The cardiovascular exercise response in children with overweight or obesity children measured by cardiovascular magnetic resonance imaging

Bongers-Karmaoui, M.N.; Hirsch, A.; Budde, R.P.J.; Roest, A.A.W.; Jaddoe, V.W.V.; Gaillard, R.

International Journal of Obesity www.nature.com/ijo

ARTICLE

Epidemiology and Population Health

The cardiovascular exercise response in children with overweight or obesity children measured by cardiovascular magnetic resonance imaging

Meddy N. Bongers-Karmaoui[1,2], Alexander Hirsch[3,4], Ricardo P. J. Budde[4], Arno A. W. Roest[5], Vincent W. V. Jaddoe[1,2] and Romy Gaillard[1,2]✉

BACKGROUND: Overweight and obesity are among the main causes of cardiovascular diseases. Exercise testing can aid in the early detection of subtle cardiac dysfunction not present in rest. We hypothesized that the cardiovascular response to exercise is impaired among children with overweight or obesity, characterized by the inability of the cardiovascular system to adapt to exercise by increasing cardiac volumes and blood pressure. We performed a cardiovascular stress test to investigate whether the cardiovascular exercise response is altered in children with overweight and obesity, as compared to children with a normal weight.
SUBJECTS: A subgroup of the Generation R population-based prospective cohort study, consisting of 41 children with overweight or obesity and 166 children with a normal weight with a mean age of 16 years, performed an isometric exercise.
METHODS: Continuous heart rate and blood pressure were measured during rest, exercise and recovery. Cardiovascular magnetic resonance (CMR) measurements were performed during rest and exercise.
RESULTS: Higher BMI was associated with a higher resting systolic and diastolic blood pressure (difference: 0.24 SDS (95% CI 0.10, 0.37) and 0.20 SDS (95% CI 0.06, 0.33)) and lower systolic and diastolic blood pressure increases from rest to peak exercise (−0.11 SDS (95% CI −0.20, −0.03) and −0.07 SDS (95% CI −0.07, −0.01)). BMI was also associated with a slower decrease in systolic and diastolic blood pressure during recovery (p values < 0.05). Higher childhood BMI was associated with lower BSA corrected left ventricular mass, end-diastolic volume and stroke volume (p values < 0.05). There were no associations of childhood BMI with the cardiac response to exercise measured by heart rate and CMR measurements.
CONCLUSION: Childhood BMI is, across the full range, associated with a blunted blood pressure response to static exercise but there were no differences in cardiac response to exercise. Our findings suggest that adiposity may especially affect the vascular exercise reaction without affecting cardiac response.

International Journal of Obesity; https://doi.org/10.1038/s41366-024-01589-1

INTRODUCTION

The overweight and obesity prevalence has increased substantially in children and adolescents worldwide and is a major contributor to the incidence of cardiovascular diseases later in life [1–4]. Already from childhood onwards, adiposity seems to lead to subclinical cardiovascular adaptations, which predispose to an increased risk of diseases later in life [5–8]. Previously, we have shown that a higher childhood body mass index (BMI) was associated with a higher blood pressure, right ventricular end-diastolic volume (RVEDV), left ventricular end-diastolic volume (LVEDV) and left ventricular mass (LVM) in a resting state [9, 10].

Exercise testing of the cardiovascular system may be used as an additional tool in the early detection of cardiovascular dysfunction, as it can reveal subtle pathology that is not present at rest [11–13]. Ideally, multiple cardiovascular measurements are obtained during rest, exercise and recovery to obtain an adequate evaluation of the response of the cardiovascular system to exercise. These measurements include heartrate and blood pressure response and changes in ventricular volumes, stroke volume, ejection fraction and cardiac output. Previous studies have mainly focused on heart rate and blood pressure measurements to determine an abnormal cardiovascular response to physical exercise in small clinical studies in children with obesity [14–16]. A study in 20

[1]The Generation R Study Group, Erasmus University Medical Center, Rotterdam, the Netherlands. [2]Department of Pediatrics, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands. [3]Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands. [4]Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands. [5]Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands.
✉email: r.gaillard@erasmusmc.nl

Received: 1 September 2023 Revised: 14 June 2024 Accepted: 10 July 2024
Published online: 06 August 2024

children with obesity and 20 children with a normal weight aged 12–16 years old, found that children with obesity had a higher resting diastolic blood pressure, but a lower increase after an isometric handgrip exercise [17]. However, these results are not consistent, and several studies reported no differences in blood pressure or heart rate response in children with overweight or obesity as compared to children with a normal weight [18–21]. Cardiac imaging during exercise would allow for more detailed structural and functional cardiac measurements [22, 23]. Thus far, no population-based paediatric cohort studies with detailed cardiovascular stress response measurements using CMR are available. We hypothesized that detailed measurements of the cardiovascular system during exercise in children among different BMI levels will reveal an affected cardiovascular exercise response in children with overweight or obesity, characterized by the inability of the cardiovascular system to adapt to exercise by increasing cardiac volumes and blood pressure. These effects may not be limited to childhood overweight and obesity, but rather present across the full range of childhood BMI.

Therefore, in a subgroup of 207 children participating in a population-based prospective cohort study, we performed a cardiovascular stress test induced by isometric handgrip exercise combined with detailed Cardiac Magnetic Resonance (CMR) measurements of the cardiovascular system to study whether the cardiovascular exercise response differs by childhood concurrent BMI. We examined the associations of childhood BMI across the full range and in clinical subgroups.

METHODS

Study design and subjects

This study was nested in the Generation R Study, a population-based prospective cohort study from early pregnancy onwards in Rotterdam, the Netherlands [24]. Approval for the study was obtained from the Medical Ethical Committee of Erasmus University Medical Center Rotterdam, The Netherlands. The study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants. In total, 8879 pregnant women were enrolled between 2001 and 2005. Of these mothers, a selected subsample of 1184 Dutch mothers, gave birth to a singleton live born child and had children with detailed assessments of fetal growth from first trimester onwards, postnatal growth and cardiovascular development until late childhood. We invited a random subgroup of 299 children from this sample to participate in the cardiovascular exercise test, of which 211 children visited our research center. The main reasons for non-participation were claustrophobia, a full school schedule or concerns regarding research center visits during the COVID-19 pandemic. After exclusion of a child with a MRI contraindication ($n = 1$) and children with missing blood pressure data during rest, peak exercise or recovery ($n = 3$), 207 children were available for analysis (Supplementary Fig. 1). Mean age (95% range) of the children was 16.2 (15.0–17.4) years. Based on a priori hypotheses, we oversampled children who were overweight or had obesity at previous research visits for this study [25].

BMI and weight status

In our Generation R research center (Erasmus MC, Rotterdam, The Netherlands), height and weight were measured without shoes and heavy clothing. BMI (kg/m^2) and body surface area (BSA) were calculated using the Haycock formula [26, 27]. We obtained sex- and age-specific BMI standard deviation scores (SDSs) based on Dutch reference growth curves [28]. Childhood overweight and obesity status were defined according to age- and sex-specific cut-off points according to the Cole criteria [25]. Due to the small numbers, children with obesity ($n = 10$) and children with overweight ($n = 31$) were merged into one group of children with overweight or obesity ($n = 41$).

Continuous heart rate and blood pressure measurements during the cardiovascular exercise test

To provoke a cardiovascular stress reaction, we used a sustained isometric handgrip exercise. The exercise protocol has been described in detail earlier [29]. Briefly, the maximal voluntary contraction (MVC) of the dominant hand was measured using a handgrip dynamometer. During CMR examination, each volunteer was asked to sustain a grasp on the handgrip at 30–40% MVC for 7 min. During the entire examination, heart rate and blood pressure were continuously measured by the CareTaker finger cuff system (Empirical Technologies Corporation, Charlottesville, Virginia). Outcomes of interest were mean heart rate, systolic, diastolic and mean arterial blood pressure at prespecified time-intervals. We calculated the mean of 5 min rest before the start of the cardiovascular exercise test and mean of each minute of the 7-min exercise. The 7th min of the exercise was defined as peak exercise response. To measure the cardiovascular recovery reaction, we calculated the mean of each 30 s in the first 2 min after exercise cessation and the mean of the 5th min after exercise cessation [29].

CMR measurements during the cardiovascular exercise test

Cardiac measures were obtained by CMR, as described previously [29]. Briefly, cardiac measurements were obtained using a wide-bore GE Discovery MR 750 3 T scanner (GE Healthcare, Milwaukee, MI, USA) in resting state and during exercise. The protocol included balanced steady-state free precession (SSFP) cine imaging and 2D phase contrast images. During rest, first we acquired localizer images. Followed by standard retrospective ECG-gated end expiration breath-held SSFP scans with coverage from base to apex of the ventricles with a slice thickness of 8 mm and interslice gap of 2 mm. All breath-holds lasted less than 15 s per breath hold. The short axis stack SSFP cine images was repeated during exercise. Furthermore, free-breathing high temporal resolution 2D phase contrast images of the ascending and descending aorta were acquired at the level of the pulmonary trunk at rest for pulse wave velocity measurements of the aorta. To determine the length of the aortic segment between the two aortic levels, sagittal angulated 3D SPGR images were acquired in a single breath hold. Finally, also SSFP images were acquired at the level of the pulmonary trunk for aortic distensibility.

Image analyses were performed by semi-automated analyses, which were manually post-processed by two trained students using software from Medis Medical Imaging Systems bv Leiden, The Netherlands: Medis Suite (v.3.2.60.6Q), QMass (v.8.1.98.2) and Qflow (v.8.1.98.2). The analysis were performed according to the guidelines of the Society for Cardiovascular Magnetic Resonance (SCMR) [30]. Both students were trained and closely supervised by a CMR specialized cardiologist (>20 years of experience in CMR). One student measured all ventricular outcomes, whereas the second student measured aortic pulse wave velocity (PWV) and aorta distensibility. We observed good reproducibility for all CMR measurements during rest and stress with coefficients of variation varying from 2 to 11 and a mean intra-class correlation coefficient (ICC) of 0.90 +/− 0.12 [29].

On the cine short-axis stack we measured left ventricular mass (LVM) during rest and left ventricular end-diastolic and end-systolic volume (LVEDV and LVESV respectively) and calculated stroke volume and ventricular ejection fraction (LVEF) during rest and exercise. Additionally, left ventricular mass–volume ratio (LMVR) was calculated as LVM divided by LVDV. Cardiac output was calculated by multiplying stroke volume with heartrate. PWV was calculated as the ratio of distance Δx per time Δt, where Δx is the length of the aortic segment measured on the 2D phase contrast images along the centerline, and Δt is the time duration needed for the pulse wave to travel that length through the aorta. Aortic distensibility (10^{-3} mm Hg^{-1}) at the level of the pulmonary trunk, was calculated using the following calculation: (maximum area – minimum area)/(minimum area $\times \Delta P$) $\times$ 1000, where ΔP is the difference between systolic and diastolic brachial pulse pressure in mmHg at time of the distensibility sequence was performed.

Statistical analysis

First, we compared population characteristics between children who were overweight or had obesity and children with a normal weight using Student's *t*-tests for independent samples for continuous variables and chi-square tests for proportions. Differences in cardiovascular measurements between rest and stress were calculated using a paired sample *t*-test. Second, we used linear mixed-effects models with cubic splines to model the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure development from rest to recovery among children with a normal weight and children with overweight or obesity. Based on findings from previous studies, we tested whether associations between weight group and cardiovascular

exercise response were different according to sex [31, 32]. As the interaction was significant, we included an interaction of weight group with sex in the models. The final models included age, sex and weight-group as fixed effects and time as random effect. We further examined the associations of childhood BMI across the full range and in clinical categories with differences in resting, peak and recovery heart rate and blood pressure and functional CMR measurements at rest and exercise using linear regression models. These models were adjusted for childhood age and sex. *Analyses with functional cardiac measurements were performed with cardiac outcomes in absolute values and adjusted for BSA, as cardiac measurements are highly dependent on body size with lean body mass being the strongest predictor of cardiac dimensions* [33]. *By adjusting cardiac outcomes for BSA, we aimed to further examine the effects of excessive childhood body fat on cardiac measurements and not only of body size. We constructed BSA adjusted SDS for the cardiac measures using generalized additive models for location, size and shape (GAMLSS) in R, version 4.0.3 (R Core Team, Vienna, Austria). GAMLSS is a flexible statistical framework that models the distributional properties of the data, including location (mean), scale (standard deviation), and shape (skewness and kurtosis), allowing for heteroscedasticity and non-linear relationships. By fitting GAMLSS to the data, we were able to simultaneously model the mean and variance of the MRI measurements as functions of BSA, thereby adjusting for differences in body size independent of age* [34, 35]. *Left ventricular ejection fraction (LVEF) and LMVR were standardized as observed value mean/standard deviation. Statistical analyses were performed using R, version 4.0.3 (R Core Team, Vienna, Austria) and SPSS software (IBM-SPSS Statistics, Version 28.0. Armonk, NY: IBM Corp.).*

RESULTS

Subject characteristics

Table 1 shows the population characteristics. In total, 41 overweight or children with obesity were included and 144 children with a normal weight were included. Median BMI was 26.4 kg/m^2 (95% range 23.5–38.4 kg/m^2) in the group of children with overweight or obesity and 20.0 kg/m^2 (95% range 16.1–23.8) in the group of children with a normal weight. There were no differences in MVC and mean voluntary contraction during the exercise between children with overweight or obesity and children with a normal weight. Children with overweight or obesity had a higher resting diastolic blood pressure and mean arterial blood pressure and also a higher resting LVEDV, LVESV, stroke volume and cardiac output, as compared to children with a normal weight (p value < 0.05). Ejection fraction was lower in children with overweight or obesity as compared to children with a normal weight (p value < 0.05).

Childhood BMI and differences in heart rate and blood pressure in response to exercise

Figure 1 shows the longitudinal patterns of heart rate and blood pressure from rest to recovery, in response to exercise. In children with a normal weight and children with overweight or obesity, heart rate showed a steep increase at start of the exercise and a steep decline at cessation. There were no differences in heart rate response between children with a normal weight and children

Table 1. Characteristics of the study population ($n = 207$).

	Children with overweight or obesity ($n = 41$)	Children with a normal weight ($n = 166$)	*P* value
Child Characteristics			
Age, mean (SD), years	16.2 (0.8)	16.2 (0.7)	0.62
Sex, n boys (%)	21 (51)	89 (54)	0.78
BMI, kg/m^2, median (95%)	26.4 (23.8–38.4)	20.0 (16.1–23.8)	<0.001
Dominant hand, n right (%)	40 (98)	153 (92)	0.22
Maximal voluntary contraction, mean (SD), kgf/m^2	6277 (1505)	6148 (1616)	0.64
Mean contraction during exercise, mean (SD), kgf/m^2	2085 (404)	2052 (421)	0.65
Resting heart rate, mean (SD), bpm	69 (10)	66 (8)	0.09
Resting systolic blood pressure, mean (SD), mmHg	119 (12)	116 (12)	0.11
Resting diastolic blood pressure, mean (SD), mmHg	72 (8)	68 (8)	0.02
Resting mean arterial blood pressure, mean (SD), mmHg	87 (9)	83 (8)	0.03
Resting CMR measurements			
Left ventricular mass, median (95%), gram	95 (68–113)	85 (60–125)	0.01
Left ventricular mass/BSA, median (95%), gram/m^2	47 (9)	50 (8)	0.01
Left ventricular end-diastolic volume, mean (SD), ml	188 (26)	168 (25)	<0.001
Left ventricular end-diastolic volume/BSA, mean (SD), ml/m^2	92 (12)	98 (11)	0.03
Left ventricular end-systolic volume, mean (SD), ml	89 (15)	76 (14)	<0.001
Left ventricular end-systolic volume /BSA, mean (SD), ml/m^2	44 (7)	44 (6)	1.00
Left ventricular mass–volume ratio, mean (SD)	0.50 (0.05)	0.52 (0.05)	0.03
Stroke volume, mean (SD), ml/heart beat	100 (16)	92 (115)	<0.01
Stroke volume/BSA, mean (SD), ml/heart beat/m^2	49 (7)	53 (7)	<0.001
Left ventricular ejection fraction, mean (SD), %	53.0 (4.1)	54.8 (4.0)	0.01
Cardiac output, mean (SD), l/min	6.8 (1.1)	6.0 (1.1)	<0.001
Cardiac index, mean (SD), l/min/m^2	3.3 (0.5)	3.5 (0.6)	0.13
Aorta distensibility, mean (SD) $^{10\text{-}3}$mmHg	11.1 (2.4)	10.7 (3.2)	0.50
Pulse Wave Velocity, median (95%), m/sec	4.1 (2.0–9.7)	3.8 (2.0–9.3)	0.57

Values are observed data and represent means (SD), medians (95% range) or numbers of subjects (valid %). Differences in subject characteristics between the children with overweight or obesity and children with a normal weight were evaluated using assessed by Student's *t*-tests for independent samples.

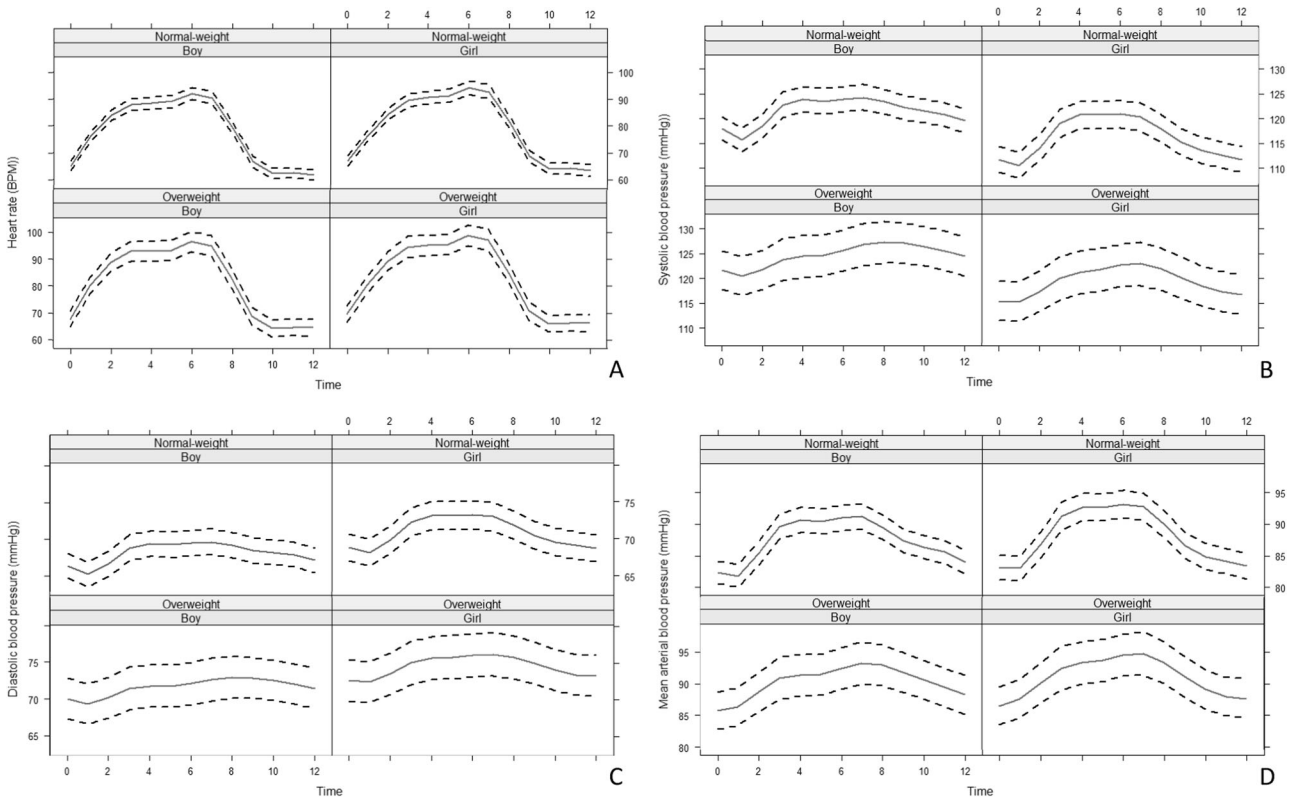

Fig. 1 Trajectories of heart rate and blood pressure values over time were T = 0 is the beginning and T = 7 the end of the exercise, Values were estimated from linear mixed models with 7-knot splines. *P* values for differences in trajectory between children with and without overweight or obesity were *p*: 0.187 for heartrate (**A**), *p*: 0.002 for systolic blood pressure (**B**), *p*:0.001 for diastolic blood pressure (**C**) and $p < 0.001$ for mean arterial pressure (**D**).

with overweight or obesity throughout the exercise. Children with overweight or obesity started with a higher blood pressure than children with a normal weight at rest. In both children with a normal weight and children with overweight or obesity, systolic and diastolic blood pressure showed a small pressure drop in the first minute of exercise with an increase thereafter. This drop was more pronounced in children with a normal weight than children with overweight or obesity, with a higher increase thereafter. After cessation of the exercise, children with a normal weight recovered faster towards resting levels of blood pressure than children with overweight or obesity. In the 5th minute of the recovery, systolic and diastolic blood pressure were still higher than resting blood pressure before exercise in children with overweight or obesity ($p < 0.05$). A similar pattern was present for mean arterial pressure. *P* values for differences in trajectories between children with and without overweight or obesity were $p = 0.187$ for heartrate, $p = 0.002$ for systolic blood pressure, $p = 0.001$ for diastolic blood pressure and $p < 0.001$ for mean arterial pressure. Patterns were more pronounced in girls than in boys.

Table 2 shows the cross-sectional associations of childhood BMI with differences in heart rate and blood pressure in response to exercise. Childhood BMI was not associated with differences in resting heart rate, peak exercise heart rate or recovery heart rate. Higher childhood BMI was associated with a higher resting systolic blood pressure and lower increase from rest to peak exercise (difference: 0.24 SDS (95% CI 0.10, 0.37) and −0.11 SDS (95% CI −0.20, −0.03) respectively). Similarly, higher childhood BMI was associated with a higher resting diastolic blood pressure and lower increase from rest to peak exercise (difference: 0.20 SDS (95% CI 0.06, 0.33) and 0.07 SDS (95% CI −0.07, −0.01) respectively. Similar associations were found for mean arterial blood pressure (*p* value < 0.05). During recovery, higher childhood BMI was associated with a lower decreases in systolic blood pressure, diastolic blood pressure and mean arterial blood pressure from cessation onwards (all *p* values < 0.05). After 5 min rest, a higher childhood BMI was still associated with a lower decrease in systolic blood pressure (difference: −0.11 SDS (95% CI −0.21, 0.−0.02), diastolic blood pressure (difference: −0.08 SDS (95% CI −0.16, −0.01), and mean arterial blood pressure (difference: −0.13 SDS (95% CI −0.23, −0.02). Categorized analyses showed a similar pattern, with an adverse blood pressure response in children with overweight or obesity as compared to children with a normal weight. Table 3 shows that no associations of childhood BMI or childhood overweight/obesity with aortic distensibility or PWV were present.

Childhood BMI and differences in CMR measurements in response to exercise

Figure 2 graphically shows all differences in CMR measurements in rest and exercise among children with a normal weight and children with overweight or obesity. In both children with a normal weight and children with overweight or obesity, LVEDV, LESV and cardiac index increased from rest to exercise following a similar pattern. LVEF slightly decreased during exercise and stroke volume remained equal from rest to exercise in both children with overweight or obesity and children with a normal weight. Thus, LVEF and BSA corrected LVEDV and stroke volume were lower in children with overweight or obesity than in children with a normal weight at rest and remained lower during the exercise.

Table 3 shows the associations of childhood BMI across the full range and in clinical categories with BSA corrected SDS scores of the cardiac measurements. During rest, higher childhood BMI was associated with a lower BSA-adjusted LVM, LVEDV, LMVR and lower stroke volume per SDS increase in BMI (*p* values < 0.05), but

Table 2. Associations of childhood BMI with differences in heart rate and blood pressure in response to exercise.

	Rest	Rest – 1st minute exercise	Rest – peak exercise	Peak exercise – 30 seconds recovery	30 – 60 seconds recovery	Peak exercise – 5th minute recovery
Heart rate, SDS						
Normal weight	Ref	Ref	Ref	Ref	Ref	Ref
Overweight/obesity	0.33 (−0.01, 0.67)	0.04 (−0.20, 0.28)	0.05 (−0.33, 0.43)	0.00 (−0.29, 0.29)	0.24 (−0.02, 0.51)	0.04 (−0.34, 0.41)
BMI, SDS	0.13 (−0.01, 0.27)	0.00 (−0.10, 0.10)	0.00 (−0.16, 0.15)	−0.04 (−0.16, 0.08)	0.08 (−0.03, 0.19)	0.03 (−0.13 0.18)
Systolic blood pressure, SDS						
Normal weight	Ref	Ref	Ref	Ref	Ref	Ref
Overweight/obesity	0.30 (−0.03, 0.63)	0.06 (−0.06, 0.18)	−0.15 (−0.35, 0.06)	−0.13 (−0.30, 0.03)	−0.11 (−0.25, 0.04)	−0.22 (−0.45, 0.01)
BMI, SDS	0.24 (0.10, 0.37)*	0.00 (−0.05, 0.05)	−0.11 (−0.20, −0.03)*	−0.07 (−0.14, −0.01)*	−0.07 (−0.13, −0.01)*	−0.11 (−0.21, −0.02)*
Diastolic blood pressure, SDS						
Normal weight	Ref	Ref	Ref	Ref	Ref	Ref
Overweight/obesity	0.41 (0.08, 0.73)*	0.04 (−0.05, 0.12)	−0.11 (−0.27, 0.05)	−0.12 (−0.25, 0.01)	−0.07 (−0.18, 0.04)	−0.18 (−0.35, −0.01)*
BMI, SDS	0.20 (0.06, 0.33)*	0.02 (−0.03, 0.04)	−0.07 (−0.14, −0.01)*	−0.05 (−0.11, −0.01)*	−0.04 (−0.09, 0.01)	−0.08 (−0.15, −0.01)*
Mean arterial blood pressure, SDS						
Normal weight	Ref	Ref	Ref	Ref	Ref	Ref
Overweight/obesity	0.39 (0.06, 0.73)*	0.11 (−0.04, 0.25)	−0.21 (−0.45, 0.03)	−0.20 (−0.37, −0.01)*	−0.13 (−0.29, 0.04)	−0.28 (−0.54, −0.02)*
BMI, SDS	0.24 (0.10, 0.37)*	0.03 (−0.04, 0.09)	−0.14 (−0.23, −0.04)*	−0.09 (−0.16, −0.01)*	−0.06 (−0.13, 0.00)	−0.13 (−0.23, −0.02)*

Values represent regression coefficients (95% confidence interval) from linear regression models that reflect differences in resting blood pressure and heart rate and in the delta between children with a normal weight ($n = 166$) and children with overweight or obesity ($n = 41$) children in the categorical analysis and per 1 SDS increase in BMI in de continuous analysis. All coefficients are corrected for age and sex.
BMI body mass index, *SDS* standard deviation score.
*P value < 0.05.

Table 3. Associations of childhood BMI with differences in CMR measurements between rest and exercise.

	Rest	Difference rest – exercise
LV mass, SDS		
Normal weight	Ref	NA
Overweight/obesity	−0.27 (−0.53, 0.00)	NA
BMI, SDS	−0.18 (−0.29, −0.07)*	NA
LV end-diastolic volume, SDS		
Normal weight	Ref	Ref
Overweight/obesity	−0.13 (−0.43, 0.17)	−0.01 (−0.29, 0.27)
BMI, SDS	−0.13 (−0.26, −0.01)*	−0.05 (−0.17, 0.07)
LV end-systolic volume, SDS		
Normal weight	Ref	Ref
Overweight/obesity	−0.03 (−0.35, 0.29)	−0.08 (−0.37, 0.21)
BMI, SDS	−0.13 (−0.26, 0.01)	−0.04 (−0.16, 0.09)
LV mass–volume ratio, SDS		
Normal weight	Ref	NA
Overweight/obesity	−0.36 (−0.68, −0.04)*	NA
BMI, SDS	−0.20 (−0.33, −0.07)*	NA
LV stroke Volume, SDS		
Normal weight	Ref	Ref
Overweight/obesity	−0.42 (−0.72, −0.12)*	−0.02 (−0.31, 0.28)
BMI, SDS	−0.17 (−0.29, −0.05)*	−0.08 (−0.20, 0.05)
LV ejection fraction, SDS		
Normal weight	Ref	Ref
Overweight/obesity	−0.01 (−0.35, 0.34)	−0.01 (−0.37, 0.36)
BMI, SDS	0.01 (−0.13, 0.15)	0.01 (−0.14, 0.17)
LV cardiac index, SDS		
Normal weight	Ref	Ref
Overweight/obesity	−0.16 (−0.49, 0.17)	0.05 (−0.30, 0.40)
BMI, SDS	−0.07 (−0.20, 0.07)	−0.06 (−0.21, 0.08)
Aortic distensibility, SDS		
Normal weight	Ref	NA
Overweight/obesity	0.09 (−0.23, 0.42)	NA
BMI, SDS	0.01 (−0.13, 0.14)	NA
Aortic pulse wave velocity, SDS		
Normal weight	Ref	NA
Overweight/obesity	0.11 (−0.26, 0.47)	NA
BMI, SDS	0.00 (−0.15, 0.15)	NA

Values represent regression coefficients (95% confidence interval) from linear regression models that reflect differences in resting CMR measurements and in the delta of the measurements (from rest to exercise) between children with a normal weight ($n = 166$) and overweight or obesity ($n = 41$) children in the categorical analysis and per 1 SDS increase in BMI in de continuous analysis. All cardiac measurements were transformed to BSA corrected SDS scores. For LV ejection fraction and LV mass-volume ratio we did not create a BSA-adjusted SDS, but standardized this measure as (observed value mean)/standard deviation. All coefficients are corrected for age and sex.

BMI body mass index, *LV* left ventricular, *SDS* standard deviation score.

*P value < 0.05.

not with resting LVESV, LVEF and cardiac index. Children with overweight or obesity had a lower stroke volume and LMVR compared to children with a normal weight (p value < 0.05). During exercise, there was a trend towards an association of childhood BMI with lower increases in LVESV, LVEDV and stroke volume, although not significant. These associations were in similar direction as compared to BSA-unadjusted cardiac outcomes. Supplementary Tables 1 and 2 show the associations with BSA corrected absolute cardiac measurements and non-BSA adjusted cardiac measurements respectively. Childhood BMI was not associated with differences in cardiac measurements from rest to exercise.

DISCUSSION

In this population-based cohort study among 207 children with a mean age of 16 years, we observed that children with overweight or obesity had a higher resting blood pressure and an impaired blood pressure response to handgrip exercise, characterized by lower increases in systolic and diastolic blood pressure during

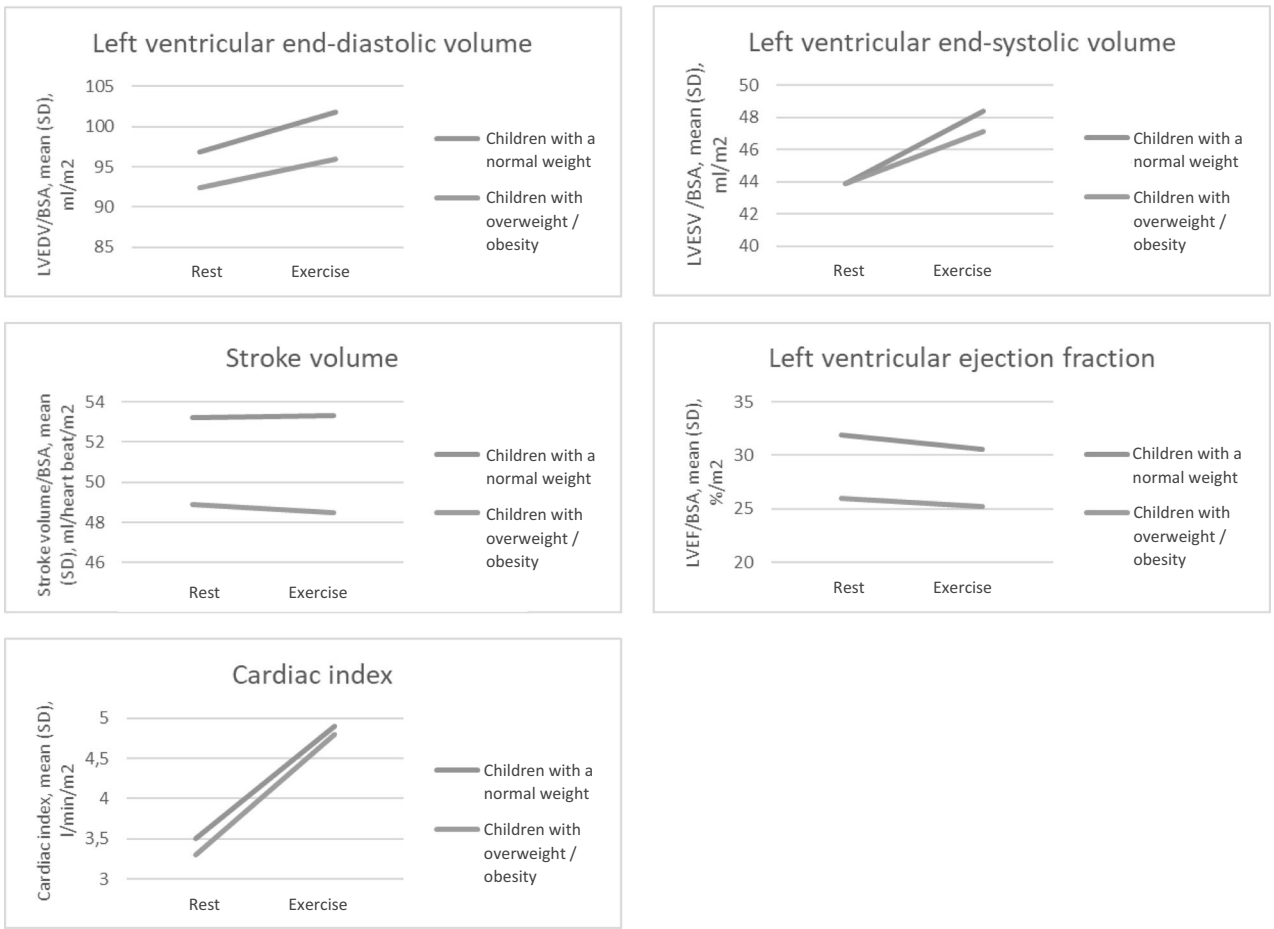

Fig. 2 Differences in cardiac measurements between rest and exercise. All volumetric measurements (except for LVEF) were corrected for BSA.

exercise and a prolonged recovery time, as compared to children with a normal weight. This pattern was present across the full range of childhood BMI. No differences in heartrate or change in cardiac volumes and ejection fraction in response to exercise were present in children with overweight or obesity as compared to children with a normal weight.

Interpretation main findings

Accumulating evidence suggests that childhood overweight and obesity can lead to minor cardiovascular structural and functional changes that track into adulthood [5–8]. These permanent adaptations in structure, physiology and function of cardiovascular systems, predispose to an increased risk of cardiovascular disease in later life [36–39].

Most previous studies focused on cardiovascular differences among children with obesity, in rest only. In this study we explored the associations of childhood BMI across the full range and in clinical categories (overweight and obesity) with cardiovascular outcomes during rest and exercise. At rest, we observed a higher blood pressure in children with overweight or obesity compared to children with a normal weight, whereas heartrate was not different. We also showed that BMI across the full range, was associated with a higher resting blood pressure. Partly in line with our findings, a large cross-sectional study in 9167 children aged 5 to 17 years old, examined the associations of obesity with cardiovascular risk factors and showed a strong relationship between childhood obesity and higher blood pressure. A study in 2460 children with a mean age of 15 years showed that children with obesity had a higher heart rate than children without obesity [40]. These studies defined obesity as a BMI >95th percentile. Possibly, stronger associations of childhood BMI with heart rate are only present in the those with clinical obesity but not below this clinical threshold. Our study population only included a low number of children with obesity.

In line with previous studies, we further observed that a higher childhood BMI is related with a higher childhood LVM, LVEDV, LVESV, stroke volume and cardiac output and a lower LMVR in rest [33]. We found no associations of childhood BMI with aortic distensibility or PWV. CMR measurements are strongly influenced by body size without reflecting an underlying disease process per se. Studies correcting for BSA show that, after correction, differences in LVM and ventricular dimensions related to obesity are no longer significant [41, 42]. In our study, we observed that higher childhood BMI was associated with a lower BSA adjusted LVM, LVEDV and stroke volume. This suggests that, not excessive fat mass, but rather lean mass is an important determinant of cardiac size. In a previous study done by our research group at the age of 9 years, we showed that, independently of childhood BMI, higher lean mass index was associated with a higher in LVEDV and LVM, whereas higher fat mass index and visceral adiposity index were associated with lower LVEDV and LVM [9]. A study among 201 children from 6 to 17 years old, suggested that not total body fat, but lean body mass is the main determinant of LVM in childhood [43]. Lean body mass is associated with an increase in blood volume, leading to a higher preload and thus increase in LVM and LVEDV, whereas adipose mass is less metabolically active [44]. Similarly, a study in 243 children with a mean age of 11 years, found that body fat as measured by suprailiac skinfold thickness was inversely associated with LVM, which persisted into adolescence [43, 45].

Exercise testing of the cardiovascular system could aid in the early detection of subtle cardiovascular adaptations, not yet present in rest [11–13]. In this unique study, we continuously measured systolic, diastolic and mean arterial blood pressure during exercise and recovery and LVM and volumes during exercise. No other studies have ever conducted a cardiovascular exercise stress test combined with CMR measurements in children. We observed that higher childhood BMI is associated with a blunted stress reaction of systolic and diastolic blood pressure during isometric handgrip exercise. Higher BMI was associated with lower increases in blood pressure during exercise and a prolonged recovery. Remarkably, these effects were not solely present in children with overweight or obesity, but rather present across the full range of BMI. Earlier studies have shown that obesity is characterized by a higher sympathetic nervous system activity, but with less variability during the day and in response to stressors [46–48]. A study in 40 normotensive women with obesity with a mean age of 32 years and 15 age-matched normotensive lean women, measured muscle sympathetic nerve activity during rest and during a static exercise at 30%MVC. They found a higher resting sympathetic nerve activity in women with obesity, but a lower increase during exercise than in lean women [49]. During exercise, the muscle metaboreflex activates the sympathetic nerve system which elicits an increase in blood pressure [50]. Presumably the muscle metaboreflex control of sympathetic nerve activity is blunted in individuals with overweight or obesity [49]. Also in children, research has already shown that obesity is associated with nervous system dysfunction and an impaired baroreflex sensitivity with less variation [51]. Decreased baroreflex sensitivity contributes to the development and progression of many cardiovascular diseases [52]. We also observed an association of higher BMI with a slower decrease in blood pressure during recovery after cessation of the exercise, exposing the left ventricle to prolonged increased afterload. A study in 14 boys with obesity and 13 boys with a normal weight of 11-12 years old showed that baroreflex sensitivity returned to baseline levels in a 3 min recovery period after isometric handgrip exercise in boys with a normal weight, but remained elevated in boys with obesity [53]. This mechanism is highly involved in the blood pressure regulation during exercise [54]. The latter study also observed a reduced capacity for total peripheral resistance adaptations from exercise to recovery in boys with obesity compared with boys with a normal weight [53]. These findings, together with the findings of the current study, suggest an early vascular dysfunction in children with overweight or obesity and children with obesity.

We did not find a difference cardiac response between children with overweight or obesity and children with a normal weight. During exercise, we found a trend towards an association of BMI with lower increases in LVEDV, LVESV, cardiac output and stroke volume, although not significant. This is in line with a meta-analysis of 7 studies with a total of 287 adolescents with obesity and 126 adolescents with a normal weight that reported no difference in peak heart rate between both groups. A study among 13 girls with obesity with a mean age of 13.6 years and a BMI of >30 compared to 13 girls with a normal weight, examined the cardiac response to exercise measured by echocardiography and found that peak exercise cardiac output, stroke volume and aortic velocity were higher in girls with obesity compared to girls with a normal weight. However, after adjustment for BSA, no significant differences were present [20]. Possibly, obesity primarily affects the muscle metaboreflex and baroreflex sensitivity that influences vascular resistance and blood pressure, without leading to an altered cardiac response in children with obesity. The cohort group in the present study consisted of relatively healthy children with lower obesity grades and the amount of children with obesity is relatively small. Studies in more affected children with higher obesity grades should determine whether the cardiac response is affected by obesity in higher risk groups. Addition of lean mass measurements can differentiate the association of excessive fat mass from lean body mass on cardiovascular function.

Although the isometric handgrip exercise led to significant changes in CMR measurements, possibly these changes were too marginal to reveal subtle differences in cardiac adaptation to exercise in children with overweight or obesity. Newer CMR techniques allow for real-time free breathing and ECG-free scanning during exercise with preservation of the image quality [55, 56]. These techniques allow for different types of exercise to higher exertions. The cardiovascular exercise response can differ depending on exercise type and body position [57]. Previous exercise studies have published increases, decreases or no significant changes in LV volumes in response to exercise [58]. Future studies should examine the effects of different exercise modalities and different exercise protocols to aim greater changes in CMR measurements to enable a more detailed measurement on the cardiovascular exercise response. These studies should also include measurements of the right ventricle and ventricular diastolic function to obtain a more detailed measurement of the cardiac function.

Strengths and limitations

This study is the first study examining the cardiovascular response to exercise in a non-diseased childhood population with detailed CMR measurements. Also, to our knowledge, no other studies measured a continuous heart rate and blood pressure during rest, exercise and recovery in a relatively large group of children. However, this subgroup of our cohort, compromised a relatively healthy population in comparison to the general population and consisted only participants with a Dutch nationality. This may affect the generalizability of our results. Studies in higher risk groups and population based studies should determine whether similar associations are present in other study populations. However, our results suggest that even in children with lower grades of obesity, there is an adjustment of the cardiovascular system to the excessive bodyweight. This underscores the importance of early intervention and prevention strategies in addressing cardiovascular health in pediatric populations. Moreover it suggest that our new CMR exercise protocol is sensitive enough to detect differences in cardiovascular exercise response, even in children with lower risks of developing cardiovascular diseases. One percent of our CMR scans during exercise were of insufficient quality for assessment and were excluded from our analysis. These exclusions were mainly due to breathing artefacts or ECG triggering problems. Studies using newer CMR techniques without the use of an ECG and breath-holds probably leads to higher image quality during exercise.

CONCLUSION

Higher childhood BMI is across the full range associated with higher resting blood pressure and an impaired blood pressure reaction to isometric handgrip exercise with a prolonged increased afterload during recovery. This suggest that children with overweight or obesity are not fully able to adapt their vascular system to stress. No associations of childhood BMI with changes in CMR and heart rate measurements in response to exercise were present suggesting that there are no effects of BMI on the cardiac response. Future studies in children with higher obesity grades should determine whether the cardiac response is also affected by obesity in higher risk groups and whether this response is associated with later cardio metabolic morbidity and mortality.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Mossberg H-O. 40-year follow-up of overweight children. Lancet. 1989;334:491–3.
2. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics. 2001;108:712–8.
3. Lai CC, Sun D, Cen R, Wang J, Li S, Fernandez-Alonso C, et al. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns: the Bogalusa Heart Study. J Am Coll Cardiol. 2014;64:1580–7.
4. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the princeton lipid research clinics follow-up study. Pediatrics. 2007;120:340–5.
5. Cote AT, Harris KC, Panagiotopoulos C, Sandor GG, Devlin AM. Childhood obesity and cardiovascular dysfunction. J Am Coll Cardiol. 2013;62:1309–19.
6. Crowley DI, Khoury PR, Urbina EM, Ippisch HM, Kimball TR. Cardiovascular impact of the pediatric obesity epidemic: higher left ventricular mass is related to higher body mass index. J Pediatr. 2011;158:709–14.e1. e1
7. Urbina EM, Khoury PR, Bazzano L, Burns TL, Daniels S, Dwyer T, et al. Relation of blood pressure in childhood to self-reported hypertension in adulthood. Hypertension. 2019;73:1224–30.
8. Wright CM, Parker L, Lamont D, Craft AW. Implications of childhood obesity for adult health: findings from thousand families cohort study. BMJ. 2001;323:1280–4.
9. Toemen L, Santos S, Roest AA, Jelic G, van der Lugt A, Felix JF, et al. Body fat distribution, overweight, and cardiac structures in school-age children: a population-based cardiac magnetic resonance imaging study. J Am Heart Assoc. 2020;9:e014933.
10. Gishti O, Gaillard R, Durmus B, Abrahamse M, van der Beek EM, Hofman A, et al. BMI, total and abdominal fat distribution, and cardiovascular risk factors in school-age children. Pediatr Res. 2015;77:710–8.
11. Bjelakovic L, Vukovic V, Jovic M, Bankovic S, Kostic T, Radovanovic D, et al. Heart rate recovery time in metabolically healthy and metabolically unhealthy obese children. Phys Sportsmed. 2017;45:438–42.
12. Jankowski M, Niedzielska A, Brzezinski M, Drabik J. Cardiorespiratory fitness in children: a simple screening test for population studies. Pediatr Cardiol. 2015;36:27–32.
13. Treiber FA, Turner JR, Davis H, Thompson W, Levy M, Strong WB. Young children's cardiovascular stress responses predict resting cardiovascular functioning 2 1/2 years later. J Cardiovasc Risk. 1996;3:95–100.
14. Washington RL, Bricker JT, Alpert BS, Daniels SR, Deckelbaum RJ, Fisher EA, et al. Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation. 1994;90:2166–79.
15. Stephens P. Sudden cardiac death in the young: the value of exercise testing. Cardiol Young-. 2017;27:S10–S8.
16. Rhodes J, Ubeda Tikkanen A, Jenkins KJ. Exercise testing and training in children with congenital heart disease. Circulation. 2010;122:1957–67.
17. Nageswari KS, Sharma R, Kohli DR. Assessment of respiratory and sympathetic cardiovascular parameters in obese school children. Indian J Physiol Pharm. 2007;51:235–43.
18. Schuster I, Karpoff L, Perez-Martin A, Oudot C, Startun A, Rubini M, et al. Cardiac function during exercise in obese prepubertal boys: effect of degree of obesity. Obesity. 2009;17:1878–83.
19. Giordano U, Ciampalini P, Turchetta A, Santilli LA, Calzolari F, Crinò A, et al. Cardiovascular hemodynamics: relationships with insulin resistance in obese children. Pediatr Cardiol. 2003;24:548–52.
20. Rowland T, Bhargava R, Parslow D, Heptulla RA. Cardiac response to progressive cycle exercise in moderately obese adolescent females. J Adolesc Health. 2003;32:422–7.
21. Aldo Ferrara L, Soro S, Mainenti G, Mancini M, Pisanti N, Borrelli R, et al. Body weight and cardiovascular response to sympathetic stimulation in childhood. Int J Obes. 1989;13:271–7.
22. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. Circulation. 2006;113:1905–20.
23. von Knobelsdorff-Brenkenhoff F, Dieringer MA, Fuchs K, Hezel F, Niendorf T, Schulz-Menger J. Isometric handgrip exercise during cardiovascular magnetic resonance imaging: set-up and cardiovascular effects. J Magn Reson Imaging. 2013;37:1342–50.
24. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IMH, et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31:1243–64.
25. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. Bmj. 2000;320:1240–3.
26. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr. 1978;93:62–6.
27. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23:465–95.
28. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res. 2000;47:316–23.
29. Bongers-Karmaoui MN, Hirsch A, Budde RPJ, Roest AAW, Jaddoe VWV, Gaillard R. Gaillard R. Physical exercise and cardiovascular response: design and implementation of a pediatric CMR cohort study. Int J Cardiovasc Imaging. 2023;39(12):2575–87.
30. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. J Cardiovasc Magn Reson. 2013;15:35.
31. Tanaka M, Sugawara M, Niki K, Ogasawara Y. Changes in cardiac contractility during graded exercise are greater in subjects with smaller body mass index, and greater in men than women: analyses using wave intensity and force–frequency relations. J Med Ultrason. 2019;46:63–8.
32. Seo J-S, Jin H-Y, Jang J-S, Yang T-H, Kim D-K, Kim D-S. The relationships between body mass index and left ventricular diastolic function in a structurally normal heart with normal ejection fraction. J Cardiovasc Ultrasound. 2017;25:5–11.
33. Koopman LP, Mertens LL. Impact of childhood obesity on cardiac structure and function. Curr Treat Options Cardiovasc Med. 2014;16:345.
34. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. J R Stat Soc: Ser C (Appl Stat). 2005;54:507–54.
35. Marmolejo-Ramos F, Tejo M, Brabec M, Kuzilek J, Joksimovic S, Kovanovic V, et al. Distributional regression modeling via generalized additive models for location, scale, and shape: An overview through a data set from learning analytics. Wiley Interdiscip Rev Data Min Knowl Discov. 2023;13:e1479.
36. Gaillard R, Steegers EA, Tiemeier H, Hofman A, Jaddoe VW. Placental vascular dysfunction, fetal and childhood growth, and cardiovascular development: the generation R study. Circulation. 2013;128:2202–10.
37. Toemen L, Jelic G, Kooijman MN, Gaillard R, Helbing WA, van der Lugt A, et al. Third trimester fetal cardiac blood flow and cardiac outcomes in school-age children assessed by magnetic resonance imaging. J Am Heart Assoc. 2019;8:e012821.
38. Geelhoed JJ, Steegers EA, van Osch-Gevers L, Verburg BO, Hofman A, Witteman JC, et al. Cardiac structures track during the first 2 years of life and are associated with fetal growth and hemodynamics: the Generation R Study. Am Heart J. 2009;158:71–7.
39. Kooijman MN, de Jonge LL, Steegers EA, van Osch-Gevers L, Verburg BO, Hofman A, et al. Third trimester fetal hemodynamics and cardiovascular outcomes in childhood: the Generation R study. J Hypertens. 2014;32:1275–82.
40. Sorof JM, Poffenbarger T, Franco K, Bernard L, Portman RJ. Isolated systolic hypertension, obesity, and hyperkinetic hemodynamic states in children. J Pediatrics. 2002;140:660–6.
41. Lorch SM, Sharkey A. Myocardial velocity, strain, and strain rate abnormalities in healthy obese children. J Cardiometab Syndr. 2007;2:30–4.
42. Ingul CB, Tjonna AE, Stolen TO, Stoylen A, Wisloff U. Impaired cardiac function among obese adolescents: effect of aerobic interval training. Arch Pediatr Adolesc Med. 2010;164:852–9.
43. Daniels SR, Kimball TR, Morrison JA, Khoury P, Witt S, Meyer RA. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. Circulation. 1995;92:3249–54.
44. Alpert MA, Omran J, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Curr Obes Rep. 2016;5:424–34.
45. Goble MM, Mosteller M, Moskowitz WB, Schieken RM. Sex differences in the determinants of left ventricular mass in childhood. The Medical College of Virginia Twin Study. Circulation. 1992;85:1661–5.

46. Balasubramanian P, Hall D, Subramanian M. Sympathetic nervous system as a target for aging and obesity-related cardiovascular diseases. Geroscience. 2019;41:13–24.
47. Indumathy J, Pal GK, Pal P, Ananthanarayanan PH, Parija SC, Balachander J, et al. Decreased baroreflex sensitivity is linked to sympathovagal imbalance, body fat mass and altered cardiometabolic profile in pre-obesity and obesity. Metabolism. 2015;64:1704–14.
48. Lambert E, Straznicky N, Schlaich M, Esler M, Dawood T, Hotchkin E, et al. Differing pattern of sympathoexcitation in normal-weight and obesity-related hypertension. Hypertension. 2007;50:862–8.
49. Carlos Eduardo N, Ivani CT, Luciana TB, Maurício Maltez R, Maria Urbana PBR, Taís T, et al. Muscle metaboreflex control is diminished in normotensive obese women. Am J Physiol-Heart Circ Physiol. 2001;281:H469–H75.
50. Boushel R. Muscle metaboreflex control of the circulation during exercise. Acta Physiol. 2010;199:367–83.
51. Lazarova Z, Tonhajzerova I, Trunkvalterova Z, Brozmanova A, Honzíková N, Javorka K, et al. Baroreflex sensitivity is reduced in obese normotensive children and adolescents. Can J Physiol Pharm. 2009;87:565–71.
52. La Rovere MT, Pinna GD, Maestri R, Sleight P. Clinical value of baroreflex sensitivity. Neth Heart J. 2013;21:61–3.
53. Dipla K, Zafeiridis A, Koidou I, Geladas N, Vrabas IS. Altered hemodynamic regulation and reflex control during exercise and recovery in obese boys. Am J Physiol Heart Circ Physiol. 2010;299:H2090–6.
54. Potts JT, Shi XR, Raven PB. Carotid baroreflex responsiveness during dynamic exercise in humans. Am J Physiol. 1993;265:H1928–38.
55. Nakamori S, Fahmy A, Jang J, El-Rewaidy H, Neisius U, Berg S, et al. Changes in myocardial native T1 and T2 after exercise stress: a noncontrast CMR pilot study. JACC: Cardiovasc Imaging. 2020;13:667–80.
56. Morales MA, Assana S, Cai X, Chow K, Haji-valizadeh H, Sai E, et al. An inline deep learning based free-breathing ECG-free cine for exercise cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2022;24:47.
57. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128:873–934.
58. Craven TP, Tsao CW, La Gerche A, Simonetti OP, Greenwood JP. Exercise cardiovascular magnetic resonance: development, current utility and future applications. J Cardiovasc Magn Reson. 2020;22:65.

ACKNOWLEDGEMENTS

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the contribution of participating mothers, general practitioners, hospitals, midwives and pharmacies in Rotterdam.

AUTHOR CONTRIBUTIONS

AH was responsible for designing the CMR protocol and image analysis. MNBK and RG were responsible for data analyses, interpreting results and writing the report. RPJB, AAWR and VWVJ provided feedback on the report. All authors made contributions to qualify as an author according to the criteria stated in the Publication Ethics, and all authors are responsible for the reported research. All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

FUNDING

The Generation R Study is financially supported by the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development. Romy Gaillard received funding from the Dutch Diabetes Foundation (Grant No. 2017.81.002), the Netherlands Organization for Health Research and Development (NWO, ZonMW, Grant No. 543003109, NWO, ZonMw 09150172110034) and from the European Union's Horizon 2020 research and innovation programme under the ERA-NET Cofund action (no 727565), EndObesity, ZonMW the Netherlands (no. 529051026). Vincent Jaddoe received a grant from the Netherlands Organization for Health Research and Development (NWO, ZonMw-VIDI 016.136.361) and a European Research Council Consolidator Grant (ERC-2014-CoG-648916).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-024-01589-1.

Correspondence and requests for materials should be addressed to Romy Gaillard.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.