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Cardiorespiratory Fitness Associates with Blood Pressure and Metabolic Health of Children—The Arkansas Active Kids Study

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Abstract

Introduction: High blood pressure (HBP) in children causes pre-clinical damage to the heart and accelerates atherosclerosis. Current pharmacological treatments have limited ability to prevent end-organ damage, particularly that of the kidneys. A contrasting element between adult vs. pediatric HPB treatment, is the emphasis in adults on exercise regimens that target increments in cardiorespiratory fitness [CRF, (peak VO_2)]. The aim of this study was to evaluate the association of CRF with blood pressure percentiles and blood pressure status in children with normal and excessive adiposity (NA vs. EA). An exploratory aim was to measure associations of CRF with a) other cardiovascular disease risk factors commonly found in children with HBP, and b) kidney function.

Methods: Children (n= 211), attended one study visit. CRF was measured using an incremental bike test, and body composition by dual-energy X-ray absorptiometry. Fat-free mass (FFM) index was calculated as kilograms of fat-free mass per square meter. Multiple logistic and linear regression analyses were used to model the probability of HBP, and other variables of interest [plasma lipids, HOMA2-IR, ALT, and glomerular filtration rate (eGRF)] against peak VO_2.

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Author's Contributions

E.C.D., J.L.W., S.H.A., S.B., and E.B. were responsible for conception and design of study. E.C.D., and C.G.Y. performed data collection. E.C.D. performed literature search. E.C.D., and S.B., analyzed the data. E.C.D., J.L.W., S.H.A., C.G.Y., S.B., and E.B interpreted the data. E.C.D. prepared the manuscript. E.C.D., J.L.W., S.H.A., C.G.Y., S.B., and E.B. critically revised and approved the final version of the manuscript.

Conflict of interest statement

The authors have no financial relationships or conflict of interests relevant to this article to disclose.

S.H. Adams is founder and principal of XenoMed, LLC, which is focused on research and discovery unrelated to the studies herein.

Results: CRF interacted with adiposity status in predicting the probability of HBP. Each additional milliliter per minute per FFMI in peak VO_2 decreased the odds of HBP by 8% in the EA group only (OR= 0.92; CI= 0.87–0.99). Systolic and diastolic blood pressure percentiles decreased, and eGFR increased with increasing CRF in both adiposity-level groups. HOMA2-IR and ALT decreased with increasing CRF in children with EA only.

Conclusions: Higher CRF associated with decreased probability of clinical HBP, lower insulin resistance, and improved liver function in children with EA. Yet, blood pressure percentiles and kidney function improved with increasing CRF irrespective of adiposity status.

Keywords

Obesity; adiposity; peak VO_2; hypertension

Introduction

Pediatric primary high blood pressure (HBP), which encompasses elevated blood pressure (previously known as pre-hypertension: blood pressure values ≥90th and <95th percentiles), stage-1, and stage-2 hypertension (HTN), is a growing public health concern (1). Data from the National Health and Nutrition Examination Survey (NHANES) revealed that between 1988–1994 and 1999–2008 the prevalence of pediatric HBP increased by 21% in boys (from 15.8% to 19.2%) and 53% in girls (from 8.2% to 12.6%) (2). In 2017, the American Academy of Pediatrics (AAP) created new pediatric blood pressure reference guidelines (1). Under these guidelines, 2.7% of children previously considered normotensive are classified as having elevated blood pressure while 26% of children with previous diagnosis of HBP are reclassified with a more severe clinical stage of HBP (3). Importantly, children whose blood pressure status worsens due to these reclassifications are more likely to present with dyslipidemia, prediabetes, and overweight/obesity (OW/OB) when compared to normotensive controls (3).

The most prevalent cardiovascular disease (CVD) risk factor associated with pediatric HBP is OW/OB. However, the clustering of multiple CVD risk factors in these patients is not uncommon, which contributes to the process of accelerated atherosclerosis (4). As 84% of children with OW/OB will continue to have excessive weight as adults, public health efforts are largely focused on this high-risk population (5). Major cardiovascular events attributable to HBP do not occur in childhood; however, there is silent damage to target organs (6, 7). Even mild elevations in blood pressure (≥90th and <95th percentiles) are associated with higher frequency of left ventricular hypertrophy and increased arterial stiffness (6). In adults, HBP is the second leading cause of end-stage renal disease. While current pharmacological treatments are effective at reducing blood pressure, their ability to prevent kidney injury is limited, which underscores the necessity of safe and effective strategies to protect target organs (8).

Unfortunately, HBP literature in children is not as robust as that in adults (1). When it comes to treatment and management of adult HBP, for example, increasing both cardiorespiratory fitness [CRF, peak oxygen consumption (Peak VO_2)] and physical activity (PA) are essential goals (quality of evidence: level A) (9–11). In contrast, the recommendation of PA as a

non-pharmacological approach to counter HBP in children is based on low quality evidence (level C) and therefore the strength of this recommendation is weak (1). Nevertheless, lifestyle modifications specifically PA and dietary changes, are the choice of treatment at the time of diagnosis for the majority of children (1, 12, 13). A contrasting element, however, that distinguishes the approach to adult vs. pediatric HBP is the emphasis in adults on exercise regimens that target increments in CRF (10, 14). Current clinical guidelines to pediatric HBP contemplate neither objective measurements of CRF to assess risk, nor CRF oriented goals to guide treatment.

Most studies evaluating the association between CRF and cardiovascular health in children rely on indirect measurements of fat mass and/or indirect measurements of CRF. Moreover, the role of CRF on blood pressure status assessed using current screening guidelines from the AAP has not been evaluated. To address these gaps and provide new insight to the field, we conducted direct measurements of CRF (peak VO_2) and adiposity (dual-energy X-ray absorptiometry, DXA) in 7 to 10-year-old children. We hypothesized that CRF improves blood pressure percentiles and blood pressure status, particularly in children at higher risk for clinical HBP (i.e., excessive adiposity). An exploratory aim was to evaluate the association of CRF with other markers of CVD risk frequently found in children with HBP (4). Finally, the association between CRF and the estimated glomerular filtration rate as a measure of kidney function was assessed.

METHODS

Subjects

Two-hundred-eleven children (7–10 years old) enrolled in the Arkansas Active Kids Study (AAK) were included for analyses (Table 1) (15). Exclusion criteria were: severe persistent asthma (determined by daily use of oral/inhaled corticosteroids to keep asthma symptoms under control and/or frequent use of rescue inhaler), metabolic/endocrine diseases (e.g., type 1 or type 2 diabetes mellitus, hypothyroidism), being on hormonal replacement therapy, cancer, autoimmune diseases and bleeding disorders. Qualifying children attended a one-day study visit at the Arkansas Children's Nutrition Center (ACNC) Laboratory for Active Kids and Families. The institutional review board at the University of Arkansas for Medical Sciences approved the study protocol. All parents and children gave written informed consent and assent, respectively.

Measures

Anthropometry and body composition—In the overnight-fasted state, body weight and height were measured using a digital scale (Seca 877, Seca GbmH & Co. KG, Hamburg, Germany) to the nearest 0.1 kg and 0.1 cm, respectively, and triplicate values averaged. Body composition and visceral fat area (cm^2) were assessed using DXA (Horizon-A with Advanced Body Composition™, Hologic, Bedford, MA, USA). Fat mass (FM) index [FMI= FM (kg)/height (m^2)] and fat-free mass (FFM) index [FFMI= FFM (kg)/height^2 (m)] z-scores were computed using normative values in children (16). Children were determined to have excess adiposity (EA) if their FMI z-score ≥1, whereas those with an FMI z-score <1 were considered to have normal adiposity (NA).

Blood pressure measurements—Children were asked to empty their bladders and rest lying down for a minimum of 20 minutes. Blood pressure was measured in duplicate at 1-minute interval on the right arm using an electronic vital sign monitor (CARESCPE™ VC150, Milwaukee, WI, USA). For data analyses, systolic (SBP) and diastolic (DBP) blood pressure percentiles as well as clinical stage [normal (SBP/DBP percentile <90th), elevated (SBP/DBP percentile ≥90th to <95th or 120/80 mmHg to <95th percentile, whichever was lower), stage-1 HTN (SBP/DBP percentile ≥95th to <95th plus 12 mmHg or 130/80–139/89 mmHg, whichever was lower), and stage-2 HTN (SBP/DBP percentile ≥95th plus 12 mmHg or ≥140/90 mmHg, whichever was lower)] were determined for each of the two measurements using the AAP 2017 pediatric blood pressure guidelines (1, 17). If blood pressure clinical stage did not change from the first to the second measurement then values from the first measurement were used, unless both systolic and diastolic blood pressure were lower in the second measurement. If clinical staging improved (i.e., HTN to elevated or elevated to normal) from the first to second measurement or vice versa, then values from the less severe clinical staging were used (18).

Blood draw and analytes—Blood was drawn from the antecubital vein via venipuncture following an overnight fast. Serum levels of sodium, chloride, calcium, creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), glycerol, and C-reactive protein (CRP) were measured using an RX Daytona clinical analyzer and following manufacturer's instructions (Randox Laboratories-US Limited, Kearneysville, WV, USA). Insulin levels were measured using enzyme-linked immunosorbent assay (Meso Scale Discovery, Rockville, MD, USA). The updated homeostasis model assessment (HOMA2) calculator from the Oxford Centre for Diabetes, Endocrinology and Metabolism (19) was used to estimate insulin resistance (HOMA2-IR), insulin secretion (HOMA2-%β), and insulin sensitivity (HOMA2-%S). Glomerular filtration rate (eGFR, ml·min^{-1}·1.73 m^{-2}) was estimated using the updated Schwartz equation (20, 21) shown below:

$$\text{eGFR} = [0.413 \times \text{height (cm)}]/\text{serum creatinine (mg/dL)}$$

Cardiorespiratory fitness—Peak VO_2 was assessed through a graded exercise test on a pediatric cycle ergometer (Corival Pediatric, Lode B.V., Groningen, the Netherlands). Oxygen consumption during the exercise test was measured using a metabolic cart (Medgraphics Ultima PFX® system, MGC Diagnostics Corporation, St. Paul, MN, USA). Sit height was adjusted to a corresponding knee angle of 15 degrees which was measured using a goniometer with the pedal at its lowest position. Crank length was set at 13 cm for 7-year-old children, and 15 cm for 8–10-year-old children (22). The workload increased every minute in increments of 10 Watts for children < 120 cm tall and 15 Watts for children ≥120 cm tall. During the test, children were instructed to keep the pedal frequency between 50–60 rpm. Children were included for analyses if they met the following criteria: 1) heart rate ≥80% of age predicted maximum, and/or 2) respiratory exchange ratio ≥ 1.0, and/or 3) ratings of perceived exertion on the children's OMNI scale ≥ 8. Careful attention was paid to not terminate the test before children displayed signs consistent with maximal effort.

In this study, peak VO_2 was normalized to FFMI ($ml \cdot min^{-1} \cdot FFMI^{-1}$; FFMI is in kg/m^2) in order to account for the effect of height on FFM [r = 0.88; $p<0.001$)] for a more accurate comparison among children of different statures (23). The ratio method which intends to remove the influence of FFM (or body weight) from peak VO_2, assumes that the relationship between these two variables is linear with a Y-intercept not different from zero (24). However, the assumption of a zero intercept is systematically violated when FFM or body weight are used as denominators. This has raised concerns and has been a topic of discussion for many years due to the possibility of spurious conclusions when deviations from assumptions occur (24). Our approach met both assumptions of the ratio method [i.e., linear association between peak VO_2 and FFMI ($\beta = 87.1$, $p<.0001$), and Y-intercept not different from zero (intercept =100.3, $p=0.4494$)] which was not the case when FFM or body weight were used.

Sodium consumption—Sodium consumption was assessed on the day of the study visit using the Block Food Screener 2007 for children ages 2 to 17 years. Records were analyzed using NutritionQuest's Data-on-Demand system (NutritionQuest, Berkley, CA) (25).

Statistical analysis

Our sample size derives from the cross-sectional study AAK (NCT03221673). A detailed description of the study design, study protocols, and statistical analysis has been published elsewhere (15). Briefly, we estimated that a sample size of 200 subjects has 80% power to detect a standardized difference of 0.23 in cardiometabolic risk profile, and a difference of 0.35 in BMI z-score at the 0.05 significance level. Cardiometabolic risk is the primary outcome of AAK and is defined as an integrated variable measured from a range of variables collected in the AAK study.

Data measures in the interval scale are summarized as mean ± SD whereas data measures in the ordinal or nominal scale are summarized as percentages and counts. Depending on the data distribution, comparisons of continuous variables between EA and NA groups were done with the two-sample Wilcoxon test or the two-sample *t*-test. Categorical variables between groups were compared using the Chi-square or Fisher exact tests. The probability of having HBP (i.e., elevated blood pressure, stage-1 HTN and stage-2 HTN) using peak VO_2 as a predictor was fitted using logistic regression analysis. The association of SBP percentile, DBP percentile, eGFR, HDL cholesterol, and LDL cholesterol (dependent variables) with peak VO_2 and adiposity status (EA vs. NA; independent variables) was modeled using simple and multiple generalized linear regression analysis. Sex, age, and race were included in the final models if a significant association ($p<0.05$) existed between these variables and the outcomes of interest.

RESULTS

Subject characteristics (Table 1)

The distribution of blood pressure status significantly differed between EA and NA groups. That is, 69% of children in the EA group had HBP vs. 24% of children in the NA group.

Metabolic profile of children with EA and NA (Table 2)

Fasting insulin, HOMA2–IR, and HOMA2-%β were 1.6 to 2.0 times higher in children with EA when compared to children with NA. Similarly, fasting LDL cholesterol, CRP and ALT were higher in children with EA vs. NA. On the other hand, HDL cholesterol was lower in children with EA when compared to children with NA. eGFR did not differ between NA and EA groups.

Logistic regression analysis and odds ratio estimates (Table 3)

The difference in the (log) odds of HBP was 8.3 units higher in children with EA compared to children with NA (β = 8.3, $p = 0.0077$) (Table 3). There was interaction between peak VO_2 and adiposity status (EA vs. NA) in predicting the probability of HBP (Wald Chi-square 4.54; $p = 0.0332$). Increasing peak VO_2 decreased the odds of HBP but only in the EA group (Figure 1). Specifically, each additional $ml \cdot min^{-1} \cdot FFMI^{-1}$ in peak VO_2 decreased the odds of HBP by 8% in children with EA (OR= 0.92; CI = 0.87–0.99). On the other hand, the effect of peak VO_2 on HBP was not statistically significant in children with NA (OR = 0.99; CI = 0.97–1.01) (Table 3).

Linear regression analyses between peak VO_2, adiposity status (EW vs. NW) and their interaction with markers of cardiometabolic health and kidney function (Table 4)

SBP and DBP percentiles negatively associated with peak VO_2. For every unit increase in peak VO_2, SBP and DBP percentiles decreased by 0.21 ($p = 0.0044$) and 0.25 ($p = 0.0001$) percentage – points, respectively (Table 4). SBP and DBP percentiles were in average 14.6 ($p<.0001$) and 8.5 ($p = 0.0074$) percentage – points higher in the EA group compared to the NA group. There was no interaction between peak VO_2 and adiposity status in predicting blood pressure percentiles. HOMA2-IR was in average 0.62 units higher in children with EA compared to children with NA ($p<0.0001$) (Table 4). There was interaction between peak VO_2 and adiposity status in predicting HOMA2-IR (Figure 2). Specifically, HOMA2-IR decreased with increasing CRF in children with EA (β = −0.01, $p = 0.0499$) but not in children with NA (Table 4).

LDL- cholesterol was on average 0.54 mmol/L higher in children with EA compared to children with NA ($p = 0.0002$). LDL - cholesterol levels were not associated with peak VO_2 nor was interaction found between adiposity status and CRF in association with LDL levels. There was a marginal association between HDL – cholesterol and peak VO_2 ($p = 0.0577$) which was primarily mediated by sex (data not shown), with girls exhibiting lower values of HDL cholesterol compared to boys. ALT was in average 5.5 IU/L higher in children with EA compared to children with NA ($p = 0.0049$). There was interaction between peak VO_2 and adiposity status in association with ALT levels. ALT decreased by 0.24 IU/L per unit increased in peak VO_2 but only in the EA group (Figure 2).

eGFR positively associated with CRF. For every unit increase in peak VO_2 eGFR increased by 0.12 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. eGFR did not associate with adiposity status nor interaction was found between peak VO2 and adiposity group (Table 4).

Multiple linear regression analyses between peak VO_2 and adiposity status (EW vs. NW) with SBP percentiles, DBP percentiles, LDL – cholesterol, HDL – cholesterol, and eGFR (Table 5)

SBP ($p = 0.0465$) and DBP ($p = 0.0003$) percentiles decreased with increasing peak VO_2 independently of adiposity status (Table 5, Figure 3). Sodium intake was marginally associated with DBP percentiles but not with SBP percentiles. Adiposity status (EW vs. NA) was the strongest predictive variable of SBP percentile followed by peak VO_2 and explained 5.5% and 1.7% of the observed variance ($p = 0.0004$) respectively. On the other hand, peak VO_2 was the strongest predictive variable of DBP percentile explaining 5.4% of the observed variance ($p = 0.0003$). Fasting levels of HDL and LDL – cholesterol did not associate with peak VO_2 after adiposity status was controlled for. Adiposity status accounted for 5.3% and 7.1% of the variance in HDL and LDL – cholesterol levels, respectively. Sex was a significant predictor of HDL - cholesterol with girls having lower fasting HDL levels compared to boys.

DISCUSSION

The present study evaluated the relationship of CRF (peak VO_2) with blood pressure percentiles and blood pressure status in children with normal (NA) and excessive adiposity (EA). Blood pressure was assessed using the 2017 clinical guidelines from the American Academy of Pediatrics for screening and management of HBP in children and adolescents (1). An additional exploratory aim, was to assess the relationship of CRF with kidney function and with other markers of CVD risk frequently found in children diagnosed with HBP. The major finding of this study was that CRF interacted with adiposity status in predicting the probability of HBP. Specifically, the probability of HBP decreased with increasing peak VO_2 in children with EA, but not in children with NA. Yet, SBP and DBP percentiles inversely associated with CRF in both adiposity-level groups. Similarly, CRF interacted with adiposity status in association with HOMA2-IR and ALT levels. That is, insulin resistance and liver function tests improved with increasing peak VO_2 in the EA group compared to the NA group. Finally, independently of age and adiposity status, eGFR directly associated with CRF. Taken together, these results suggest that increasing CRF confers protection against HBP, insulin resistance, and liver injury in children with EA. However, all children benefit from increasing CRF as evidenced by improved blood pressure percentiles and kidney function.

We saw a slightly higher prevalence of elevated blood pressure (14% vs. 11%), and HTN (19% vs. 15%) in our study compared to data reported following an initial screening in 10-to-12 year old children from Houston, Texas where childhood overweight and obesity rates are similar to those of Arkansas (26). It is worth noting that in the aforementioned study 6.9% of children who were initially classified as having HTN did not meet HTN criteria in follow-up visits which resulted in a much lower confirmed HTN prevalence of 2.3% (estimated prevalence of 3.2% after accounting for those lost to follow up). The decrease in HTN prevalence from initial to follow-up measurements was directly mediated by a reduction in stage-1 HTN. It is known that HBP readings fluctuate within and between visits (i.e., accommodation effect) which is why repeated measurements over time are

needed to confirm HTN diagnosis (18). The cross-sectional design of our study prevented us from measuring changes in blood pressure status in the overall group and in relation to CRF.

In adults, a wealth of evidence has demonstrated that low CRF is a major risk factor for the development of CVD and mortality (27). While the role of CRF in pediatric health is gaining recognition (28), the quantity and quality of the current evidence are insufficient to inform pediatric clinical practice guidelines. Elevated blood pressure (previously known as pre-hypertension), and hypertension are classic CVD risk factors that track from childhood to adulthood (29, 30). Recently, in a study involving 3,800 Canadian children ages 6 to 17 years (31), a negative association was reported between indirect measurements of CRF (i.e., submaximal step test) and systolic and diastolic blood pressure values. The study, however, did not evaluate the relationship between CRF and clinical blood pressure status in children with different body habitus.

Obesity is a strong determinant of HBP risk in children (32). On the other hand, many questions remain unanswered around the role of CRF for blood pressure status and other physiological responses during childhood. In other words, to what degree is the obesity-associated increased risk for hypertension driven by sedentary behavior and sub-optimal PA, versus body weight *per se*? Epidemiological data derived from NHANES surveys between 1988 and 2008 show a parallel increase in the prevalence of HBP and pediatric obesity (2, 33). In contrast, research on trajectories of CRF over time is limited but there is evidence that running performance, an indirect measure of aerobic capacity, in children from developed countries (n= ~120,000) declined at a rate of 0.43% per year between 1981 and 2000 (34).

Ekelund *et. al.* (35) evaluated the association between CRF in children 9–10 years old (n = 1,092) and clustered cardiovascular risk. A composite score that incorporated standardized values of fasting glucose, insulin, HDL - cholesterol, triglycerides, waist circumference, and the average of the sum of SBP and DBP (in mmHg) was used. Clustered cardiovascular risk decreased with increasing CRF, but the association was confounded by adiposity (i.e., waist circumference). Analyses were not further stratified by BMI status. The authors also reported a negative association between CRF and fasting glucose levels. Similarly, our findings showed a negative association between CRF and insulin resistance (HOMA2-IR), but only in children with EA. β - cell secretion estimated using the HOMA2-%β decreased with increasing peak VO_2 ($\beta = -0.01$, $p = 0.0008$) but only at higher levels of adiposity (CRF × FMI – z scores interaction, data not shown). A similar trend was seen for fasting glucose levels (data not shown, $\beta = -0.006$, $p = 0.0516$).

The same authors (35) also reported no association between CRF and systolic or diastolic blood pressure. It is worth noting, however, that systolic and diastolic blood pressure values were standardized to the mean by sex and age, and height was not considered in multiple linear regression analysis. The latter may be a limitation since height is a major determinant of blood pressure in children and should always be considered in conjunction with age and sex (1). We found a negative linear association between systolic and diastolic blood pressure percentiles and peak VO_2 in children, regardless of adiposity status. In this study, the effect of peak VO_2 on DBP percentile was greater compared to that on SBP percentile.

Greater improvement in DBP vs. SBP in relation to exercise training and peak VO2 was recently reported in adults with solid organ transplant (36). The diastolic component of blood pressure is generated by the systemic vascular resistance which in turns regulate blood supply to peripheral tissues and organs (36).

Interestingly, in this study, kidney function measured using the eGFR directly associated with CRF. In agreement with our finding, Vanden Wyngaert and colleagues (37) reported a significant increase in eGFR (+2.16 $ml \cdot min^{-1} \cdot 1.73m^{-2}$) and peak VO_2 (+2.39 $ml \cdot kg^{-1} \cdot min^{-1}$) in patients with chronic kidney disease (CKD) participating in aerobic endurance training. While our study does not explore mechanisms of action, there is evidence to support that systemic vascular resistance, sympathetic nervous system activity, and plasma renin activity decrease with endurance training (38). Sympathetic stimulation of the afferent arteriole of the glomeruli leads to vasoconstriction and reduced hydrostatic pressure within the lumen of glomerular capillaries which in turns reduces the glomerular filtration rate (39). We did not find an association between DBP / SBP percentiles and eGFR (data not shown). Similarly, Vanden Wyngaert *et. al.* (37) reported that improvements in eGFR occurred in the absence of significant changes in blood pressure in patients with CKD.

Blood ALT concentration is currently the recommended screening test for nonalcoholic fatty liver disease (NAFLD) in children with OW/OB (40). Our data showed a negative association between CRF and ALT levels in children with EA. While the etiology of NAFLD is multifactorial, insulin resistance has been proposed as a crucial mechanism in the pathogenesis and progression of NAFLD (41). Our study shows that HOMA2-IR and ALT levels decrease in relation to CRF in children with EA. Including HOMA2-IR in the model ($\beta = 3.4$, $p = 0.0280$), however, did not modify the association between CRF and ALT. In 15-year-old boys with obesity, a 3-month exercise intervention resulted in a ~2% reduction in intrahepatic lipid content measured by proton magnetic resonance spectroscopy (42). Children were randomized to participate in aerobic or resistance training. In both groups, peak VO_2 increased by ~8 $ml \cdot kg^{-1} \cdot min^{-1}$, and visceral fat decreased by 0.5 kg. However, insulin sensitivity measured using the hyperinsulinemic-euglycemic clamp technique improved only in the resistance training group (42). Taken together, these results suggest that the observed decrease of ALT in relation to CRF cannot solely be explained by improvements in insulin sensitivity. Other pathways (e.g., lipid production, lipid processing, and lipid clearance capacity by the liver) may be involved.

Our study is limited by its cross-sectional design. Blood pressure measurements were done during a single study visit, which may result in overestimation of HBP in some cases. On the other hand, this study has significant strengths. Children underwent direct measurements of CRF and of body composition which are lacking in most of the published studies in this area. Also, blood pressure percentiles and blood pressure status were assessed using the most updated guidelines from the AAP, allowing for interpretations that are meaningful for both health care providers and researchers.

In summary, higher CRF associates with improved SBP and DBP percentiles, and kidney function in children, regardless of adiposity status. Increasing CRF in children with EA

associates with decreased probability of clinical HBP, lower levels of insulin resistance, and improved liver function. The current results support the idea that improvement in CRF should be considered as a therapeutic strategy for the reduction of CVD risk in children with EA.

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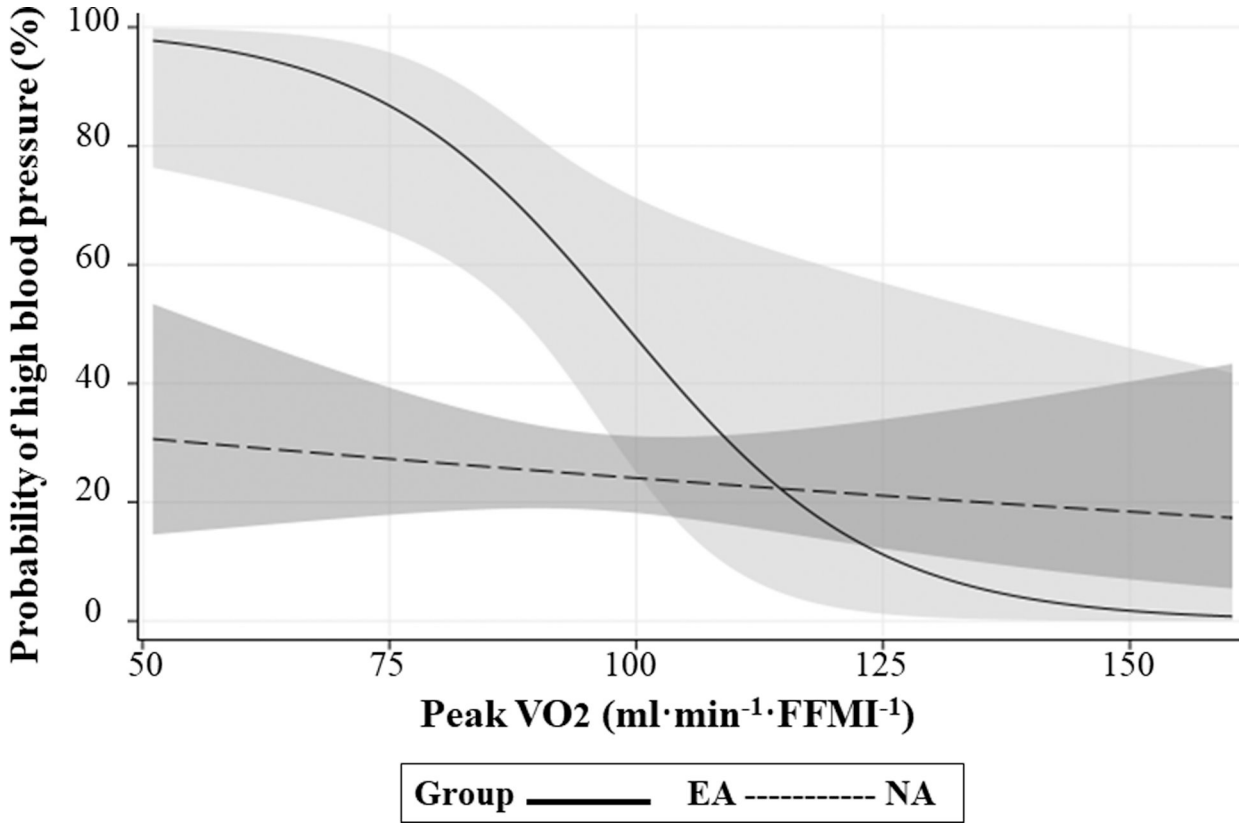

Figure 1.

Logistic plot showing the association between peak aerobic capacity (X axis) and probability of high blood pressure plus 95% confidence intervals (Y axis) in 7–10-year-old children with normal or excess adiposity. High blood pressure refers to elevated blood pressure, stage-1 and stage-2 hypertension.

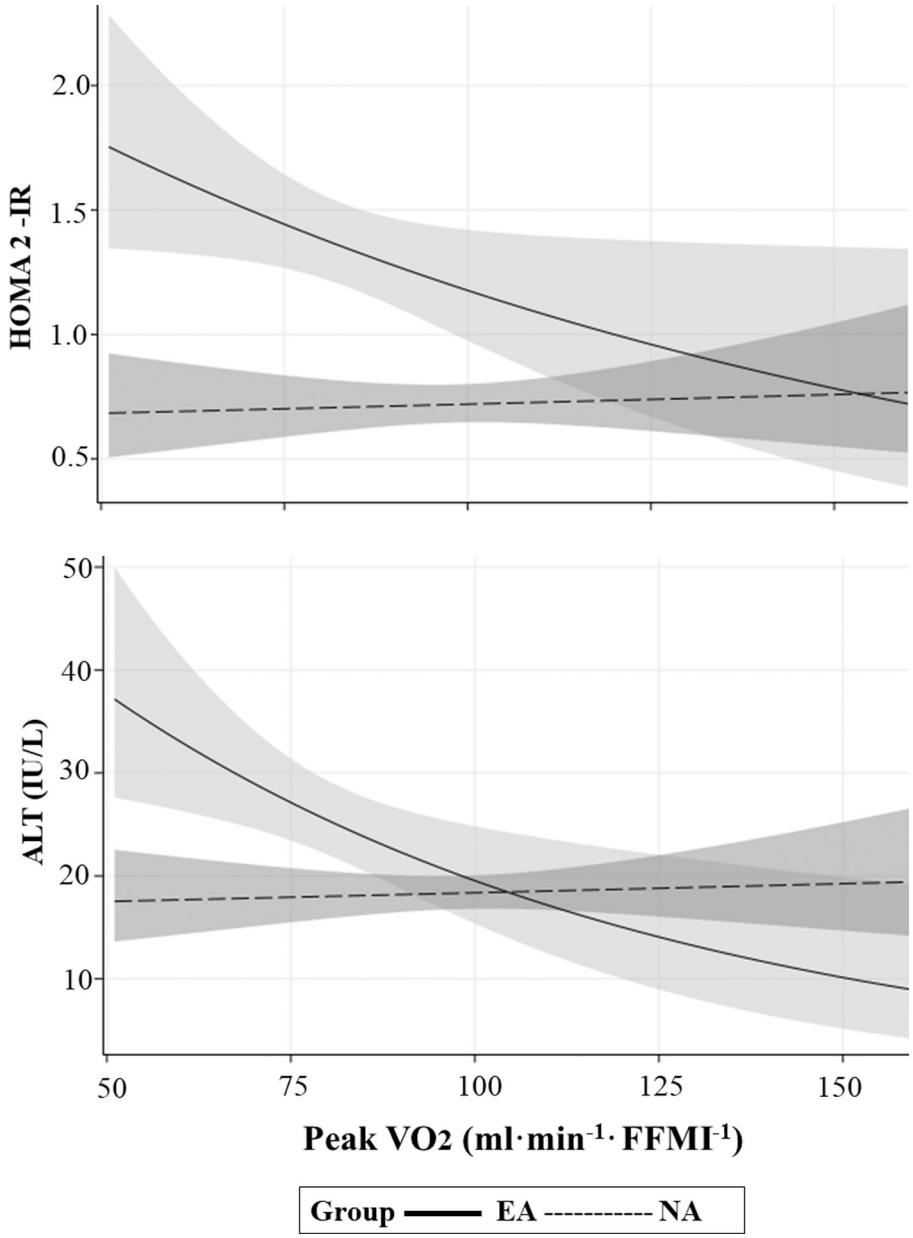

Figure 2.

Regression plot showing the association of peak aerobic capacity (X axis) with HOMA2-IR, and plasma ALT (IU/L) levels plus 95% confidence intervals (Y axis) in 7–10-year-old children with normal or excess adiposity.

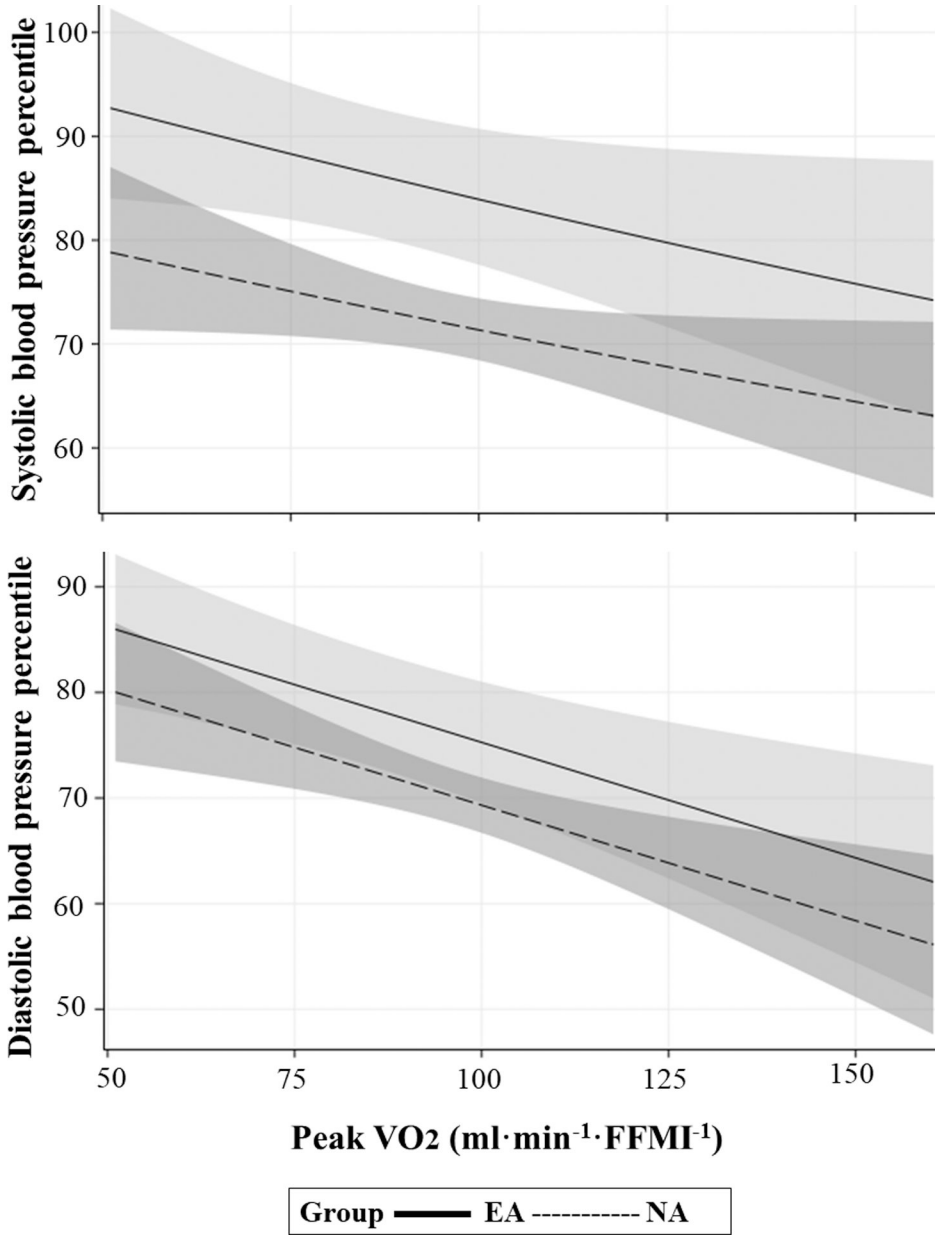

Figure 3.

Regression plot showing the association of peak aerobic capacity (X axis) with systolic, and diastolic blood pressure percentiles plus 95% confidence intervals (Y axis) in 7–10-year-old children with normal or excess adiposity.

Table 1.

Subject characteristics

Variable	All (n=211)	EA (n=39)	NA (n=172)	p-value
Age (years)	9.0 ± 1.2	9.0 ± 1.3	9.0 ± 1.2	0.9722
Sex, n (%)				0.0772
-Girls	113.0 (54)	26.0 (67)	87.0 (51)	
-Boys	98.0 (46)	13.0 (33)	85.0 (49)	
Race, n (%)				0.1686
-White	154 (73)	25.0 (64)	129 (75)	
-Black	57.0 (27)	14.0 (36)	43 (25)	
BMI percentile	63.8 ± 28.7	95.9 ± 3.0	56.5 ± 26.9	<.0001
Peak VO_2 ($ml \cdot min^{-1} \cdot FFMI^{-1}$)	95.6 ± 18.8	86.1 ± 19.3	97.7 ± 18.1	0.0004
FMI z-score	0.29 ± 0.72	1.40 ± 0.25	0.04 ± 0.54	<.0001
FFMI z-score	−0.02 ± 0.88	0.93 ± 0.72	−0.23 ± 0.76	<.0001
Visceral fat area (cm^2)	34.6 ± 14.9	51.8 ± 14.5	30.7 ± 12.0	<.0001
Systolic BP percentile	0.74 ± 0.21	0.86 ± 0.17	0.72 ± 0.21	<.0001
Diastolic BP percentile	0.71 ± 0.18	0.78 ± 0.18	0.70 ± 0.18	0.006
Blood pressure status, n (%)				<.0001
-Normal	142.0 (67.30)	12.0 (30.77)	130.0 (75.58)	
-Elevated	29.0 (13.74)	9.0 (23.08)	20.0 (11.63)	
-HTN	40.0 (18.96)	18.0 (46.15)	22.0 (12.79)	

Data presented as means and SD or counts and percentages. BMI = body mass index; Peak VO_2 = peak oxygen consumption; FMI = fat mass index; FFMI = fat free mass index; AC = activity counts; BP = blood pressure; HTN = hypertension. Clinical measures were collected in the overnight fasted state.

Table 2.

Metabolic profile of 7 to 10-year-old children with excess adiposity (EA) and normal adiposity (NA) participating in the Arkansas Active Kids Study.

Variable	All (n=211)	EA (n=39)	NA (n=172)	p-value
Insulin (pmol/L)	44.7 ± 29.6	72.8 ± 38.7	38.5 ± 23.2	<.0001
Glucose (mmol/L)	4.9 ± 0.5	4.8 ± 0.5	4.9 ± 0.5	0.8233
HOMA2-IR	0.8 ± 0.5	1.3 ± 0.7	0.7 ± 0.4	<.0001
HOMA2-%S	179.0 ± 134.5	107.2 ± 95.5	194.9 ± 137.0	<.0001
HOMA2-%β	86.7 ± 38.4	123.4 ± 50.7	78.6 ± 29.7	<.0001
Cholesterol (mmol/L)	4.3 ± 0.8	4.5 ± 0.8	4.3 ± 0.8	0.1449
HDL cholesterol (mmol/L)	1.7 ± 0.4	1.5 ± 0.4	1.8 ± 0.4	0.0003
LDL cholesterol (mmol/L)	2.8 ± 0.8	3.3 ± 0.8	2.7 ± 0.8	0.0005
Glycerol (mmol/L)	87.5 ± 28.3	90.5 ± 23.9	86.8 ± 29.2	0.1809
CRP (mg/L)	1.5 ± 3.1	3.7 ± 4.9	1.0 ± 2.3	<.0001
Urea (mmol/L)	4.4 ± 1.0	4.4 ± 0.9	4.4 ± 1.0	0.9960
Potassium (mmol/L)	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.3346
Sodium (mmol/L)	146.7 ± 4.4	146.6 ± 4.3	146.8 ± 4.4	0.8019
Chloride (mmol/L)	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.0675
Calcium (mmol/L)	91.7 ± 3.9	92.5 ± 3.4	91.5 ± 4.0	0.2109
Creatinine (mg/dL)	2.6 ± 0.2	2.6 ± 0.1	2.6 ± 0.2	0.7242
Glomerular filtration rate (ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2})	80.7 ± 7.3	80.9 ± 7.3	80.7 ± 7.3	0.8807
AST (IU/L)	34.9 ± 15.7	33.7 ± 26.0	35.2 ± 12.4	0.0010
ALT (IU/L)	19.3 ± 10.8	23.9 ± 18.4	18.3 ± 8.0	0.0280

Data presented as means and SD. HOMA2 = updated homeostatic model assessment; IR = insulin resistance; %S = percent insulin sensibility; %β = percent β cell function; TG = triglycerides; HDL = high density lipoprotein; LDL = low density lipoprotein; CRP = C reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase. Results are from serum or plasma collected in the overnight-fasted state (see Methods)

Table 3.

Logistic regression analysis and odds ratio estimates exploring the relationship of high blood pressure (response variable) with adiposity status (EA vs. NA), peak VO_2 ($ml \cdot min^{-1} \cdot FFMI^{-1}$), and their interaction in 7 to 10-year-old children.

Logistic Regression Analysis				
Parameter	**Estimate**	**SE**	**Wald Chi-Square**	***p*-value**
Group				
Normal Adiposity	Reference			
Excess Adiposity	8.29	3.11	7.10	0.0077
Peak VO_2	−0.01	0.01	0.47	0.4943
Peak VO_2 × Group				
Normal Adiposity	Reference			
Excess Adiposity	−0.07	0.03	4.54	0.0332
Odd Ratio Estimates and Wald Confidence Intervals				
Group	**Estimate**	**95% Confidence Limits**		
Excess Adiposity	0.92	0.87 – 0.99		
Normal Adiposity	0.99	0.97 – 1.01		

Table 4.

Linear regression analysis between peak VO_2, adiposity status (NA vs. EA), peak VO_2 × adiposity status interaction (independent variables) and blood pressure percentiles, HOMA2-IR, LDL cholesterol, HDL cholesterol and eGFR (dependent variables).

Variable	Peak VO_2				*Group (EW vs NA)				Peak VO_2 × *Group Interaction			
	β	95% CI		*p*-value	β	95% CI		*p*-value	β	95% CI		*p*-value
Systolic BP percentile	−0.213	−0.360	−0.066	0.0044	14.615	7.662	21.568	<.0001	−0.082	−0.448	0.283	0.6586
Diastolic BP percentile	−0.248	−0.375	−0.122	0.0001	8.488	2.272	14.704	0.0074	−0.092	−0.413	0.230	0.5770
HOMA2-IR	−0.004	−0.008	0.000	0.0502	0.619	0.437	0.800	<.0001	−0.011	−0.023	0.000	0.0499
LDL cholesterol	0.000	−0.006	0.006	0.9540	0.540	0.256	0.823	0.0002	−0.009	−0.023	0.006	0.2471
HDL cholesterol	0.003	0.000	0.006	0.0577	−0.259	−0.399	−0.120	0.0003	−0.007	−0.014	0.000	0.0631
ALT	−0.056	−0.136	0.025	0.1761	5.546	1.680	9.411	0.0049	−0.238	−0.436	−0.041	0.0181
eGFR	0.117	0.065	0.170	<.0001	0.208	−2.494	2.911	0.8799	−0.105	−0.235	0.026	0.1178

EA= excess adiposity; NA = normal adiposity;

*= NA used as reference group; BP= blood pressure; HOMA2 = updated homeostatic model assessment; IR = insulin resistance; HDL = high density lipoprotein; LDL = low density lipoprotein; ALT = alanine aminotransferase. eGFR = estimated glomerular filtration rate.

Table 5.

Multiple linear regression analyses between peak VO_2 and adiposity status (EW vs. NW) with SBP percentiles, DBP percentiles, HDL cholesterol, LDL cholesterol, and eGFR.

Model		β	95% CI		Pr2	p-value
SBP percentile	Peak VO_2	−0.150	−0.300	−0.002	1.7	0.0465
	EA vs. NA (reference)	12.90	5.790	19.982	5.5	0.0004
DBP percentile	Peak VO_2	−0.235	−0.364	−0.106	5.4	0.0003
	EA vs. NA (reference)	5.957	−0.229	12.143	2.2	0.0591
	Sodium intake	3.318	−0.021	6.657	1.6	0.0515
HDL cholesterol	Peak VO_2	0.001	−0.002	0.004	0.2	0.5044
	EA vs. NA (reference)	−0.236	−0.374	−0.098	5.3	0.0008
	Girls vs. Boys (reference)	−0.126	−0.234	−0.019	2.5	0.0216
LDL cholesterol	Peak VO_2	0.002	−0.004	0.008	0.3	0.4522
	EA vs. NA (reference)	0.563	0.274	0.853	7.1	0.0001
eGFR	Peak VO_2	0.060	−0.003	0.122	5.1	0.0009
	EA vs. NA (reference)	1.148	−1.472	3.768	0.3	0.3905
	Age	0.098	0.040	0.156	2.0	0.0391

Pr2 = squared partial correlation; SBP = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein; EA = excess adiposity group; NA = normal adiposity group.