Cardiovascular Risk Factors in Childhood and Left Ventricular Diastolic Function in Adulthood

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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. Cardiovascular risk burden accumulated across the lifetime contributes to cardiovascular disease outcomes that are the leading causes of death globally. 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. Adverse effects of childhood obesity on adulthood LV mass have been previously shown in the Bogalusa Heart Study. Additionally, obese children have been reported to have worse LV diastolic function in adulthood. Conversely, achieving ideal cardiovascular health, defined by the American Heart Association, in childhood has been associated with better LV diastolic function in adulthood.

Heart failure with preserved ejection fraction is a clinical syndrome characterized by symptoms of heart failure without a decrease of LV systolic function. Instead, LV diastolic function is decreased, including slow LV filling and increased diastolic LV stiffness. 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. 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. Population characteristics from the year 2011 are presented in Table 1. Detailed information on the YFS population and study protocol has been reported earlier. 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. 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, California, USA) with Acuson Sequoia 512 (Mountain View, California, USA) and Acuson Sequoia 512 (Mountain View, California, USA). The echocardiographic protocol included parasternal long-axis, apical five-chamber, apical four-chamber, and subcostal views.

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

<table>
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<tr>
<th></th>
<th>Women (n = 1012)</th>
<th>Men (n = 859)</th>
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<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
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<tr>
<td>E/e ratio</td>
<td>5.0 1.0</td>
<td>4.6 0.9</td>
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<td>Age, y</td>
<td>41.9 5.0</td>
<td>41.7 5.0</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>115.3 13.6</td>
<td>122.9 13.4</td>
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<tr>
<td>Height, cm</td>
<td>166.1 6.0</td>
<td>179.8 6.6</td>
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<tr>
<td>Waist circumference, cm</td>
<td>87.0 13.5</td>
<td>96.4 12.0</td>
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<tr>
<td>Weight, kg</td>
<td>71.4 14.8</td>
<td>86.9 15.2</td>
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<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>
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<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 —</td>
<td>44.4 —</td>
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<tr>
<td>Obese, %</td>
<td>18.8 —</td>
<td>19.9 —</td>
</tr>
<tr>
<td>Overweight or obese, %</td>
<td>49.3 —</td>
<td>64.3 —</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.
states. The complete mortality in several disease has been associated with all-cause pressure in early diastole. Pulsed-wave Doppler imaging was used to measure E. Pulsed-wave tissue Doppler imaging was used 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 by using the average of lateral and septal values of É velocity. High E/É ratio reflects low LV diastolic function and has been associated with all-cause mortality in several disease states. The complete methodology of the cardiac imaging and the off-line analysis of the cardiac measurements in the YFS have been published earlier.

**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 subcapular, 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). 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,
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 2 Associations Between LV Diastolic Function (E/é Ratio) and Childhood Risk Factors |
|------------------------------------------|------------------------------------------|
|                                          | Childhood Model                          | Combined Model                          |
|                                          | Estimate | SE     | P     | Estimate | SE     | P     |
| Female sex                               | 0.084    | 0.066  | .202  | −0.217   | 0.072  | .003  |
| Age, y                                   | 0.093    | 0.022  | <.001 | 0.084    | 0.023  | <.001 |
| Height in adulthood, cm                  | −0.140   | 0.051  | <.001 | −0.137   | 0.052  | <.001 |
| Cumulative systolic blood pressure in childhood | 0.100    | 0.022  | <.001 | 0.015    | 0.025  | .557  |
| Cumulative physical activity in childhood | −0.061   | 0.023  | .007  | −0.053   | 0.024  | .029  |
| Cumulative adiposity in childhood        | 0.081    | 0.025  | <.001 | 0.075    | 0.028  | .007  |
| Systolic blood pressure in adulthood, mm Hg | —       | —     | —    | 0.180    | 0.025  | <.001 |
| Physical activity in adulthood (index score 5–15) | —       | —     | —    | 0.018    | 0.022  | .410  |
| Adiposity in adulthood, cm               | —       | —     | —    | 0.039    | 0.028  | .166  |

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.

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).
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 4 to 9. Importantly, the associations of childhood adiposity and physical activity with adulthood LV diastolic function were independent of adulthood LV systolic blood pressure independent of adulthood LV systolic blood pressure and LV mass in separate models. The results from the main analyses were similar to those of the main analyses reported in Table 2 and Fig 2 (data not shown). Therefore, our results suggest that the association between LV diastolic function in adulthood and childhood obesity may be driven by changes in LV diastolic function. Importantly, although adverse in childhood, adverse changes in LV diastolic function in adulthood were independent of the cumulative burden of cardiovascular risk factors and serum lipoproteins, systolic and diastolic blood pressure, glucose, waist circumference, physical activity, and waist-to-hip ratio. The analyses were adjusted for age, sex, race, center, and adiposity, as well as other cardiovascular risk factors. The number of childhood risk factors was categorized into four groups on the basis of the sum of the associations between childhood risk factors and worse LV diastolic function were independent of adulthood LV systolic blood pressure. Sensitivity analyses were conducted by using (1) arithmetic mean instead of least-squares means or (2) cutoff values of 0.047, 0.0066, and 0.0066, respectively. Sensitivity analyses were conducted by using (1) arithmetic mean instead of least-squares means or (2) cutoff values of 0.047, 0.0066, and 0.0066, respectively. Sensitivity analyses were conducted by using (1) arithmetic mean instead of least-squares means or (2) cutoff values of 0.047, 0.0066, and 0.0066, respectively. Sensitivity analyses were conducted by using (1) arithmetic mean instead of least-squares means or (2) cutoff values of 0.047, 0.0066, and 0.0066, respectively.
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.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.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.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.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.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.14,40 Additionally, in a population-based follow-up study by Kane et al,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.

ACKNOWLEDGMENTS

Expert technical assistance in data management and statistical analyses by Johanna Ikonen, Noora Kartiósuo, 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 Ruohonen and Raitakari 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, Paikhala, Kyösto, 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.

The preliminary results of this article were presented in a poster session of the American Heart Association Scientific Sessions; November 10–12, 2018, Chicago, IL.
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