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

EVA C. DIAZ[1,2,3], JUDITH L. WEBER[2,3], SEAN H. ADAMS[1,3,4,5], CATARINA G. YOUNG[1,2,3], SHASHA BAI[2,3], and ELISABET BØRSHEIM[1,2,3]

[1]Arkansas Children's Nutrition Center, Little Rock, AR; [2]Arkansas Children's Research Institute, Little Rock, AR; [3]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR; [4]Department of Surgery, University of California Davis School of Medicine, Sacramento, CA; and [5]Center for Alimentary and Metabolic Science, University of California Davis School of Medicine, Sacramento, CA

ABSTRACT

DIAZ, E. C., J. L. WEBER, S. H. ADAMS, C. G. YOUNG, S. BAI, and E. BØRSHEIM. Cardiorespiratory Fitness Associates with Blood Pressure and Metabolic Health of Children—The Arkansas Active Kids Study. *Med. Sci. Sports Exerc.*, Vol. 53, No. 11, pp. 2225–2232, 2021. **Introduction:** High blood pressure (HBP) in children causes preclinical 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 versus pediatric HPB treatment is the emphasis in adults on exercise regimens that target increments in cardiorespiratory fitness (CRF; peak oxygen consumption [$\dot{V}O_{2peak}$]). 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 FFM 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, alanine aminotransferase, and estimated glomerular filtration rate) against $\dot{V}O_{2peak}$. **Results:** CRF interacted with adiposity status in predicting the probability of HBP. Each additional milliliter per minute per FFM index in $\dot{V}O_{2peak}$ decreased the odds of HBP by 8% in the EA group only (odds ratio = 0.92, 95% confidence interval = 0.87–0.99). Systolic and diastolic blood pressure percentiles decreased, and estimated glomerular filtration rate increased with increasing CRF in both adiposity-level groups. HOMA2-IR and alanine aminotransferase 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. **Key Words:** OBESITY, ADIPOSITY, $\dot{V}O_{2peak}$, HYPERTENSION

Pediatric primary high blood pressure (HBP), which encompasses elevated blood pressure (previously known as prehypertension: blood pressure values ≥90th and <95th percentiles), stage 1 hypertension (HTN), and stage 2 HTN, is a growing public health concern (1). Data from the National Health and Nutrition Examination Survey 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, whereas 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 because of these reclassifications are more likely to present with dyslipidemia, prediabetes, and overweight/obesity (OW/OB) when compared with 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

Address for correspondence: Eva C. Diaz, M.D., M.M.Sc., Arkansas Children's Nutrition Center, 15 Children's Way, Slot 317 Little Rock, AR 72202; E-mail: ecdiazfuentes@uams.edu.
Submitted for publication December 2020.
Accepted for publication April 2021.

0195-9131/21/5311-2225/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000002701

(6). In adults, HBP is the second leading cause of end-stage renal disease. Although 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 [$\dot{V}O_{2peak}$]) and physical activity (PA) are essential goals (quality of evidence, level A) (9–11). By contrast, the recommendation of PA as a nonpharmacological 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 versus 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 to provide new insight into the field, we conducted direct measurements of CRF ($\dot{V}O_{2peak}$) and adiposity (dual-energy x-ray absorptiometry) in 7- to 10-yr-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 [EA]). 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 estimated glomerular filtration rate (eGFR) as a measure of kidney function was assessed.

METHODS

Subjects

Two hundred and eleven children (7–10 yr old) enrolled in the Arkansas Active Kids (AAK) study were included for analyses (Table 1) (15). Exclusion criteria were as follows: 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 1-d study visit at the Arkansas Children's Nutrition Center 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.

TABLE 1. Subject characteristics.

Variable	All (N = 211)	EA (n = 39)	NA (n = 172)	P
Age (yr)	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	<0.0001
$\dot{V}O_{2peak}$ (mL·min^{-1}·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	<0.0001
FFMI z-score	–0.02 ± 0.88	0.93 ± 0.72	–0.23 ± 0.76	<0.0001
Visceral fat area (cm^2)	34.6 ± 14.9	51.8 ± 14.5	30.7 ± 12.0	<0.0001
SBP percentile	0.74 ± 0.21	0.86 ± 0.17	0.72 ± 0.21	<0.0001
DBP percentile	0.71 ± 0.18	0.78 ± 0.18	0.70 ± 0.18	0.006
Blood pressure status, n (%)				<0.0001
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 are presented as mean ± SD or counts and percentages. Clinical measures were collected in the overnight-fasted state.
BMI, body mass index.

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 were averaged. Body composition and visceral fat area (cm^2) were assessed using dual-energy x-ray absorptiometry (Horizon-A with Advanced Body Composition™; Hologic, Bedford, MA). Fat mass index [FMI = fat mass (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 min. Blood pressure was measured in duplicate at 1-min interval on the right arm using an electronic vital sign monitor (CARESCPE™ VC150, Milwaukee, WI). 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 mm Hg to <95th percentile, whichever was lower], stage 1 HTN [SBP/DBP percentile ≥95th to <95th plus 12 mm Hg or 130/80–139/89 mm Hg, whichever was lower], and stage 2 HTN [SBP/DBP percentile ≥95th plus 12 mm Hg or ≥140/90 mm Hg, 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 SBP and DBP were lower in the second measurement. If clinical staging improved (i.e., HTN to elevated or elevated to normal) from the first to the 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 after an overnight fast. Serum levels of sodium, chloride, calcium, creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase, glucose, total cholesterol, HDL, LDL, glycerol, and C-reactive protein were measured using an RX Daytona clinical analyzer and following manufacturer's instructions (Randox Laboratories-US Limited, Kearneysville, WV). Insulin levels were measured using enzyme-linked immunosorbent assay (Meso Scale Discovery, Rockville, MD). 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). eGFR ($mL \cdot min^{-1}$ per 1.73 m^2) was estimated using the following updated Schwartz equation (20,21):

$$\text{eGFR} = \frac{[0.413 \times \text{height (cm)}]}{\text{serum creatinine } \left(\text{mg} \cdot \text{dL}^{-1}\right)}$$

CRF. $\dot{V}O_{2peak}$ 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). Sit height was adjusted to a corresponding knee angle of 15°, which was measured using a goniometer with the pedal at its lowest position. Crank length was set at 13 cm for 7-yr-old children and 15 cm for 8- to 10-yr-old children (22). The workload increased every minute in increments of 10 W for children <120 cm tall and 15 W for children ≥120 cm tall. During the test, children were instructed to keep the pedal frequency between 50 and 60 rpm. Children were included for analyses if they met the following criteria: 1) heart rate ≥80% of age predicted maximum, 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, $\dot{V}O_{2peak}$ was normalized to FFMI ($mL \cdot min^{-1} \cdot FFMI^{-1}$; FFMI is in $kg \cdot m^{-2}$) 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 $\dot{V}O_{2peak}$, 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 is used as denominator. This has raised concerns and has been a topic of discussion for many years because of 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 $\dot{V}O_{2peak}$ and FFMI [$\beta = 87.1$, $P < 0.0001$], and the *y*-intercept not different from zero [intercept = 100.3, $P = 0.4494$]), which was not the case when FFM or body weight was 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 yr. 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 the AAK study 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 the Fisher exact tests. The probability of having HBP (i.e., elevated blood pressure, stage 1 HTN, and stage 2 HTN) using $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ 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. The distribution of blood pressure status significantly differed between EA and NA groups. That is, 69% of children in the EA group had HBP versus 24% of children in the NA group (Table 1).

Metabolic profile of children with EA and NA. Fasting insulin, HOMA2-IR, and HOMA2-%β were 1.6 to 2.0 times higher in children with EA when compared with children with NA. Similarly, fasting LDL cholesterol, C-reactive protein, and ALT were higher in children with EA versus NA. On the other hand, HDL cholesterol was lower in children with EA when compared with children with NA. eGFR did not differ between NA and EA groups (Table 2).

Logistic regression analysis and odds ratio estimates. The difference in the (log) odds of HBP was 8.3 U higher in children with EA compared with children with NA ($\beta = 8.3$, $P = 0.0077$) (Table 3). There was interaction between $\dot{V}O_{2peak}$ and adiposity status (EA vs NA) in predicting the probability of HBP (Wald chi-square, 4.54; $P = 0.0332$).

TABLE 2. Metabolic profile of 7- to 10-yr-old children with EA and NA participating in the AAK study.

Variable	All (*N* = 211)	EA (*n* = 39)	NA (*n* = 172)	*P*
Insulin (pmol·L^{-1})	44.7 ± 29.6	72.8 ± 38.7	38.5 ± 23.2	<0.0001
Glucose (mmol·L^{-1})	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	<0.0001
HOMA2-%S	179.0 ± 134.5	107.2 ± 95.5	194.9 ± 137.0	<0.0001
HOMA2-%β	86.7 ± 38.4	123.4 ± 50.7	78.6 ± 29.7	<0.0001
Cholesterol (mmol·L^{-1})	4.3 ± 0.8	4.5 ± 0.8	4.3 ± 0.8	0.1449
HDL cholesterol (mmol·L^{-1})	1.7 ± 0.4	1.5 ± 0.4	1.8 ± 0.4	0.0003
LDL cholesterol (mmol·L^{-1})	2.8 ± 0.8	3.3 ± 0.8	2.7 ± 0.8	0.0005
Glycerol (mmol·L^{-1})	87.5 ± 28.3	90.5 ± 23.9	86.8 ± 29.2	0.1809
CRP (mg·L^{-1})	1.5 ± 3.1	3.7 ± 4.9	1.0 ± 2.3	<0.0001
Urea (mmol·L^{-1})	4.4 ± 1.0	4.4 ± 0.9	4.4 ± 1.0	0.9960
Potassium (mmol·L^{-1})	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.3346
Sodium (mmol·L^{-1})	146.7 ± 4.4	146.6 ± 4.3	146.8 ± 4.4	0.8019
Creatinine (mg·dL^{-1})	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.0675
Chloride (mmol·L^{-1})	91.7 ± 3.9	92.5 ± 3.4	91.5 ± 4.0	0.2109
Calcium (mmol·L^{-1})	2.6 ± 0.2	2.6 ± 0.1	2.6 ± 0.2	0.7242
Glomerular filtration rate (mL·min^{-1} per 1.73 m^2)	80.7 ± 7.3	80.9 ± 7.3	80.7 ± 7.3	0.8807
AST (IU·L^{-1})	34.9 ± 15.7	33.7 ± 26.0	35.2 ± 12.4	0.0010
ALT (IU·L^{-1})	19.3 ± 10.8	23.9 ± 18.4	18.3 ± 8.0	0.0280

Data are presented as mean ± SD. Results are from serum or plasma collected in the overnight-fasted state (see Methods).
HOMA2, updated homeostatic model assessment; IR, insulin resistance; %S, percent insulin sensibility; %β, percent β-cell function; TG, triglycerides; CRP, C-reactive protein; AST, aspartate aminotransferase.

Increasing $\dot{V}O_{2peak}$ decreased the odds of HBP but only in the EA group (Fig. 1). Specifically, each additional mL·min^{-1}·FFMI^{-1} in $\dot{V}O_{2peak}$ decreased the odds of HBP by 8% in children with EA (odds ratio [OR] = 0.92, 95% confidence interval [CI] = 0.87–0.99). On the other hand, the effect of $\dot{V}O_{2peak}$ on HBP was not statistically significant in children with NA (OR = 0.99, 95% CI = 0.97–1.01) (Table 3).

Linear regression analyses between $\dot{V}O_{2peak}$, adiposity status (EW vs NW), and their interaction with markers of cardiometabolic health and kidney function. SBP and DBP percentiles negatively associated with $\dot{V}O_{2peak}$. For every unit increase in $\dot{V}O_{2peak}$, 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 < 0.0001) and 8.5 (P = 0.0074) percentage points higher in the EA group compared with the NA group. There was no interaction between $\dot{V}O_{2peak}$ and adiposity status in predicting blood pressure percentiles. HOMA2-IR was in average 0.62 U higher in children with EA

TABLE 3. Logistic regression analysis and OR estimates exploring the relationship of HBP (response variable) with adiposity status (EA vs NA), $\dot{V}O_{2peak}$ (mL·min^{-1}·FFMI^{-1}), and their interaction in 7- to 10-yr-old children.

Logistic Regression Analysis

Parameter	Estimate	SE	Wald Chi-Square	*P*
Group				
Normal adiposity	Reference			
Excess adiposity	8.29	3.11	7.10	0.0077
$\dot{V}O_{2peak}$	–0.01	0.01	0.47	0.4943
$\dot{V}_{2peak}$–group				
Normal adiposity	Reference			
Excess adiposity	–0.07	0.03	4.54	0.0332

Odd Ratio Estimates and Wald CI

Group	Estimate	95% CI
Excess adiposity	0.92	0.87–0.99
Normal adiposity	0.99	0.97–1.01

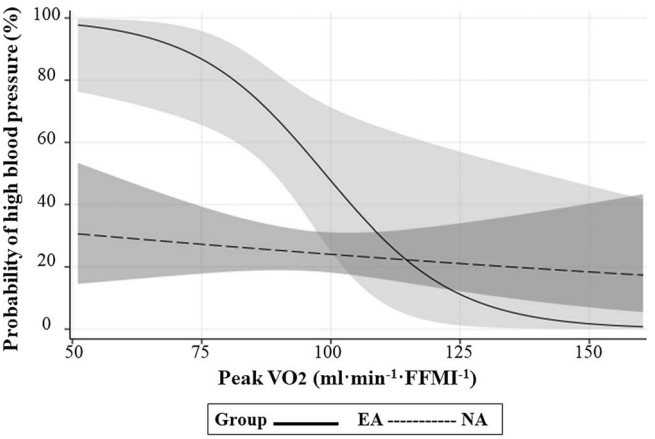

FIGURE 1—Logistic plot showing the association between peak aerobic capacity (*x*-axis) and probability of HBP plus 95% CI (*y*-axis) in 7- to 10-yr-old children with NA or EA. HBP refers to elevated blood pressure, stage 1 HTN, and stage 2 HTN.

compared with children with NA (P < 0.0001) (Table 4). There was interaction between $\dot{V}O_{2peak}$ and adiposity status in predicting HOMA2-IR (Fig. 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^{-1} higher in children with EA compared with children with NA (P = 0.0002). LDL cholesterol levels were not associated with $\dot{V}O_{2peak}$ nor was interaction found between adiposity status and CRF in association with LDL levels. There was a marginal association between HDL cholesterol and $\dot{V}O_{2peak}$ (P = 0.0577), which was primarily mediated by sex (data not shown), with girls exhibiting lower values of HDL cholesterol compared with boys. ALT was in average 5.5 IU·L^{-1} higher in children with EA compared with children with NA (P = 0.0049). There was interaction between $\dot{V}O_{2peak}$ and adiposity status in association with ALT levels. ALT decreased by 0.24 IU·L^{-1} per unit increased in $\dot{V}O_{2peak}$ but only in the EA group (Fig. 2).

eGFR positively associated with CRF. For every unit increase in $\dot{V}O_{2peak}$, eGFR increased by 0.12 mL·min^{-1} per 1.73 m^2. eGFR did not associate with adiposity status, nor was interaction found between $\dot{V}O_{2peak}$ and adiposity group (Table 4).

Multiple linear regression analyses between $\dot{V}O_{2peak}$ and adiposity status (EW vs NW) with SBP percentiles, DBP percentiles, LDL cholesterol, HDL cholesterol, and eGFR. SBP (P = 0.0465) and DBP (P = 0.0003) percentiles decreased with increasing $\dot{V}O_{2peak}$ independently of adiposity status (Table 5, Fig. 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 $\dot{V}O_{2peak}$ and explained 5.5% and 1.7% of the observed variance (P = 0.0004), respectively. On the other hand, $\dot{V}O_{2peak}$ was the strongest predictive variable of DBP percentile explaining 5.4% of the observed variance (P = 0.0003). Fasting levels of HDL and LDL cholesterols did not associate with $\dot{V}O_{2peak}$ 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

TABLE 4. Linear regression analysis between $\dot{V}O_{2peak}$, adiposity status (NA vs EA), $\dot{V}O_{2peak}$–adiposity status interaction (independent variables), and blood pressure percentiles, HOMA2-IR, LDL cholesterol, HDL cholesterol, and eGFR (dependent variables).

	$\dot{V}O_{2peak}$				Group* (EW vs NA)				$\dot{V}O_{2peak}$–Group* Interaction			
Variable	**β**	**95% CI**		**P**	**β**	**95% CI**		**P**	**β**	**95% CI**		**P**
SBP percentile	−0.213	−0.360	−0.066	0.0044	14.615	7.662	21.568	<0.0001	−0.082	−0.448	0.283	0.6586
DBP 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	<0.0001	−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	<0.0001	0.208	−2.494	2.911	0.8799	−0.105	−0.235	0.026	0.1178

*NA used as reference group.
HOMA2 = updated homeostatic model assessment; IR = insulin resistance.

a significant predictor of HDL cholesterol with girls having lower fasting HDL levels compared with boys.

DISCUSSION

The present study evaluated the relationship of CRF ($\dot{V}O_{2peak}$) with blood pressure percentiles and blood pressure status in children with NA and EA. Blood pressure was assessed using the 2017 clinical guidelines from the AAP 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 $\dot{V}O_{2peak}$ 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 $\dot{V}O_{2peak}$ in the EA group compared with 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.

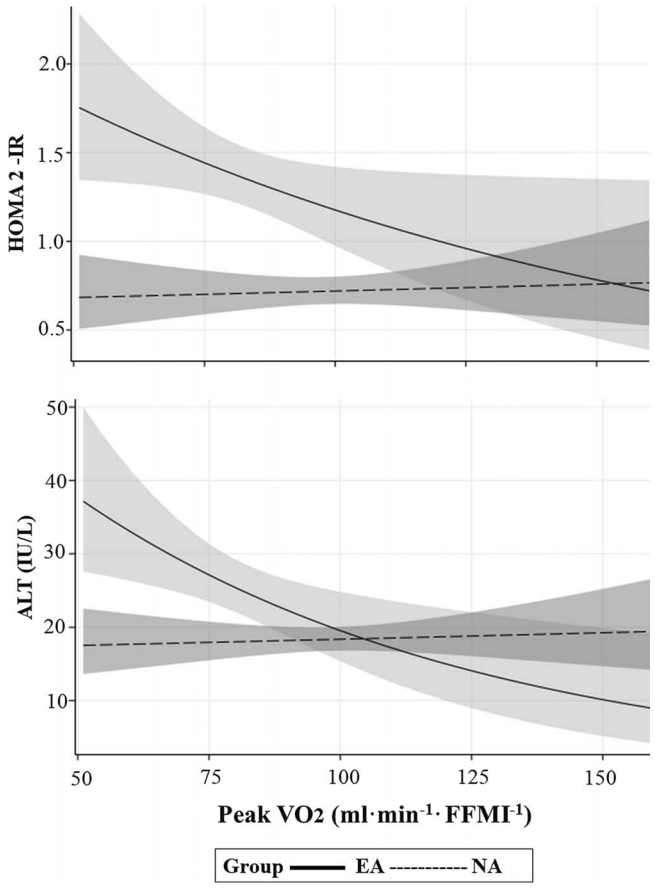

FIGURE 2—Regression plot showing the association of peak aerobic capacity (*x*-axis) with HOMA2-IR and plasma ALT ($IU \cdot L^{-1}$) levels plus 95% CI (*y*-axis) in 7- to 10-yr-old children with NA or EA.

We saw a slightly higher prevalence of elevated blood pressure (14% vs 11%) and HTN (19% vs 15%) in our study compared with data reported after an initial screening in 10- to 12-yr-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

TABLE 5. Multiple linear regression analyses between $\dot{V}O_{2peak}$ and adiposity status (EW vs NW) with SBP percentiles, DBP percentiles, HDL cholesterol, LDL cholesterol, and eGFR.

Model		**β**	**95% CI**		**Pr2**	**P**
SBP percentile	$\dot{V}O_{2peak}$	−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	$\dot{V}O_{2peak}$	−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	$\dot{V}O_{2peak}$	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	$\dot{V}O_{2peak}$	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	$\dot{V}O_{2peak}$	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; EA, excess adiposity group; NA, normal adiposity group.

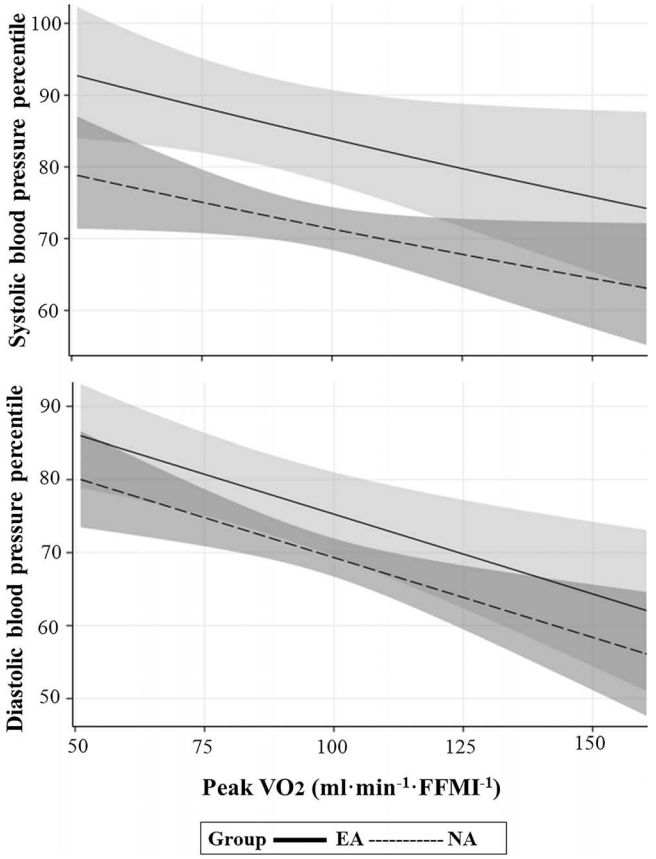

FIGURE 3—Regression plot showing the association of peak aerobic capacity (*x*-axis) with SBP and DBP percentiles plus 95% CI (*y*-axis) in 7- to 10-yr-old children with NA or EA.

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). Although the role of CRF in pediatric health is gaining recognition (28), the quantity and the quality of the current evidence are insufficient to inform pediatric clinical practice guidelines. Elevated blood pressure (previously known as prehypertension) and HTN are classic CVD risk factors that track from childhood to adulthood (29,30). Recently, in a study involving 3800 Canadian children 6 to 17 yr of age (31), a negative association was reported between indirect measurements of CRF (i.e., submaximal step test) and SBP and DBP 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 HTN driven by sedentary behavior and suboptimal PA versus body weight *per se*? Epidemiological data derived from the National Health and Nutrition Examination Survey between 1988 and 2008 show a parallel increase in the prevalence of HBP and pediatric obesity (2,33). By 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 yr old (n = 1092) 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 mm Hg) 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 $\dot{V}O_{2peak}$ (β = −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, β = −0.006, P = 0.0516).

The same authors (35) also reported no association between CRF and SBP and DBP. It is worth noting, however, that SBP and DBP 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 because 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 SBP and DBP percentiles and $\dot{V}O_{2peak}$ in children, regardless of adiposity status. In this study, the effect of $\dot{V}O_{2peak}$ on DBP percentile was greater compared with that on SBP percentile. Greater improvement in DBP versus SBP in relation to exercise training and $\dot{V}O_{2peak}$ 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 turn regulates 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·min^{-1} per 1.73 m^2) and $\dot{V}O_{2peak}$ (+2.39 mL·kg^{-1}·min^{-1}) in patients with chronic kidney disease participating in aerobic endurance training. Although 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 turn 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 chronic kidney disease.

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. Although 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-yr-old boys with obesity, a 3-month exercise intervention resulted in ~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, $\dot{V}O_{2peak}$ 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.

This work was funded by USDA-ARS Projects 3092-51000-056- 04A and 6026-51000-012-06S. E. C. D., E. B., C. G. Y., and J. L. W. are partially supported by the Center for Childhood Obesity Prevention (NIH-NIGMS award 5P20GM109096). E. C. D. is partially supported by the Arkansas Center for Advancing Pediatric Therapeutics (NIH award no. 8UG1OD024945). E. B. is partially supported by the UAMS-TRI (NCATS UL1-TR003107).

The authors thank the children and their parents for participating in this study. They thank the recruitment team in the Clinical Research Core at the Arkansas Children's Nutrition Center, as well as Matthew Cotter, Oleksandra Pavliv, and Timothy Edwards for their assistance in obtaining study measurements.

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.

Dr. Adams is an adjunct faculty in the UAMS Department of Pediatrics and former investigator at the Arkansas Children's Nutrition Center.

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.

REFERENCES

1. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.
2. Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988–2008. *Hypertension*. 2013;62(2):247–54.
3. Sharma AK, Metzger DL, Rodd CJ. Prevalence and severity of high blood pressure among children based on the 2017 American Academy of Pediatrics Guidelines. *JAMA Pediatr*. 2018;172(6):557–65.
4. Raitakari OT, Juonala M, Kahonen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003; 290(17):2277–83.
5. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. *Pediatrics*. 2005;115(1):22–7.
6. Obrycki Ł, Feber J, Derezinski T, Lewandowska W, Kułaga Z, Litwin M. Hemodynamic patterns and target organ damage in adolescents with ambulatory prehypertension. *Hypertension*. 2019;75(3):826–34.
7. Mikola H, Pahkala K, Niinikoski H, et al. Cardiometabolic determinants of carotid and aortic distensibility from childhood to early adulthood. *Hypertension*. 2017;70(2):452–60.
8. Ghatage T, Goyal SG, Dhar A, Bhat A. Novel therapeutics for the treatment of hypertension and its associated complications: peptide- and nonpeptide-based strategies. *Hypertens Res*. 2021;1–16.
9. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. *Hypertension*. 2013;61(6):1360–83.
10. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653–99.
11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13–115.
12. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(5 Suppl):S213–56.

13. Rebholz CM, Gu D, Chen J, et al. Physical activity reduces salt sensitivity of blood pressure: the Genetic Epidemiology Network of Salt Sensitivity Study. *Am J Epidemiol*. 2012;176(7 Suppl):S106–13.
14. Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine Position Stand: exercise and hypertension. *Med Sci Sports Exerc*. 2004;36(3):533–53.
15. Bai S, Goudie A, Børsheim E, Weber JL. The Arkansas Active Kids Study: identifying contributing factors to metabolic health and obesity status in prepubertal school-age children. *Nutr Health*. 2021; 27(2):273–81.
16. Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *Am J Clin Nutr*. 2013;98(1):49–56.
17. Canadian Pediatric Endocrine Group. R Shiny Apps from CPEG-GCEP [9-11-2019]. Available from: https://www.cpeg-gcep.net/.
18. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111(5):697–716.
19. The Oxford Centre for Diabetes EaM. HOMA calculator 2013. Available from: https://www.dtu.ox.ac.uk/homacalculator/download.php.
20. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629–37.
21. Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. *Pediatr Nephrol*. 2010;25(11):2321–6.
22. Klimt F, Voigt GB. Investigations on the standardization of ergometry in children. *Acta Paediatr Scand suppl*. 1971;217:35–6.
23. Forbes GB. Relation of lean body mass to height in children and adolescents. *Pediatr Res*. 1972;6(1):32–7.
24. Toth MJ, Goran MI, Ades PA, Howard DB, Poehlman ET. Examination of data normalization procedures for expressing peak $\dot{V}O_2$ data. *J Appl Physiol*. 1993;75(5):2288–92.
25. NutritionQuest. Food Frequency Questionnaires and Screeners for Children and Adolescents [12-17-2019]. Available from: https://nutritionquest.com/assessment/list-of-questionnaires-and-screeners/.
26. Bell CS, Samuel JP, Samuels JA. Prevalence of hypertension in children. *Hypertension*. 2019;73(1):148–52.
27. Lie H, Mundal R, Erikssen J. Coronary risk factors and incidence of coronary death in relation to physical fitness. Seven-year follow-up study of middle-aged and elderly men. *Eur Heart J*. 1985;6(2):147–57.
28. Lang JJ, Wolfe Phillips E, Hoffmann MD, Prince SA. Establishing modified Canadian Aerobic Fitness Test (mCAFT) cut-points to detect clustered cardiometabolic risk among Canadian children and youth aged 9 to 17 years. *Appl Physiol Nutr Metab*. 2020;45(3):311–7.
29. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. 2008;117(25):3171–80.
30. Theodore RF, Broadbent J, Nagin D, et al. Childhood to early-midlife systolic blood pressure trajectories: early-life predictors, effect modifiers, and adult cardiovascular outcomes. *Hypertension*. 2015;66(6): 1108–15.
31. Lang JJ, Larouche R, Tremblay MS. The association between physical fitness and health in a nationally representative sample of Canadian children and youth aged 6 to 17 years. *Health Promot Chronic Dis Prev Can*. 2019;39(3):104–11.
32. Shi Y, de Groh M, Morrison H. Increasing blood pressure and its associated factors in Canadian children and adolescents from the Canadian Health Measures Survey. *BMC Public Health*. 2012;12:388.
33. Ogden CL, Carroll MD, Lawman HG, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988–1994 through 2013–2014. *JAMA*. 2016;315(21):2292–9.
34. Tomkinson GR, Léger LA, Olds TS, Cazorla G. Secular trends in the performance of children and adolescents (1980–2000): an analysis of 55 studies of the 20m shuttle run test in 11 countries. *Sports Med*. 2003;33(4):285–300.
35. Ekelund U, Anderssen SA, Froberg K, et al. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia*. 2007;50(9):1832–40.
36. de Simone G, Pasanisi F. Systolic, diastolic and pulse pressure: pathophysiology. *Ital Heart J Suppl*. 2001;2(4):359–62.
37. Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W, et al. The effects of aerobic exercise on eGFR, blood pressure and $\dot{V}O_{2peak}$ in patients with chronic kidney disease stages 3–4: a systematic review and meta-analysis. *PLoS One*. 2018;13(9):e0203662.
38. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension*. 2005;46(4):667–75.
39. Kaufman DP, Basit H, Knohl SJ. Physiology, Glomerular Filtration Rate [Internet]. 2020 [cited 3-30-2021]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500032/.
40. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr*. 2017;64(2):319–34.
41. Khan RS, Bril F, Cusi K, Newsome PN. Modulation of insulin resistance in nonalcoholic fatty liver disease. *Hepatology*. 2019;70(2):711–24.
42. Lee S, Bacha F, Hannon T, Kuk JL, Boesch C, Arslanian S. Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. *Diabetes*. 2012;61(11): 2787–95.