.e.*, adulthood adiposity, physical activity, and systolic blood pressure).

To study the associations of childhood cardiovascular risk factor clustering on adulthood LV diastolic function, we calculated a childhood risk score using those childhood risk factors that associated significantly with LV diastolic function in the multivariable models. The factors included in the score

were: 1) childhood adiposity, 2) physical activity, and 3) systolic blood pressure. First, for all three risk factors, the participants were categorised into those having the risk factor (1 point) and those without the risk factor (0 points). Having a risk factor was defined as having the AUC value within the highest quartile for adiposity and systolic blood pressure and in the lowest quartile for physical activity. The risk score was then calculated by summing all three risk factors (range 0-3), resulting in four groups: 0 risk factors (N=870), 1 risk factor (N=652), 2 risk factors (N=296), and 3 risk factors (N=53). Finally, the mean E/é-ratio was calculated for each group using least-squares means (The R Package lsmeans)[24] adjusting the analyses according to Combined-model.

We used all available data in the analyses, and therefore, the number of participants varies between the models. Variance inflation factors were used to detect multicollinearity in multivariable models (no significant multicollinearities were found). P values ≤ 0.05 were considered statistically significant in all analyses. Data were analysed 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

Childhood risk factors and adulthood LV diastolic function

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

To study whether the associations of childhood risk factors remained significant after controlling for the counterpart adulthood risk factors, we conducted a multivariable model including systolic blood pressure, physical activity, and adiposity measurements from both childhood and adulthood (Table 2, Combined-model). Childhood adiposity was found to have an association with worse adulthood LV diastolic function independent of adulthood adiposity. The adjustment with the counterpart adulthood risk factors diluted the effect estimate by ~18%. Childhood physical activity had an association with better adulthood LV diastolic function independent of adulthood physical activity. After further adjustment with the counterpart adulthood risk factors, the effect estimate of childhood physical activity was diluted by ~13%. The association of childhood systolic blood pressure with adulthood LV diastolic function was no longer significant when the adulthood risk factors were taken into account (the effect estimate was diluted by 85%).

Clustering of the childhood risk factors

The results from the analyses for the childhood risk factor score, indicating the number of childhood risk factors, are shown in Figure 2. A significant trend was found between a higher

number of childhood cardiovascular risk factors and worse LV diastolic function (p=0.007). Compared to the participants with no childhood risk factors, the participants with 2 or 3 childhood risk factors had a higher E/é-ratio denoting worse LV diastolic function (p=0.047 and p=0.0066, respectively).

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

Sensitivity analyses

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

DISCUSSION

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

Childhood obesity is known to associate with adverse changes in cardiovascular risk factors, such as serum lipoproteins, systolic and diastolic blood pressure, and glucose metabolism.[25] Moreover, both childhood and adulthood obesity are associated with myocardium remodeling and alteration of LV systolic and diastolic function.[26,27] This deterioration in LV diastolic function has been suggested to affect the elastic properties of the myocardium through multifactorial mechanisms.[26,28,29] Our present results indicate that increased childhood adiposity has an inverse association with LV diastolic function in adulthood and that this link remains significant after controlling for adulthood risk factor profile. This suggests that excess childhood adiposity may have long-term adverse influences on LV diastolic function. Importantly, even though childhood adiposity was associated independently with adulthood LV diastolic function, the cardiometabolic markers closely linked to adiposity, including childhood insulin, triglycerides, total cholesterol, HDL-C, and LDL-C, were not. Therefore, our results suggest that the association between childhood adiposity and adulthood LV diastolic function is not driven by these cardiometabolic markers.

Previous studies have shown that physical activity has numerous beneficial effects on cardiovascular health.[30,31] Physically active individuals have fewer cardiovascular comorbidities, including diabetes mellitus, hypertension, and dyslipidemia than those with low physical activity levels.[32] Previous

studies have shown that lower cardiorespiratory fitness is a risk factor for worse LV diastolic function and heart failure with preserved ejection fraction and may contribute to the prognosis of the disease.[33–36] Furthermore, worse cardiorespiratory fitness in young adulthood was found to associate with higher LV diastolic filling pressures independent of cardiovascular risk factor burden in a middle-aged population.[37] Our findings, showing that the childhood cumulative physical activity is associated with better adulthood LV diastolic function, extend these previous observations by demonstrating that the beneficial effects of childhood physical activity may carry on to adulthood.

Hypertension is considered a key risk factor for LV diastolic dysfunction in adults, deterring it through several potential mechanistic pathways, including pressure overload causing LV hypertrophy and alterations in the neurohumoral activity and inflammation.[14,38] In contrast, childhood systolic blood pressure has not been previously linked with adulthood LV diastolic function. In our study, a higher cumulative burden of systolic pressure in childhood was associated with worse LV diastolic function in adulthood. However, the association diluted when adulthood systolic blood pressure was taken into account, suggesting that adulthood systolic blood pressure level is a more powerful determinant for the adulthood LV diastolic function compared to childhood systolic blood pressure.

Cardiovascular risk factors tend to cluster already in childhood, and the clustering of risk factors is thought to be a useful measure of cardiovascular health in children.[39] Our present study extends current knowledge by showing that the cardiovascular risk factor clustering (*i.e.,* an increasing number of risk factors) already in childhood associates with lower LV diastolic function in adulthood. Noteworthy, by broadening the outlook to the long-term effects of childhood risk factor clustering on cardiovascular health, and by highlighting the role of lifestyle-related childhood risk factors, the findings from our study underline the need for guideline-recommended active prevention strategies targeted to the individuals with several cardiovascular risk factors beginning from childhood.[40]

The major strengths of this study include the longitudinal study design and the long follow-up of participants who were well-phenotyped in both childhood and adulthood. A potential limitation of the study is a possible selection of the study population. As in every longitudinal study, there is a loss in the follow-up. However, detailed assessments of the representativeness have previously demonstrated no significant differences between the participants and non-participants in the age and sex-adjusted analyses.[11,16] The YFS population consists of Caucasian descents and may not adequately represent the general population of different ethnic backgrounds. E/é-ratio is a generally used marker for LV diastolic function, but it is not a consistent indicator of LV filling pressures in individual patients in specific clinical situations.[15] However, at a population level, E/é-ratio has been shown to associate with an increased incidence of heart failure and has been used in multiple studies to predict all-cause mortality, cardiovascular death, and heart failure hospitalizations in several diseases states.[14,41] Additionally, in a population-based follow-up study by Kane et al.[42], baseline E/é-ratio was found to be a predictive factor for worse LV diastolic dysfunction in the follow-up examination. Our study population with no significant cardiac diseases strengthens the significance of these results as the possibility for bias caused by cardiac diseases is low.

CONCLUSION

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

ACKNOWLEDGMENTS

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

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FIGURE LEGENDS

Figure 1.
Title: Standardized β-estimates for the associations between each separate childhood (age 6 to 18 years) cumulative cardiovascular risk factor and adulthood E/é-ratio.
Legend: Linear regression analyses conducted separately for each cardiovascular risk factor adjusting age, sex, study center (in the year 2011), and adulthood height. Standardized cardiovascular risk factor variables (mean 0 and SD 1). Error bars denote 95% confidence intervals. HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

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

TABLES

Table 1. Population characteristics (the follow-up year 2011)				
	Women (n=1,012)		Men (n=859)	
	Mean	SD	Mean	SD
E/é-ratio	5.0	1.0	4.6	0.9
Age (years)	41.9	5.0	41.7	5.0
Systolic blood pressure (mmHg)	115.3	13.6	122.9	13.4
Height (cm)	166.1	6.0	179.8	6.6
Waist circumference (cm)	87.0	13.5	96.4	12.0
Weight (kg)	71.4	14.8	86.9	15.2
Body-Mass Index (kg/m2)	25.9	5.2	26.8	4.2
Serum total-cholesterol (mmol/l)	5.1	0.9	5.3	1.0
Triglycerides (mmol/l)	1.1	1.2	1.6	1.1
HDL-C (mmol/l)	1.4	0.3	1.2	0.3
LDL-C (mmol/l)	3.1	0.8	3.4	0.9
Insulin (mU/I)	8.8	10.8	10.1	9.6
Physical activity (index score 5-15)	9.2	1.9	8.9	1.9
Overweight	30.5 %		44.4 %	
Obese	18.8 %		19.9 %	
Overweight or obese	49.3 %		64.3 %	

Overweight defined as body-mass index between 25 and 30, Obese defined as body-mass index ≥ 30, SD = standard deviation, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol

Table 2. Associations between LV diastolic function (E/é-ratio) and childhood risk factors						
	Childhood-model			Combined-model		
	Estimate	SE	P-value	Estimate	SE	P-value
Female sex	0.084	0.066	0.202	-0.217	0.072	0.003
Age (years)	0.093	0.022	<0.001	0.084	0.023	<0.001
Height in adulthood (cm)	-0.140	0.031	<0.001	-0.137	0.032	<0.001
Cumulative systolic blood pressure in childhood	0.100	0.022	<0.001	0.015	0.025	0.557
Cumulative physical activity in childhood	-0.061	0.023	0.007	-0.053	0.024	0.029
Cumulative adiposity in childhood	0.091	0.025	<0.001	0.075	0.028	0.007
Systolic blood pressure in adulthood (mmHg)				0.180	0.025	<0.001
Physical activity in adulthood (index score 5-15)				0.018	0.022	0.410
Adiposity in adulthood (cm)				0.039	0.028	0.166

Caption: Both models were additionally adjusted for study center. Childhood cumulative parameters were calculated as an area under curve variables from estimated participant-specific curves (age-window 6-18 years). Explanatory variables were standardized (mean 0 and SD 1). SE = standard error