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1 **Associations of cardiometabolic risk factors with heart rate variability in 6–8-year-old children:**  
2 **the PANIC Study**

3  
4 **Running head:** Metabolic profile and autonomic nervous system

5  
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23

24 **ABSTRACT**

25

26 **Background:** Associations of cardiometabolic risk factors with heart rate variability (HRV) in  
27 children are unclear. We examined associations of cardiometabolic risk score (CRS) and individual  
28 cardiometabolic risk factors with HRV variables in 6-8-year-olds.

29

30 **Methods:** The participants were a population-based sample of 443 children participating in baseline  
31 measurements of the PANIC trial. Cardiometabolic risk factors included waist circumference (WC),  
32 insulin, glucose, triglycerides, HDL cholesterol, systolic blood pressure (SBP), and diastolic blood  
33 pressure (DBP). CRS was calculated as WC + insulin + glucose + triglycerides – HDL cholesterol +  
34 the mean of SBP and DBP. HRV variables (SDNN, RMSSD, HF, LF, LF/HF, Mean RR) were  
35 measured using 5-minute electrocardiography at rest and analyzed using the Kubios® HRV software.  
36 In this cross-sectional study, associations of CRS and individual cardiometabolic risk factors  
37 with HRV were investigated using linear regression analyses adjusted for sex and peak height  
38 velocity.

39

40 **Results:** CRS was negatively associated with RMSSD, HF, Mean RR (P value<0.05) and positively  
41 with LF/HF (P value=0.005). Insulin was negatively associated with SDNN, RMSSD, HF, LF, and  
42 Mean RR (P value<0.05) and positively with LF/HF (P value=0.008). SBP was negatively associated  
43 with SDNN, RMSSD, HF, LF, and Mean RR (P value<0.05). DBP was negatively associated with  
44 SDNN, RMSSD, and Mean RR (P value<0.05). WC, glucose, triglycerides, or HDL cholesterol were  
45 not associated with HRV variables.

46

47 **Conclusions:** Higher CRS, insulin, and blood pressure were associated with smaller HRV, mainly  
48 indicating lower parasympathetic activity, in young children. This knowledge may help improving  
49 the clinical management of metabolic syndrome and cardiovascular diseases since childhood.

50

51

52 **Keywords:** metabolic profile, body fat, autonomic nervous system, cardiorespiratory fitness,  
53 pediatrics

54 **INTRODUCTION**

55

56 Cardiovascular diseases are the main cause of premature mortality worldwide<sup>1</sup>. The main  
57 pathophysiological mechanism for these diseases is atherosclerosis that starts to develop during the  
58 early years of life<sup>2,3</sup>. Metabolic syndrome refers to a cluster of traditional cardiometabolic risk factors,  
59 such as central obesity, insulin resistance, hyperglycemia, hypertriglyceridemia, low plasma high-  
60 density lipoprotein (HDL) cholesterol and hypertension<sup>4</sup>. The definition of childhood metabolic  
61 syndrome is problematic due to its multiple definitions. Nevertheless, a large systematic review<sup>5</sup> has  
62 been proposed that the prevalence increases in accordance with weight status and the reported rates  
63 has been reported to vary from 0-1% in normal weight children, to 12% in overweight children, and  
64 29% in obese children<sup>5</sup>. Thus, one of the main risk factors for metabolic syndrome is childhood  
65 obesity<sup>6</sup>, which is a growing public health problem worldwide<sup>7</sup>. Moreover, children with overweight  
66 are more likely to become overweight adults indicating an increased lifelong risk for cardiometabolic  
67 diseases<sup>8</sup>. However, there is limited knowledge on the associations of metabolic syndrome and its  
68 components with cardiac autonomic modulation.

69

70 Heart rate variability (HRV) is a non-invasive measure of cardiac autonomic nervous system  
71 regulation<sup>9</sup>, and it is influenced by parasympathetic and sympathetic activity<sup>10</sup>. Reduced HRV is a  
72 risk factor for serious health problems, such as coronary heart disease, hypertension, and overall  
73 mortality<sup>11</sup>. Recently, it has been suggested that increased HRV reduces cardiovascular risk beyond  
74 traditional risk factors in children<sup>12</sup>, adolescents<sup>12,13</sup>, and adults<sup>14</sup>. On the other hand, children with  
75 overweight have been reported to have decreased HRV<sup>15,16</sup>, which may be due to the delaying effect  
76 of overweight on the natural increase in parasympathetic activity with growth<sup>16</sup>. Yet, there is a lack  
77 of studies in early childhood, although such knowledge would help screening the children who may  
78 need support the most.

79

80 In addition to overweight, there are other cardiometabolic risk factors that have been related to  
81 decreased HRV in children aged about 10 years<sup>17</sup>. For example, elevated blood pressure<sup>18,19</sup> and  
82 increased fasting plasma insulin<sup>20,21</sup> have been associated with reduced HRV. Furthermore, the use  
83 of a cardiometabolic risk score (CRS) as an indicator of clustered cardiometabolic risk instead of a  
84 dichotomous variable for metabolic syndrome is preferred in children<sup>6,22,23</sup>. To the best of our  
85 knowledge, there are only two previous cross-sectional studies on the association between CRS and  
86 HRV in general populations of children or adolescents<sup>24,25</sup>. A higher CRS was associated with a  
87 smaller HRV in children 5-6 years of age<sup>24</sup> and in adolescents aged 17 years<sup>25</sup>. However, there have

88 been differences in calculating CRS, which may have affected the results and made it difficult to  
89 compare the observations of earlier studies. Studies in different age groups and using recommended  
90 CRS are needed in order to fill in the gap in the current literature.

91

92 Since cardiometabolic risk factors have been found to track from childhood to adolescence<sup>26</sup> and  
93 adulthood<sup>27,28</sup>, understanding the impact of CRS on cardiac autonomic nervous system regulation  
94 could help improving the clinical management of metabolic syndrome and cardiovascular diseases  
95 already in young people. The aim of the present study was to investigate the associations of CRS and  
96 its components with various HRV variables in a population sample of Finnish children 6–8 years of  
97 age. We hypothesized that higher CRS and its components would be associated with smaller HRV in  
98 a general population of children.

99

100

## 101 **METHODS**

102

### 103 **Study design and participants**

104 The present study utilizes baseline data from the Physical Activity and Nutrition in Children (PANIC)  
105 study (clinicaltrials.gov NCT01803776) that is an 8-year controlled trial on the effects of a combined  
106 physical activity and dietary intervention on cardiometabolic risk factors and associated outcomes in  
107 a population sample of children aged 6-8 years at baseline from the city of Kuopio, Finland<sup>29</sup>. The  
108 Research Ethics Committee of the Hospital District of Northern Savo approved the study protocol in  
109 2006 (Statement 69/2006). The parents or caregivers of the children gave their written informed  
110 consent, and the children provided their assent to participation.

111

112 We invited 736 children 6–8 years of age who started the first grade in 16 primary schools of the city  
113 of Kuopio in 2007–2009 to participate in the study. Altogether 512 children (248 girls, 264 boys),  
114 who accounted for 70% of those invited, participated in the baseline examinations in 2007–2009. The  
115 participants did not differ in sex, age, or body mass index - standard deviation score (BMI-SDS) from  
116 all children who started the first grade in the city of Kuopio in 2007–2009 based on data from the  
117 standard school health examinations performed for all Finnish children before the first grade. Six  
118 children were excluded from the study at baseline because of physical disabilities that could hamper  
119 participation in the intervention or no time or motivation to attend in the study. We also excluded two  
120 children whose parents withdrew their permission to use the data of their children. Complete data on

121 adiposity and other cardiometabolic risk factors at baseline used in the statistical analyses were  
122 available in 232 boys and in 211 girls.

123

#### 124 **Assessment of adiposity**

125 All children were asked to empty their bladder, and thereafter, body weight was measured twice using  
126 a calibrated InBody<sup>®</sup> 720 bioelectrical impedance device (Biospace, Seoul, South Korea) to accuracy  
127 of 0.1 kg. The mean of the two measurements was used for the analyses. Height was measured three  
128 times using a wall-mounted stadiometer without shoes to the nearest of 0.1 cm, and the mean of the  
129 closest two values was used for the analyses. Body mass index (BMI) was calculated by dividing  
130 body weight (kg) by body height (m) squared, and BMI-SDS was obtained using Finnish references<sup>30</sup>.  
131 The prevalence of normal weight, overweight, and obesity were defined using the cut-off values  
132 provided by Cole and coworkers<sup>31</sup>. Waist circumference (WC) was measured three times at mid-  
133 distance between the bottom of the rib cage and the top of the iliac crest after expiration, and the mean  
134 of the closest two values was used in the analyses. Body fat percentage (BF%) and lean body mass  
135 were measured using the Lunar<sup>®</sup> dual-energy X-ray absorptiometry device (GE Medical Systems,  
136 Madison, WI, USA), as described earlier<sup>32</sup>.

137

#### 138 **Assessment of other cardiometabolic risk factors**

139 A research nurse took blood samples in the morning after a 12-hour overnight fast. Plasma glucose  
140 was measured by a hexokinase method, serum insulin by an electrochemiluminescence immunoassay,  
141 plasma triglycerides by a colorimetric enzymatic assay, and plasma HDL cholesterol by a  
142 homogeneous colorimetric enzymatic assay<sup>33</sup>. A research nurse measured systolic blood pressure  
143 (SBP) and diastolic blood pressure (DBP) from the right arm using the Heine Gamma<sup>®</sup> G7 aneroid  
144 sphygmomanometer (Heine Optotechnik, Herrsching, Germany) to accuracy of 2 mmHg. The  
145 measurement protocol included a 5-minute seated resting period followed by three measurements  
146 with a 2-minute interval in between. The average SBP and DBP of all three values was used in the  
147 analysis. Age-, sex-, and height-standardized z-scores were calculated for WC, insulin, glucose,  
148 triglycerides, HDL cholesterol, and the mean of SBP and DBP. Thereafter, CRS was calculated using  
149 a formula  $WC + \text{insulin} + \text{glucose} + \text{triglycerides} - \text{HDL cholesterol} + \text{the mean of SBP and DBP}$ , a  
150 larger score indicating a higher cardiometabolic risk<sup>33</sup>.

151

#### 152 **Assessment of heart rate variability**

153 A physician performed a standard clinical examination<sup>32</sup> for each child before the  
154 electrocardiographic (ECG) registration. Before the ECG registration, children were told to lay down

155 still for 10 minutes in order to stabilize their heart rate. Thereafter, the ECG was registered for 5  
156 minutes. For the HRV analyses, 5-minute samples were selected from the ECG. The ECG signals  
157 were measured using the Cardiosoft® V6.5 Diagnostic System (GE Healthcare Medical Systems,  
158 Freiburg, Germany) at a frequency of 500 Hz. The ECG electrodes were placed according to the  
159 conventional 12-lead system, and a chest lead of good quality presenting a high R-wave amplitude  
160 was chosen for the HRV analysis. The ECG data were analyzed using the Kubios® HRV software  
161 (Kubios Co., Kuopio, Finland), and the details of the techniques and analysis methods employed to  
162 assess HRV have been described elsewhere<sup>34</sup>. Briefly, the R-wave peaks were first detected using an  
163 adaptive QRS detection algorithm, and the RR interval time series (time intervals between successive  
164 R waves as a function of R-wave time instants) were formed. Prior to the analyses, the data were  
165 checked for potential ectopic or aberrant beats and, if necessary, such erroneous beats were corrected  
166 using interpolation methods. The HRV variables used in the analyses were SDNN, the standard  
167 deviation of all RR intervals (ms), a marker of overall HRV and RMSSD, the square root of the mean  
168 of the sum of the squares of differences between adjacent RR intervals (ms), a marker of  
169 parasympathetic activity as well as Mean RR, the mean of RR intervals<sup>10</sup>. These HRV variables were  
170 used to measure HRV in a time domain with a lower value indicating a lowered parasympathetic  
171 modulation. In addition, we calculated high frequency power (HF: 0.15 – 0.40 Hz), which represents  
172 parasympathetic modulation; low frequency power (LF: 0.04 – 0.15 Hz), which represents a mixture  
173 of sympathetic and parasympathetic modulation; and LF/HF, which estimates the ratio between  
174 sympathetic and parasympathetic nervous system activity<sup>11</sup>.

175

## 176 **Covariates**

177 Sex was reported by the parents. Years from peak height velocity was used as an indicator of maturity  
178 in children<sup>35</sup>, and it was calculated separately for boys and girls using formula provided by Moore et  
179 al.<sup>36</sup>. Cardiorespiratory fitness (CRF) was assessed by a maximal exercise test using an  
180 electromagnetically braked Ergoselect 200K® bicycle ergometer with a pediatric saddle module  
181 (Ergoline, Bitz, Germany). Maximal power output (watt) achieved at the end of the exercise test per  
182 lean body mass (kg) was used as the measure of CRF<sup>37</sup>.

183

## 184 **Statistical methods**

185 All statistical tests were conducted using the two-sided 5% level of significance and performed using  
186 SPSS statistical software, Version 24.0 (IBM Corp., Armonk, NY). The characteristics of children  
187 are provided as arithmetic means (standard deviations, SD) or frequencies (percentages, %). Before  
188 the analyses, HRV variables (SDNN, RMSSD, HF, LF, LF/HF, and Mean RR) were logarithmically

189 transformed due to skewed distributions. The associations of CRS and individual cardiometabolic  
190 risk factors (BF%, WC, insulin, glucose, triglycerides, HDL cholesterol, SBP, and DBP) with HRV  
191 variables were investigated using linear regression analyses, and we applied four different models.  
192 Firstly, data on the associations of CRS with HRV variables were analyzed without adjustment, since  
193 CRS was calculated using age-, sex-, and height-standardized z-scores for cardiometabolic risk  
194 factors. Secondly, data on the associations of individual cardiometabolic risk factors with HRV  
195 variables were adjusted for sex and peak height velocity. Thirdly, we also included BF% together  
196 with sex and peak height velocity in additional linear regression models, since increased BF% has  
197 been associated with reduced HRV<sup>15</sup> and it is a key component of clustered cardiometabolic risk.  
198 However, due to the multicollinearity, we excluded BF% from the model regarding WC. Finally, we  
199 included CRF % together with sex and peak height velocity in further linear regression models,  
200 because increased CRF has been associated with increased HRV<sup>12</sup> and decreased cardiometabolic  
201 risk factors<sup>38,39</sup>. We also studied whether the associations of CRS and individual cardiometabolic risk  
202 factors with HRV variables were different between boys and girls by adding an interaction term for  
203 CRS and individual cardiometabolic risk factors in the linear regression models. There was no  
204 evidence for the modifying effect of sex on these associations, and the results are thus presented for  
205 boys and girls together.

206

207

## 208 **RESULTS**

209

210 Participants' characteristics are presented in **Table 1**. Boys were taller, had lower BF%, and were  
211 further away from peak height velocity than girls. Boys also had higher WC, glucose, HDL  
212 cholesterol, LF, and Mean RR as well as lower insulin than girls.

213

### 214 **Associations of CRS with HRV variables**

215 CRS was negatively associated with RMSSD, HF, and Mean RR as well as positively associated with  
216 LF/HF (**Table 2**). All of these associations remained statistically significant after adjusting for CRF,  
217 but they became statistically non-significant after further adjustment for BF% (Table 2).

218

### 219 **Associations of BF% and WC with HRV variables**

220 BF% was negatively associated with RMSSD, HF, and Mean RR as well as positively associated with  
221 LF/HF adjusted for sex and peak height velocity (Table 2). These associations were no longer  
222 statistically significant after further adjustment for CRF ( $p > 0.05$ ). WC was not associated with HRV



223 variables after adjustment for sex and peak height velocity, or after further adjustment for CRF  
224 (p>0.05).

225

### 226 **Associations of insulin and glucose with HRV variables**

227 Insulin was negatively associated with SDNN, RMSSD, HF, LF, and Mean RR as well as positively  
228 associated with LF/HF after adjustment for sex and peak height velocity (Table 2). The associations  
229 of insulin with SDNN, RMSSD, HF, and Mean RR remained statistically significant after further  
230 adjustment for BF% (Table 2) or CRF (SDNN:  $\beta = -2.64$ , P value=0.002; RMSSD:  $\beta = -0.14$ , P  
231 value=0.004; HF:  $\beta = -0.14$ , P value=0.003; and Mean RR:  $\beta = -0.15$ , P value=0.001). Glucose was  
232 not associated with HRV variables (P value>0.05) (Table 2).

233

### 234 **Associations of triglycerides and HDL cholesterol with HRV variables**

235 Triglycerides or HDL cholesterol was not statistically significantly associated with HRV variables (P  
236 value>0.05) (Table 2).

237

### 238 **Associations of SBP and DBP with HRV variables**

239 SBP was negatively associated with SDNN, RMSSD, HF, LF, and Mean RR after adjustment for sex  
240 and peak height velocity (Table 2). These associations were slightly attenuated after additional  
241 adjustment for BF%, but further adjustment for CRF had no effect on the magnitude of these  
242 associations (P value<0.05). DBP was negatively associated with SDNN, RMSSD, and Mean RR  
243 when adjusting for sex and peak height velocity. These associations remained statistically significant  
244 after further adjustment for CRF (SDNN:  $\beta = -0.10$ , P value=0.044; RMSSD:  $\beta = -0.11$ , P value=0.026;  
245 Mean RR:  $\beta = -0.16$ , P value=0.001) but only Mean RR remained significant after additional  
246 adjustment for BF% (Table 2).

247

248

## 249 **DISCUSSION**

250

251 This is the first study on the association between cardiometabolic risk and autonomic modulation in  
252 young children. The novelty of our study is that we investigated the associations of a continuous CRS  
253 and individual cardiometabolic risk factors with HRV variables in children. We found that CRS was  
254 negatively associated with HRV variables independently of CRF, but these associations were partly  
255 explained by BF%. We also observed that fasting plasma insulin was negatively associated with HRV

256 variables, although these associations were partly accounted by BF%. In addition, SBP and DBP were  
257 negatively associated with HRV variables independently of CRF.

258

259 A higher CRS was associated with lower parasympathetic activity, as indicated by lower RMSSD  
260 and HF and higher LF/HF. This finding is at least partly due to the strong association between insulin  
261 and decreased HRV, since insulin resistance has been recognized as one of the key components in  
262 the development of metabolic syndrome<sup>40</sup>. To the best of our knowledge, there are only a few previous  
263 studies on the associations of CRS with HRV variables in children<sup>17,24</sup>. Vrijkotte et al.<sup>24</sup> found that a  
264 higher CRS as well as higher waist-to-height ratio and SBP of its components were associated with  
265 lower parasympathetic activity indicating smaller HRV, in children aged 5-6 years, which is in line  
266 with the present study. We also found a positive association between CRS and the balance between  
267 sympathetic and parasympathetic activity, which was not reported in the study by Vrijkotte et al.<sup>24</sup>.  
268 However, direct comparison between the studies is not possible due to the differences in  
269 methodology, as in their study, parasympathetic activity was measured by respiratory sinus  
270 arrhythmia and sympathetic activity by pre-ejection period<sup>24</sup>. Nevertheless, these findings together  
271 suggest that increased CRS is linked to lower parasympathetic activity. Zhou et al.<sup>17</sup> found inverse  
272 dose-response relationships of clustered cardiometabolic risk factors with SDNN, RMSSD, LF, and  
273 HF in children aged 9–11 years. However, children in their study had elevated levels of  
274 cardiometabolic risk factors, and thus, comparison of these results with our observations based on a  
275 general population of children needs to be done with caution. When discussing the relationships  
276 between CRS and HRV based on studies in different age groups, it is notable that HRV is likely to  
277 change during childhood<sup>16</sup> highlighting the need to study the associations in children with varying  
278 ages. Finally, we weighted each cardiometabolic risk factor similarly in calculating CRS, and it is  
279 therefore difficult to compare their true contribution to the association between CRS. In future studies,  
280 it should be further examined whether some of the components of CRS play a bigger role in  
281 autonomic nervous system regulation than others.

282

283 We found that BF% was negatively associated with RMSSD and HF power, both of which are  
284 measures of parasympathetic activity, and positively associated with LF/HF, which reflects the  
285 balance between sympathetic and parasympathetic nervous system activity. One explanation for these  
286 observations may be that overweight makes cardiac ventricles larger and their walls thicker and  
287 thereby worsens ventricular relaxation during diastole that impairs the balance of cardiac autonomic  
288 modulation<sup>15</sup>. There is evidence that overweight is associated with impaired cardiac autonomic  
289 balance in children<sup>15</sup>, but more evidence is needed in young children. Furthermore, BMI has been

290 used in defining childhood obesity in young children<sup>41</sup>, although it is not an optimal measure of  
291 pediatric obesity<sup>42</sup>. Therefore, the observed associations of increased BF%, assessed by whole-body  
292 DXA, with HRV in our study expands the knowledge on the associations of adiposity with HRV  
293 variables in children. Moreover, we found that CRF partly explained the associations of BF% with  
294 HRV variables, suggesting that higher CRF might be associated with larger HRV independent of  
295 body fat mass among pre-pubertal children. This highlights the beneficial associations of higher CRF  
296 with larger HRV already in childhood.

297

298 Fasting insulin had strong negative associations with SDNN, RMSSD, and HF, which reflect cardiac  
299 parasympathetic tone, and a strong positive association with LF/HF, a measure of the balance between  
300 sympathetic and parasympathetic activity. Moreover, these associations of fasting insulin with HRV  
301 variables were slightly attenuated after controlling for BF%. Consistent with our findings, previous  
302 studies have also shown that insulin resistance was associated with reduced HRV in children aged 11  
303 years and that this relationship was partly accounted by body fat mass<sup>20,21</sup>. Thus, the results of this  
304 study together with our findings suggest that excess fat mass partly explains the relationship between  
305 insulin resistance and decreased HRV in children. On the other hand, Taşçılar et al.<sup>21</sup> demonstrated  
306 that obese children with insulin resistance had lower HF and higher LF/HF than obese children  
307 without it, suggesting that insulin resistance has an independent association with reduced HRV.  
308 Unlike other studies in children, we took CRF into account in the analyses and found that the  
309 associations of fasting insulin with HRV variables remained after controlling for CRF.

310

311 We found no association of triglycerides or HDL cholesterol with HRV. To the best of our knowledge,  
312 there are no previous studies on these associations in young children. However, Rodríguez-Colón and  
313 coworkers<sup>25</sup> found that triglycerides was negatively and HDL cholesterol positively associated with  
314 HRV in adolescents. Such associations have also been observed in young adults<sup>43</sup>. In line with the  
315 results of previous studies in adults<sup>44</sup>, our findings suggest that triglycerides and HDL cholesterol do  
316 not play a major role in cardiac autonomic nervous system regulation in children. However, further  
317 studies are needed to investigate the associations of plasma lipids with HRV in all age groups.

318

319 Both SBP and DBP were negatively related to HRV variables SDNN and RMSSD. These  
320 associations, particularly that of SBP, became even stronger after controlling for CRF, whereas they  
321 weakened after accounting for BF%. These observations indicate that SBP and DBP are associated  
322 with cardiac autonomic regulation. The negative association between SBP and HRV has been  
323 reported previously in children aged 10-13 years<sup>18,19</sup>, yet, our results show that the relationship seems

324 to exist already in younger children aged 6-8 years. Moreover, we found that SBP was negatively  
325 associated with HF and LF and that these associations remained after controlling for CRF but  
326 weakened after taking BF% into account. These observations suggest that BF% plays a bigger role in  
327 the association between SBP and cardiac autonomic modulation than CRF among children.

328

### 329 **Strengths and limitations**

330 The strengths of the present study include a relatively large population sample of children, the  
331 comprehensive and valid assessments of cardiometabolic risk factors and HRV variables, the use of  
332 a continuous CRS instead of arbitrary cut-offs for single risk factors, and the ability to control for  
333 important confounding factors in the statistical analyses. These characteristics of the study provided  
334 us sufficient statistical power to investigate the independent associations of cardiometabolic risk  
335 factors with HRV variables in children. However, few limitations should be considered when  
336 interpreting the present findings. Firstly, the cross-sectional study design limits the conclusion about  
337 causality between the observed associations. Furthermore, a large number of analyses may increase  
338 the risk of type I errors, and thus some of the observed associations might have been found by chance.  
339 Finally, although we measured CRF, the possible confounding effects of physical activity was not  
340 addressed, and therefore, future studies are encouraged to investigate the role of physical activity.

341

342 In conclusion, higher overall cardiometabolic risk, fasting insulin, and blood pressure were associated  
343 with smaller HRV, mainly indicating lower parasympathetic activity, in children 6-8 years of age.  
344 Most of these associations were independent of CRF, whereas BF% partly explained them. The  
345 results of our study suggest that adiposity and other cardiometabolic risk factors, including poor CRF  
346 have multifaceted relationships with cardiac autonomic modulation in children, and further, the  
347 associations are similar in boys and girls. Furthermore, our results indicate that metabolic syndrome  
348 does not only lead to metabolic disturbances but also to reduction in cardiac autonomic modulation,  
349 which may in turn have a role in the development of cardiovascular diseases in later life. Such  
350 knowledge is essential in improving the clinical management of metabolic syndrome and  
351 cardiovascular diseases already in young children. However, the sample in the current study included  
352 mainly normal weight children, and therefore, the associations should be studied in populations with  
353 a higher prevalence of overweight and obesity in order to increase knowledge of the clinical  
354 significance. In addition, there is a need to further study the role of change in cardiometabolic risk  
355 factors to HRV during mid-childhood.

356

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358

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370

371

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