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Original research

Is low cardiorespiratory fitness a feature of metabolic syndrome in children and adults?

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ABSTRACT

Objectives: Cardiorespiratory fitness has been inversely associated with risk of cardiometabolic diseases. However, there are no studies comparing the independent associations of cardiorespiratory fitness scaled by body size and composition using different approaches with cardiometabolic risk factors between children and adults. We therefore investigated these associations in children and adults using same measures for cardiorespiratory fitness and cardiometabolic risk factors.
Design: Cross-sectional.
Methods: A total of 352 children (47.2 % girls) and 572 men were included in the study. Peak oxygen uptake ($\dot{V}O_{2peak}$) was measured during a maximal exercise test on a cycle ergometer and was scaled by total body mass, total fat free mass, and allometrically modelled body mass, fat free mass, and stature. Insulin, glucose, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were assessed from fasting blood samples and systolic blood pressure and diastolic blood pressure were measured. Homeostatic model assessment for insulin resistance and continuous metabolic risk score were computed.
Results: $\dot{V}O_{2peak}$ scaled by body mass was inversely associated with insulin, homeostatic model assessment for insulin resistance, triglycerides, diastolic blood pressure, the cardiometabolic risk score and the number of cardiometabolic risk factors in children and adults. However, these associations attenuated remarkably when $\dot{V}O_{2peak}$ was scaled by total fat free mass or allometrically modelled body mass, fat free mass, or stature. $\dot{V}O_{2peak}$ was consistently and positively associated with high-density lipoprotein cholesterol in children and adults irrespective of the scaling approach.
Conclusions: The inverse associations of cardiorespiratory fitness with cardiometabolic risk factors among children and adults attenuated remarkably when body size and composition were appropriately controlled for. However, the positive association between cardiorespiratory fitness and high-density lipoprotein cholesterol was consistent irrespective of the scaling approach.

Practical implications

- Cardiorespiratory fitness has been considered as an important marker of health in children and adults, but previous studies have used measures of cardiorespiratory fitness scaled by whole body mass introducing a confounding by adiposity.
- Using whole body mass as a scaling factor inflates the associations between cardiorespiratory fitness and cardiometabolic risk in children and adults.
- We found that peak oxygen uptake scaled by whole body mass was strongly and inversely associated with individual cardiometabolic risk factors and the metabolic syndrome in children and adults.
- The inverse associations of peak oxygen uptake and cardiometabolic risk factors and the metabolic syndrome disappeared or

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attenuated when peak oxygen uptake was scaled by fat free mass or allometrically modelled fat free mass or whole body mass.

1. Introduction

Cardiorespiratory fitness (CRF) has been considered one of the most accurate indicators of health status.[1] Higher CRF has been related to lower risk of metabolic syndrome[2] and its subsequent clinical manifestations such as type 2 diabetes, cardiovascular diseases, acute myocardial infarction,[3] and cardiovascular and all-cause mortality in adults.[4] Furthermore, CRF has been inversely associated with the clustering of cardiometabolic risk factors in youth.[5] However, whether the evidence from previous studies reflects the true effect of maximal aerobic power or differences in body size and composition is not clear. Most previous studies have assumed that using a simple ratio standard for body mass^{-1} (BM^{-1}), e.g. scaling a measure of CRF by BM^{-1}, removes the effect of body size on CRF.[6,7] However, a ratio standard for total BM has been shown to be inadequate in controlling the effect of body size on CRF.[6,7]

Maximal oxygen uptake ($\dot{V}O_{2max}$) stands for the reference method in assessing CRF.[4] Cardiac output is the main determinant of VO_{2max} and fat free mass (FFM) has been found to be the strongest body composition-related determinant of cardiac output.[6,7] The development of cardiac structures and cardiac output also follows the growth of stature.[8,9] Therefore, the evidence suggests that FFM[7] and stature[10] could serve as the best physiological scaling factors. On the other hand, commonly used scaling by a ratio standard for BM includes both FFM and fat mass (FM) diminishing the physiological rationale for using BM as a scaling factor. FM has been found to have a negligible role in cardiac muscle growth and left ventricular mass[11] and FM does not contribute to venous return and $\dot{V}O_{2max}$.[7,12] Furthermore, FM is strongly associated with metabolic disturbances and therefore using $\dot{V}O_{2max}$ scaled by BM^{-1} could inflate the associations between CRF and cardiometabolic health outcomes.[13]

Few previous studies suggest that $\dot{V}O_{2max}$ scaled by FFM using either ratio standard or allometrical methods or by BM using allometric or other statistical approaches used to control for body size attenuates or diminishes the association between CRF and cardiometabolic health.[13,14] Furthermore, adjustment for FFM and FM has also weakened the associations of absolute $\dot{V}O_{2max}$ with insulin sensitivity[15] and metabolic syndrome.[16] Although scaling CRF by BM^{-1} may cause spurious association between CRF and cardiometabolic health,[13] few studies have comprehensively investigated if various scaling approaches influence the associations of CRF with cardiometabolic risk factors in children and adults.

Therefore, we first investigated the associations of CRF scaled by the measures of body size and composition with cardiometabolic risk factors in children and adults. Second, we studied whether CRF scaled by different approaches differs in individuals with varying number of characteristics of metabolic syndrome.

2. Methods

The data for this study were drawn from the participants who attended the 2-year follow-up examinations of the Physical Activity and Nutrition in Children (PANIC) Study and the 11-year follow-up examinations of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD).

The PANIC Study is a physical activity and dietary intervention study which continues as a follow-up study in a population sample of children living in the city of Kuopio, Finland. Altogether 736 children 6–9 years of age who had been registered for the first grade in one of the 16 public schools of the city of Kuopio were invited for baseline examinations in 2007–2009. Altogether 512 children (248 girls, 264 boys), who accounted for 70 % of those invited, participated in the baseline examinations in 2007–2009. Of them, 440 participated in the 2-year follow-up assessments. We had complete data on variables needed in the present analyses for 352 children (186 boys, 166 girls) 9–11 years of age.

The KIHD Study is an ongoing follow-up study designed to investigate risk factors for cardiovascular diseases and related outcomes in a randomly selected sample of middle-aged men. The participants initially included 3235 eligible men who resided in the town of Kuopio or its surrounding rural communities. We had complete data on variables needed in the present analyses for 572 men aged 53–72 years.

The PANIC Study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. A written informed consent was acquired from the parent or caregiver of each child and every child provided assent to participation. The KIHD Study was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland, and all participants provided written informed consent.

Stature, BM, and waist circumference were measured and FFM, FM, and body fat percentage (BF%) were estimated using bioelectrical impedance analysis in the PANIC Study and skinfolds in the KIHD Study. In the PANIC Study, lean body mass (LM), FM, and BF% were also measured by the dual-energy X-ray absorptiometry (DXA) device. Body mass index (BMI), BMI-standard deviation score (SDS), and the prevalence of overweight and obesity were defined according to established thresholds for children and adults (see Electronic supplementary material (ESM) methods for details).

Peak $\dot{V}O_2$ (i.e. highest achieved $\dot{V}O_2$; $\dot{V}O_{2peak}$, mL×min^{-1}) was assessed during an incremental exercise test to volitional fatigue on a electromagnetically braked cycle ergometer by either the Oxycon Pro® (Jaeger, Hoechberg, Germany, the PANIC Study) or Medical Graphics (St. Paul, MI, USA, the KIHD Study) respiratory gas analyser. $\dot{V}O_{2peak}$ was scaled by BM, FFM or LM, and stature using ratio standard and allometric procedures (see the ESM methods for details).

Children and adults were asked to fast for 12 h before blood sampling. In the KIHD Study, participants were also asked to refrain from smoking for 12 h and to avoid alcohol intake for three days before blood sampling. Serum insulin, plasma glucose, triglycerides, plasma HDL and LDL cholesterol, and systolic and diastolic blood pressure were measured using standardised procedures and homeostatic model assessment for insulin resistance (HOMA-IR) and a continuous cardiometabolic risk score were computed (see the ESM methods for details). In the PANIC Study, we used the modified National Cholesterol Education Program definition using the population specific highest 25th percentiles of waist circumference, HDL cholesterol (lowest 25th percentile), triglycerides, glucose, and blood pressure to define cut-offs for an increased cardiometabolic risk.[17] In the KIHD Study, we defined metabolic syndrome using the ATPIII criteria.[18]

Statistical analyses were performed using the SPSS statistics software, version 25.0 (IBM Corp, Armonk, NY). Differences in the variables between boys and girls and between children and adults were tested using Student's *t*-test for normally distributed continuous variables, Mann–Whitney *U* test for skewed continuous variables, and Chi-square test for dichotomous variables. The associations of CRF scaled by either ratio standards or allometric models for BM or FFM with cardiometabolic risk factors were investigated with linear regression analyses adjusted for age and sex in the PANIC Study and age in the KIHD Study. The data were further adjusted for total dietary energy intake and intake of dietary fats in children and for total dietary energy intake, intake of dietary fats, alcohol consumption, and smoking in adults. We combined boys and girls to achieve a higher statistical power and because we found that sex did not modify the associations of the measures of CRF with cardiometabolic risk factors ($p > 0.100$ for interactions). The only exception was the associations of $\dot{V}O_{2peak}/BM^{-0.45}$ with HOMA-IR ($p = 0.052$ for interaction) that was reported separately for boys and girls. We also computed the percentage change of the standardised regression coefficients of measures of $\dot{V}O_{2peak}$ compared to $\dot{V}O_{2peak}$ scaled by BM^{-1} (ESM Table 1). We

Table 1
Associations of the measures of cardiorespiratory fitness with cardiometabolic risk factors in children and adults.

	Fasting serum insulin (mU/L)	Fasting plasma glucose (mmol/L)	Triglycerides (mmol/L)	Fasting HDL cholesterol (mmol/L)	Fasting plasma LDL cholesterol (mmol/L)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	HOMA-IR	Cardiometabolic risk score
The PANIC Study									
$\dot{V}O_{2peak}/BM^{-1}$	−0.481 (−0.578 to −0.384)***	−0.055 (−0.165 to 0.056)	−0.249 (−0.359 to −0.140)***	0.288 (0.180 to 0.396)***	−0.181 (−0.291 to −0.071)**	−0.085 (−0.197 to 0.026)	−0.180 (−0.291 to −0.069)**	−0.441 (−0.550 to −0.352)***	−0.557 (−0.652 to −0.462)***
$\dot{V}O_{2peak}/BM^{-0.45}$	−0.173 (−0.291 to −0.056)**	−0.013 (−0.133 to 0.108)	−0.132 (−0.254 to −0.010)*	0.149 (0.028 to 0.270)*	−0.167 (−0.288 to −0.046)**	0.027 (−0.095 to 0.148)	−0.075 (−0.197 to 0.047)	−0.163 (−0.281 to −0.044)**	−0.173 (−0.292 to −0.053)**
$\dot{V}O_{2peak}/FFM^{-1}$	−0.223 (−0.330 to −0.116)***	−0.045 (−0.155 to 0.066)	−0.131 (−0.243 to −0.019)*	0.188 (0.078 to 0.298)**	−0.082 (−0.193 to 0.030)	−0.047 (−0.159 to 0.065)	−0.061 (−0.173 to 0.052)	−0.215 (−0.323 to −0.107)***	−0.250 (−0.358 to −0.141)***
$\dot{V}O_{2peak}/FFM^{-0.85}$	−0.154 (−0.264 to −0.043)**	−0.033 (−0.146 to 0.081)	−0.105 (−0.220 to 0.010)	0.151 (0.038 to 0.265)**	−0.087 (−0.202 to 0.028)	−0.017 (−0.131 to 0.097)	−0.041 (−0.156 to 0.074)	−0.149 (−0.261 to −0.038)**	−0.161 (−0.274 to −0.049)
$\dot{V}O_{2peak}/stature^{-2.0}$	0.046 (−0.070 to 0.162)	0.024 (−0.093 to 0.142)	−0.033 (−0.153 to 0.086)	0.090 (−0.029 to 0.209)	−0.019 (−0.138 to 0.101)	0.060 (−0.059 to 0.178)	−0.027 (−0.146 to 0.092)	0.046 (−0.071 to 0.162)	0.072 (−0.046 to 0.190)
VO2max (adjusted for FFM and FM)	−0.150 (−0.295 to −0.004)*	−0.055 (−0.233 to 0.122)	−0.111 (−0.285 to 0.062)	0.194 (0.023 to 0.365)*	−0.086 (−0.263 to 0.090)	−0.007 (−0.183 to 0.170)	−0.001 (−0.078 to 0.177)	−0.145 (−0.296 to 0.007)	−0.142 (−0.276 to −0.009)*
The KIHD Study									
$\dot{V}O_{2peak}/BM^{-1}$	−0.497 (−0.578 to −0.415)***	−0.237 (−0.326 to −0.148)***	−0.378 (−0.463 to −0.292)***	0.349 (0.262 to 0.435)***	−0.001 (−0.092 to 0.090)	−0.164 (−0.253 to −0.076)***	−0.149 (−0.238 to −0.059)**	−0.492 (−0.577 to −0.410)***	−0.554 (−0.633 to −0.475)***
$\dot{V}O_{2peak}/BM^{-0.44}$	−0.312 (−0.403 to −0.221)***	−0.147 (−0.241 to −0.052)**	−0.284 (−0.376 to −0.192)***	0.245 (0.152 to 0.337)***	−0.001 (−0.096 to 0.093)	−0.109 (−0.202 to −0.016)*	−0.048 (−0.142 to 0.046)	−0.321 (−0.413 to −0.227)***	−0.331 (−0.422 to −0.240)***
$\dot{V}O_{2peak}/FFM^{-1}$	−0.355 (−0.433 to −0.268)***	−0.193 (−0.284 to −0.103)***	−0.310 (−0.399 to −0.222)***	0.293 (0.204 to 0.382)***	0.043 (−0.049 to 0.135)	−0.110 (−0.200 to −0.020)*	−0.061 (−0.152 to 0.030)	−0.369 (−0.457 to −0.280)***	−0.399 (−0.486 to −0.313)***
$\dot{V}O_{2peak}/FFM^{-0.73}$	−0.300 (−0.390 to −0.209)***	−0.160 (−0.253 to −0.067)**	−0.282 (−0.372 to −0.191)***	0.256 (−0.165 to 0.348)***	0.032 (−0.062 to 0.125)	−0.097 (−0.189 to −0.005)*	−0.033 (−0.126 to 0.060)	−0.315 (−0.406 to −0.223)***	−0.328 (−0.418 to −0.238)***
$\dot{V}O_{2peak}/height^{-1.99}$	−0.139 (−0.232 to −0.046)**	−0.073 (−0.167 to 0.020)	−0.186 (−0.278 to −0.094)***	0.163 (0.070 to 0.255)**	0.022 (−0.072 to 0.115)	−0.045 (−0.136 to 0.047)	0.040 (−0.053 to 0.132)	−0.150 (−0.243 to −0.056)**	−0.143 (−0.235 to −0.050)**
VO2max (adjusted) for FFM and FM	−0.280 (−0.362 to −0.198)***	−0.164 (−0.264 to −0.064)**	−0.286 (−0.383 to −0.190)***	0.264 (0.166 to 0.361)***	0.051 (−0.052 to 0.155)	−0.086 (−0.187 to 0.016)	−0.006 (−0.105 to 0.093)	−0.300 (−0.384 to −0.216)***	−0.309 (−0.382 to −0.235)***

Data are standardised regression coefficient and their 95 % confidence intervals from multivariate linear regression analyses adjusted for age and sex in the PANIC Study and for age in the KIHD Study. $\dot{V}O_{2peak}$, peak oxygen uptake ($mL \times min^{-1} \times kg/cm$ of the measure of body size^{-x}); BM, body mass; FFM, fat free mass; $\dot{V}O_{2peak}$ (adjusted), $\dot{V}O_{2peak}$ ($mL \times min^{-1}$) statistically adjusted for fat free mass and fat mass (FM); HOMA-IR, homeostatic model assessment for insulin resistance.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

compared $\dot{V}O_{2peak}$ scaled by the measures of body size and composition between participants with different numbers of cardiometabolic risk factors using general linear models adjusted for age and sex in the PANIC Study and age in the KIHD Study. In the PANIC Study, we performed sensitivity analyses and conducted the linear regression analyses using LM and FM assessed by DXA.

3. Results

Girls had a shorter waist circumference, higher BF%, less FFM, and lower absolute and scaled $\dot{V}O_{2peak}$ than boys (ESM Table 2). Girls also had higher insulin and lower glucose concentrations and HDL cholesterol and higher HOMA-IR than boys. Children had lower prevalence of overweight and obesity, lower BF%, lower absolute $\dot{V}O_{2peak}$, and higher $\dot{V}O_{2peak}$ scaled by BM or FFM using either ratio standard or allometry than men. Children also had lower insulin, triglycerides, LDL cholesterol, blood pressure, and HOMA-IR, and higher HDL cholesterol than men. All these differences remained similar when only boys were compared to men. Moreover, boys had higher $\dot{V}O_{2peak}$ scaled by stature than men ($p < 0.001$). The associations of $\dot{V}O_{2peak}$ with the measures of adiposity have been described in ESM Table 3.

In children, $\dot{V}O_{2peak}/BM^{-1}$ and $\dot{V}O_{2peak}/BM^{-0.45}$ were inversely associated with insulin, triglycerides, LDL cholesterol, HOMA-IR, and the cardiometabolic risk score and directly associated with HDL cholesterol after adjustment for age and sex (Table 1). $\dot{V}O_{2peak}/BM^{-1}$ was also inversely associated with diastolic blood pressure. $\dot{V}O_{2peak}/FFM^{-1}$ was inversely associated with insulin, triglycerides, HOMA-IR, and the cardiometabolic risk score and directly associated with HDL cholesterol. $\dot{V}O_{2peak}/FFM^{-0.85}$ was inversely associated with insulin, HOMA-IR, and cardiometabolic risk score and directly associated with HDL cholesterol. $\dot{V}O_{2peak}/stature^{-2.0}$ was not associated with the cardiometabolic risk factors. $\dot{V}O_{2peak}$/adjusted was inversely associated with insulin and the

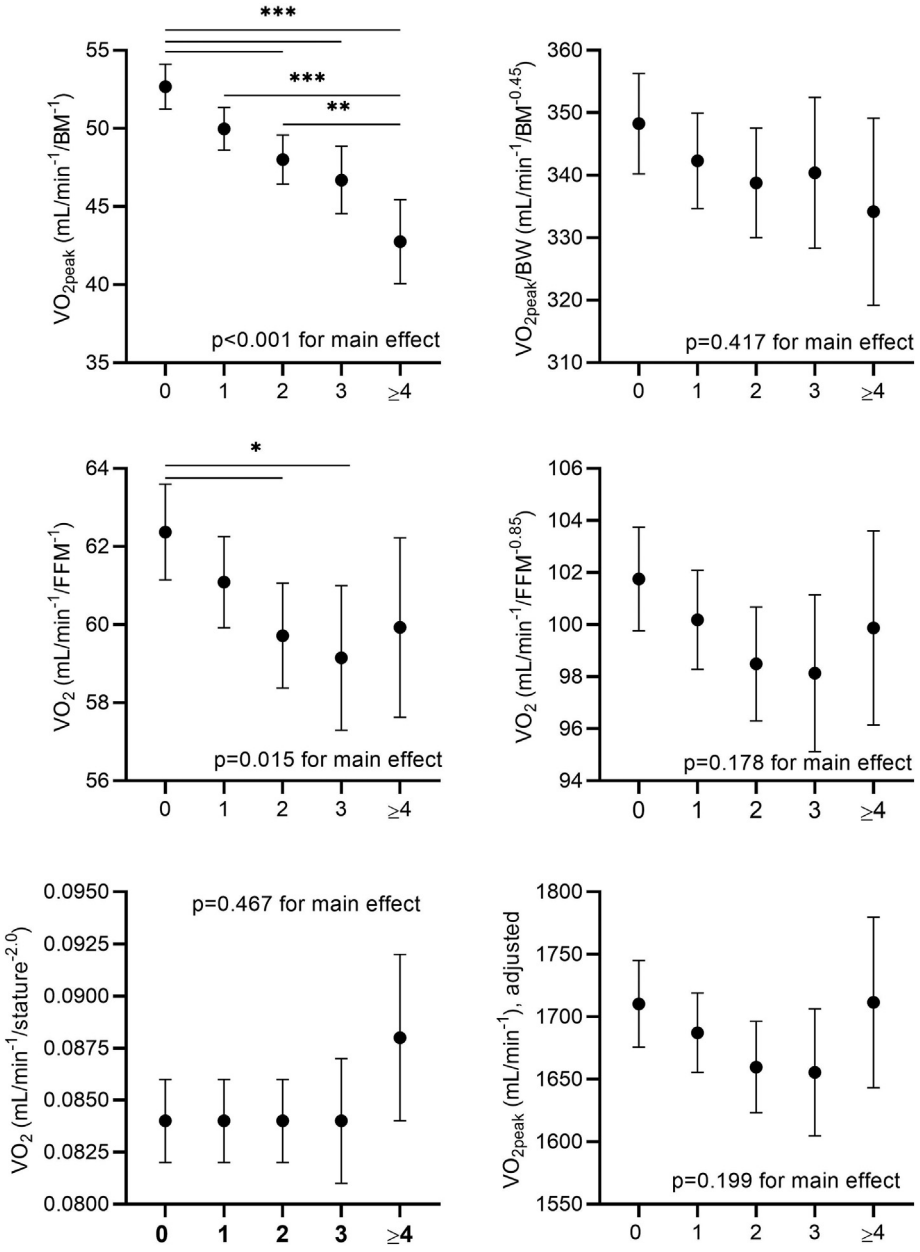

Fig. 1. Differences in $\dot{V}O_{2peak}$ among children with different numbers of cardiometabolic risk factors. The metabolic syndrome was defined using the modified National Cholesterol Education Program definition and using the population specific highest 25th percentiles of waist circumference, HDL cholesterol (lowest 25th percentile), triglycerides, glucose, and blood pressure to define cut-offs for an increased cardiometabolic risk.[17] *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

cardiometabolic risk score and directly associated with HDL cholesterol. Furthermore, $\dot{V}O_{2peak}/BM^{-0.45}$ was inversely associated with HOMA-IR in boys ($\beta = -0.217$, $p = 0.004$) but not in girls ($\beta = -0.028$, $p = 0.725$). Further adjustment for total dietary energy intake and the intake of dietary fats had no effect on the magnitude of these associations (data not shown).

In the sensitivity analyses, $\dot{V}O_{2peak}$ scaled by LM or adjusted for LM and FM measured by DXA was positively associated with HDL cholesterol but not with other cardiometabolic risk factors after adjustment for age and sex (ESM Table 4).

In adults, $\dot{V}O_{2peak}/BM^{-1}$ was inversely associated with insulin, glucose, triglycerides, systolic blood pressure, diastolic blood pressure, HOMA-IR, and the cardiometabolic risk score and directly associated with HDL cholesterol (Table 1). $\dot{V}O_{2peak}/BM^{-0.44}$, $\dot{V}O_{2peak}/FFM^{-1}$, and $\dot{V}O_{2peak}/FFM^{-0.73}$ were inversely associated with glucose, insulin, triglycerides, systolic blood pressure, HOMA-IR, and the cardiometabolic risk score and directly associated with HDL cholesterol. $\dot{V}O_{2peak}/stature^{-1.99}$ was inversely associated with insulin, triglycerides, HOMA-IR, and the cardiometabolic risk score and directly associated with HDL cholesterol. $\dot{V}O_{2peak}$/adjusted was inversely associated with glucose, insulin, triglycerides, HOMA-IR, and the cardiometabolic risk score and directly associated with HDL cholesterol. Further adjustment for total dietary energy intake and the intake of dietary fats or for total alcohol consumption and smoking had no effect on the magnitude of these associations (data not shown).

Children without cardiometabolic risk factors had higher $\dot{V}O_{2peak}/BM^{-1}$ than children with at least 2 risk factors (Fig. 1). Children without risk factors had also higher $\dot{V}O_{2peak}/FFM^{-1}$ than children with 2 or 3 risk factors (Fig. 1). However, there were no statistically significant differences in $\dot{V}O_{2peak}/BM^{-0.45}$, $\dot{V}O_{2peak}/FFM^{-0.85}$, $\dot{V}O_{2peak}/stature^{-2.0}$, or $\dot{V}O_{2peak}$/adjusted between children without risk factors and those with risk factors (Fig. 1).

Adult men without cardiometabolic risk factors had higher $\dot{V}O_{2peak}/BM^{-1}$ than all other men (Fig. 2). Moreover, men with 1 risk factor had

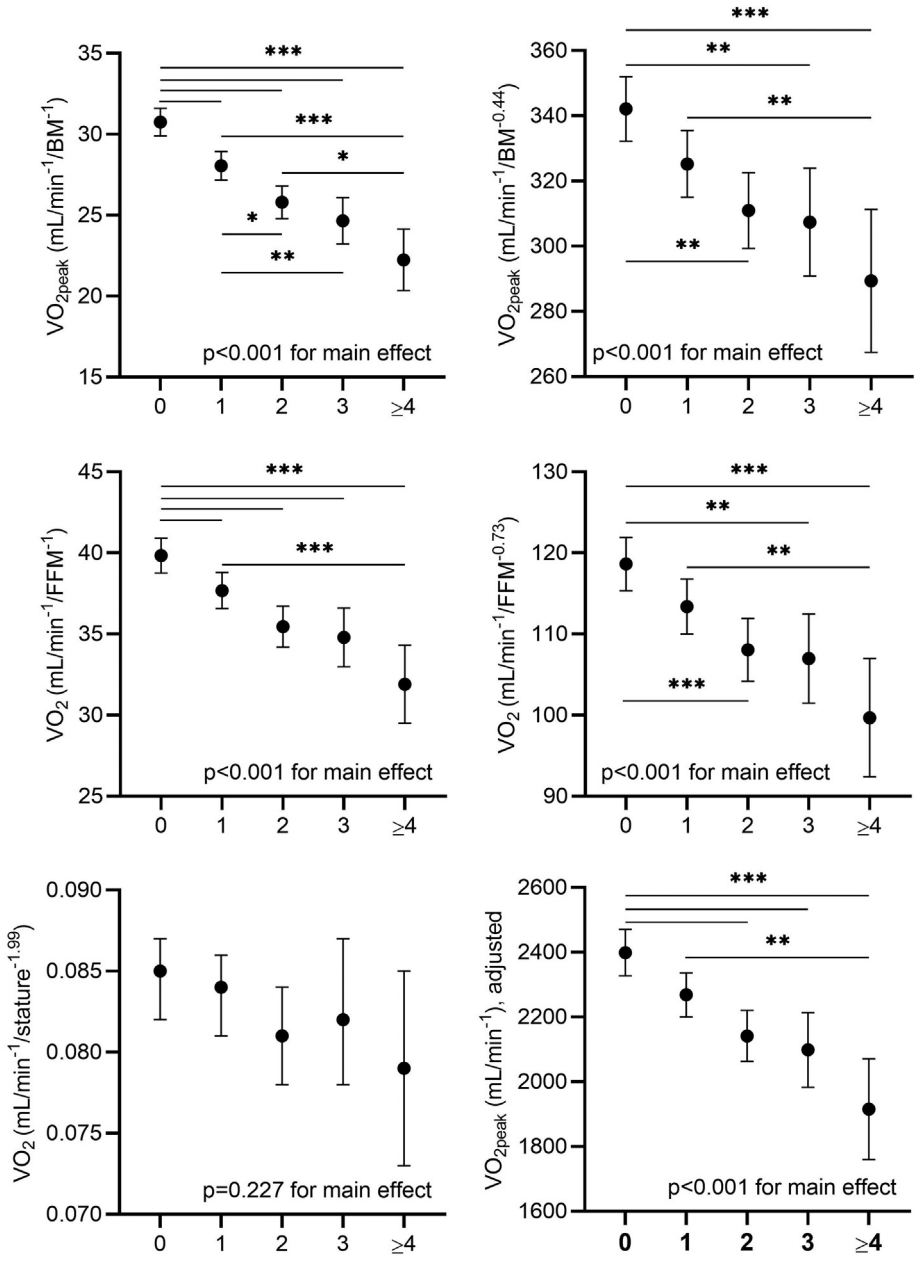

Fig. 2. Differences in $\dot{V}O_{2peak}$ among adults with different numbers of cardiometabolic risk factors. The metabolic syndrome was defined using the ATPIII criteria.[18] *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

higher $\dot{V}O_{2peak}/BM^{-1}$ than those with at least 2 risk factors. Men with 2 risk factors had higher $\dot{V}O_{2peak}/BM^{-1}$ than men with ≥4 risk factors (Fig. 2). Men without risk factors had higher $\dot{V}O_{2peak}/FFM^{-1}$ than all other men. Furthermore, men with 1 risk factor had higher $\dot{V}O_{2peak}/FFM^{-1}$ than those with ≥4 risk factors (Fig. 2).

Men without cardiometabolic risk factors had higher $\dot{V}O_{2peak}/BM^{-0.44}$ than those with 2, 3 or ≥4 risk factors (Fig. 1). Men with 1 risk factor had higher $\dot{V}O_{2peak}/BM^{-0.44}$ than those with ≥4 risk factors. Men without risk factors for metabolic syndrome had higher $\dot{V}O_{2peak}/FFM^{-0.73}$ than men with 2 or more risk factors. Furthermore, men with one risk factor had higher $\dot{V}O_{2peak}/FFM^{-0.73}$ than those with ≥4 risk factors. Men without risk factors for metabolic syndrome had higher $\dot{V}O_{2peak}$/adjusted than men with 2 or more risk factors. Furthermore, men with one risk factor had higher $\dot{V}O_{2peak}$/adjusted than those with ≥4 risk factors. There were no statistically significant differences in $\dot{V}O_{2peak}/height^{-1.99}$ between men with different numbers of risk factors (Fig. 2E).

4. Discussion

We found strong inverse associations of $\dot{V}O_{2peak}$ scaled by BM^{-1} with insulin, triglycerides, HOMA-IR, diastolic blood pressure, and the cardiometabolic risk score as well as the number of clustered components of metabolic syndrome in children and adults. However, these associations attenuated remarkably when $\dot{V}O_{2peak}$ was scaled by allometrically modelled BM, FFM, or stature (percentage change from 18 to 127 %). $\dot{V}O_{2peak}$ was consistently and positively associated with HDL cholesterol in children and adults irrespective of the scaling approach. In children, scaling $\dot{V}O_{2peak}$ by LM assessed by DXA was directly associated with HDL cholesterol but not with any other cardiometabolic risk factors. These findings suggest that scaling $\dot{V}O_{2peak}$ by FFM or allometrically by FFM and BM may provide more accurate presentation of the association between CRF and cardiometabolic health in children and adults, whereas traditional scaling $\dot{V}O_{2peak}$ by BM^{-1} may inflate this association by underestimating maximal aerobic capacity in heavier individuals.

In line with the results of previous studies,[1,4] we found strong inverse associations between $\dot{V}O_{2peak}$ scaled by BM^{-1} and cardiometabolic risk factors in children and adults. However, these associations between $\dot{V}O_{2peak}$ and cardiometabolic risk factors attenuated remarkably when $\dot{V}O_{2peak}$ was scaled by FFM or scaled allometrically by BM, FFM, or stature. Similarly, children and adults with a higher number of cardiometabolic risk factors had lower $\dot{V}O_{2peak}$ scaled by BM^{-1}. However, in line with earlier findings in youth,[16] these differences largely disappeared in children when other scaling approaches were used. Furthermore, adults without cardiometabolic risk factors had higher $\dot{V}O_{2peak}$ than those with 2 or more risk factors, suggesting that higher levels of CRF could be a feature of absence of metabolic syndrome because our results suggest that low CRF is not necessarily present in metabolic syndrome.[2] Increased fat mass plausibly explains why low $\dot{V}O_{2peak}$ scaled by BM^{-1} has an accentuated role in the increased risk of cardiometabolic disturbances in children and adults. These results together suggest that $\dot{V}O_{2peak}$ scaled by BM^{-1} causes spurious association between CRF and cardiometabolic health through the confounding of adiposity leading to an underestimation of CRF in overweight and obese individuals.

We observed a consistent positive association between $\dot{V}O_{2peak}$ and HDL cholesterol regardless of the scaling approach, excluding the scaling by stature in children. The reason for this finding in children and adults could be that higher HDL cholesterol improves $\dot{V}O_{2peak}$ by enhancing glucose oxidation and muscle mitochondrial function.[19] It is also possible that HDL cholesterol directly or indirectly improves cardiac structure and function and thereby increases $\dot{V}O_{2peak}$.[20] Furthermore, our findings may reflect the positive effects of physical activity on CRF and HDL cholesterol.[21]

In our study, the associations of $\dot{V}O_{2peak}$ scaled by BM^{-1} with cardiometabolic risk factors were quite similar in children and adults suggesting that lower CRF was associated with worse cardiometabolic health. Most associations between $\dot{V}O_{2peak}$ and cardiometabolic risk factors also attenuated but remained statistically significant in children and adults after other scaling approaches, with few exceptions, such as the associations of $\dot{V}O_{2peak}$ with triglycerides, HOMA-IR, and the cardiometabolic risk score. The reason for these mild differences may be that children were relatively healthy and <20 % were overweight or obese, whereas 75 % of the adult men were overweight or obese. It has been suggested that higher levels of CRF could be a more important determinant of cardiometabolic health in overweight and obese men than in generally healthy and normal-weight children.[23] CRF may also be more strongly related to habitual physical activity in adults than in children[24] and CRF may mediate the association between habitual physical activity and cardiometabolic risk factors in adults. Nevertheless, CRF scaled by BM^{-1} could be valuable in identifying individuals at an increased cardiometabolic risk in clinical and public health settings.

In the sensitivity analyses among children, we found that CRF scaled by FFM assessed by BIA was inversely associated with insulin, HOMA-IR, and the cardiometabolic risk score and positively associated with HDL cholesterol. However, when LM assessed by DXA was used as a scaling factor, the associations of CRF with insulin, HOMA-IR, and the cardiometabolic risk score were weak and statistically non-significant. These results correspond to our previous findings that CRF scaled by LM assessed by DXA is not associated with insulin resistance,[25] whereas CRF scaled by FFM assessed by BIA was inversely associated with the cardiometabolic risk score.[22] One reason for these observations is that BIA is more vulnerable to bias caused by hydration and nutrition status. Furthermore, whilst LM and FFM assessed by DXA and BIA agree reasonably well, we have found that BIA overestimates LM in children with higher levels of adiposity[26] that may influence the association of CRF with cardiometabolic risk factors. Although a previous study showed an inverse association between CRF scaled by FFM assessed by skinfolds and cardiometabolic risk in youth,[27] another study proposed that FFM assessed by skinfolds may not completely remove the effect of body size and composition on CRF.[28] Similarly, different methods used to assess FFM or LM may influence the estimate of CRF in adults[29] thereby confounding the association between CRF and cardiometabolic risk factors. These results together suggest that various methods to assess body composition should not be used interchangeably in scaling of CRF.

The strengths of the present study include valid and reproducible measurements of CRF using an exercise test until exhaustion with respiratory gas analysis, body composition using BIA and whole-body DXA or skinfolds, and cardiometabolic risk factors using standardised measures in population-based study samples. When comparing $\dot{V}O_{2peak}$ between children with cardiometabolic risk factors and without them we used arbitrary cut-offs for elevated levels of risk factors. The results could therefore have been slightly different if other cut-offs would have been used. Our analyses also concentrated on linear associations between CRF and cardiometabolic risk factors and therefore it is possible that latent non-linear associations were not revealed. We also used only skinfolds in the assessment of body composition in adults. In addition, our adult sample included only men and more research in women is warranted. As our study was cross-sectional, no causal interferences can be done, and prospective studies would be also needed to assess the value of allometrically scaled CRF with respect to disease outcomes. Finally, we did not consider physical activity in our analyses. Cross-sectional, longitudinal, and especially experimental studies investigating the role of different measures of physical activity in the associations of cardiorespiratory fitness scaled using different approaches with the metabolic syndrome are warranted to reveal the detailed information about the importance of CRF and its changes in cardiometabolic health.

5. Conclusions

In conclusion, we found that the associations of CRF with cardiometabolic risk factors among children and adults attenuated remarkably

when body size and composition were appropriately controlled for. Further longitudinal studies on the predictive power of CRF scaled by different measures of body size and composition with cardiometabolic risk factors and hard endpoints in children and adults are warranted.

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Declaration of interest statement

The authors declare that they have no conflict of interest.

Confirmation of ethical compliance

The PANIC Study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. A written informed consent was acquired from the parent or caregiver of each child and every child provided assent to participation. The KIHD Study was approved by the Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland, and all participants provided written informed consent.

All authors significantly contributed to the manuscript as follows:

EAH and JAL conceptualised and designed the study; EAH analysed the data, drafted the manuscript; TT, AV, KS, TAL, and JAL conducted the study; All authors critically revised the manuscript for its intellectual content and approved the final version of the manuscript.

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Appendix A. Supplementary data

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