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 associated with LV diastolic function in the participants of the Cardiovascular Risk in Young Finns Study.

METHODS: Study participants (N = 1871; 45.9% men; aged 34–49 years) were 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 by using skinfold and waist circumference measurements), physical activity, serum insulin, triglycerides, total cholesterol, and high- and low-density lipoprotein cholesterols. Adulthood LV diastolic function was defined by using E/e 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 < .001 for all). The associations of childhood adiposity and physical activity with adulthood LV diastolic function remained significant (both P < .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 nonsignificant (P = .56).

CONCLUSIONS: Adiposity status and the level of physical activity in childhood are independently associated with LV diastolic function in adulthood.
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 the 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 with 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 associated with LV diastolic function in the 34- to 49-year-old participants of the Cardiovascular Risk in Young Finns Study (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

The YFS is an ongoing multicenter, 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 3596 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 were 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 1994 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 current study consisted of 1871 participants (859 men and 1012 women; mean age 41.8 ± 5.0 years).

Trained ultrasound technicians performed the echocardiographic examinations at 5 YFS study centers. All ultrasound technicians were trained by a cardiac imaging specialist. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Mountain View, Calif, USA) transthoracic echocardiography. Additional information is given in Table 1.

TABLE 1 Population Characteristics (the Follow-up Year 2011)

<table>
<thead>
<tr>
<th></th>
<th>Women (n = 1012)</th>
<th>Men (n = 859)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/e ratio</td>
<td>5.0 ± 1.0</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>Age, y</td>
<td>41.9 ± 5.0</td>
<td>41.7 ± 5.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>115.3 ± 13.6</td>
<td>122.9 ± 13.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.1 ± 6.0</td>
<td>179.8 ± 6.6</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>87.0 ± 13.5</td>
<td>96.4 ± 12.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.4 ± 14.8</td>
<td>86.9 ± 15.2</td>
</tr>
<tr>
<td>BMI</td>
<td>25.9 ± 5.2</td>
<td>26.8 ± 4.2</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.1 ± 0.9</td>
<td>5.3 ± 1.0</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.1 ± 1.2</td>
<td>1.6 ± 1.1</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.4 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.1 ± 0.8</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td>Insulin, µU/L</td>
<td>8.8 ± 10.8</td>
<td>10.1 ± 9.6</td>
</tr>
<tr>
<td>Physical activity (index score 5–15)</td>
<td>9.2 ± 1.9</td>
<td>8.9 ± 1.9</td>
</tr>
<tr>
<td>Overweight, %</td>
<td>30.5 ± 44.4</td>
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</tr>
<tr>
<td>Obese, %</td>
<td>18.8 ± —</td>
<td>—</td>
</tr>
<tr>
<td>Overweight or obese, %</td>
<td>49.3 ± —</td>
<td>—</td>
</tr>
</tbody>
</table>

Overweight defined as BMI between 25 and 30; obese defined as BMI ≥30. —, not applicable.

* Parameters with “%” indicate percentage rather than mean.
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. Low-density lipoprotein cholesterol (LDL-C) was calculated according to Friedewald et al. In 1980, 1983, and 1986, serum insulin was measured with a modification of the immunoassay method of Herbert et al. The concentration of serum insulin was determined with an immunoassay in years 2001, 2007, and 2011. At all follow-ups, the participants’ weight (kilograms) and height (centimeters) were measured. In the follow-up studies conducted in 1980, 1983, and 1986, childhood adiposity was measured by using subscapular, biceps, and triceps skinfold measurements in triplicate from the nondominant arm by using a Harpenden skinfold caliper. Using these adiposity measures, an area under the curve (AUC) variable was created for childhood adiposity (standardized mean = 100; SD = 15). In the adulthood follow-up studies in 2001, 2007, and 2011, waist circumference (centimeters) was used to indicate adiposity. Data on leisure-time physical activity were collected by using a validated self-report questionnaire from participants aged 9 to 18 years (Supplemental Information). The questionnaire was administered in connection with the medical examination. For participants aged 6 years, physical activity was collected by using parents’ ratings (Supplemental Information).

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

Statistical Analysis

The distributions of the study variables were confirmed by visual evaluation and the Kolmogorov-Smirnov test. Unmodifiable parameters with a strong association with LV diastolic function, namely, age, sex, and adulthood height, 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 among the studied risk factors and to visualize the results as a forest plot. Second, all childhood variables revealing significant associations with adulthood LV diastolic function in the previous model (ie, 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 (ie, 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 3 risk factors, the participants were categorized 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 3 risk factors (range 0–3), resulting in 4 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 by using least-squares means (The R Package lsmeans) adjusting the analyses according to the combined model.

We used all available data in the analyses; 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 ≤.05 were considered statistically significant in all analyses. Data were analyzed by using the R statistical package,
version 3.3.2. (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 (Fig 1). The results remained similar when all 3 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 (Fig 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

<table>
<thead>
<tr>
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<th>Childhood Model</th>
<th>Combined Model</th>
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<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.084</td>
<td>0.066</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.083</td>
<td>0.022</td>
</tr>
<tr>
<td>Height in adulthood, cm</td>
<td>-0.140</td>
<td>0.051</td>
</tr>
<tr>
<td>Cumulative systolic blood pressure in childhood</td>
<td>0.100</td>
<td>0.022</td>
</tr>
<tr>
<td>Cumulative physical activity in childhood</td>
<td>-0.061</td>
<td>0.023</td>
</tr>
<tr>
<td>Cumulative adiposity in childhood</td>
<td>0.081</td>
<td>0.025</td>
</tr>
<tr>
<td>Systolic blood pressure in adulthood, mm Hg</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Physical activity in adulthood (index score 5–15)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adiposity in adulthood, cm</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Both models were additionally adjusted for study center. Childhood cumulative parameters were calculated as AUC variables from estimated participant-specific curves (age window 6–18 y). Explanatory variables were standardized (mean 0 and SD 1). —, not applicable.

### TABLE 2: Associations Between LV Diastolic Function (E/é Ratio) and Childhood Risk Factors

![Figure 1](https://via.placeholder.com/150)

**FIGURE 1**

Standardized β-estimates for the associations between each separate childhood (age 6–18 years) cumulative cardiovascular risk factor and adulthood E/é ratio. Linear regression analyses were conducted separately for each cardiovascular risk factor adjusting for age, sex, study center (in the year 2011), and adulthood height. Standardized cardiovascular risk factor variables (mean 0 and SD 1) are shown. Error bars denote 95% confidence intervals (CIs).
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 Fig 2. A significant trend was found between a higher number of childhood cardiovascular risk factors and worse LV diastolic function ($P = .007$). Compared with 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 ($P = .047$ and $P = .0066$, 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 those of the main analyses reported in Table 2 and Fig 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 by using (1) arithmetic means instead of least-squares means or (2) cutoff limits of 80th/20th 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).

![Figure 2](https://example.com/figure2.png)

**DISCUSSION**

This study reveals that the cumulative burden of adiposity, physical activity, and systolic blood pressure in childhood is associated with LV diastolic function at ages 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. Moreover, both childhood and adulthood obesity are associated with myocardium remodeling and alteration of LV systolic and diastolic function. This deterioration in LV diastolic function has been suggested to affect the elastic properties of the myocardium through multifactorial mechanisms. 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, although 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 revealed that physical activity has numerous beneficial effects on cardiovascular health. Physically active individuals have fewer cardiovascular comorbidities, including diabetes mellitus, hypertension, and dyslipidemia, than those with low physical activity levels. Previous studies have revealed 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. 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. Our
findings, revealing 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.\textsuperscript{14,37} 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.\textsuperscript{38} Our present study extends current knowledge by revealing that the cardiovascular risk factor clustering (ie, 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.\textsuperscript{39}

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 revealed no significant differences between the participants and nonparticipants in the age- and sex-adjusted analyses.\textsuperscript{11,16} The YFS population is racially homogeneous, therefore our results are generalizable to white European subjects. 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.\textsuperscript{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.\textsuperscript{14,40} Additionally, in a population-based follow-up study by Kane et al,\textsuperscript{31} 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 because the possibility for bias caused by cardiac diseases is low.

CONCLUSIONS

This study reveals 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.

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

ABBREVIATIONS

AUC: area under the curve
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
LV: left ventricular
YFS: Cardiovascular Risk in Young Finns Study

Deidentified individual participant data will not be made available.

Dr Heiskanen contributed to the conception and design of the work, contributed to acquisition, analysis, and interpretation of the data, and drafted the manuscript; Drs Ruohon and Raiatkar contributed to the conception and design of the work, contributed to acquisition, analysis, and interpretation of the data, and critically revised the manuscript; Drs Rovio, Parkala, Kytö, Kähönen, Lehtimäki, Viikari, Juonala, Laitinen, Tossavainen, Jokinen, and Hutri-Kähönen contributed to the acquisition, analysis, and interpretation of data for the work and critically revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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