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ORIGINAL RESEARCH

Body Fat Distribution, Overweight, and Cardiac Structures in School-Age Children: A Population-Based Cardiac Magnetic Resonance Imaging Study

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BACKGROUND: Adiposity is associated with larger left ventricular mass in children and adults. The role of body fat distribution in these associations is not clear. We examined the associations of body fat distribution and overweight with cardiac measures obtained by cardiac magnetic resonance imaging in school-age children.

METHODS AND RESULTS: In a population-based cohort study including 2836 children, 10 years of age, we used anthropometric measures, dual-energy X-ray absorptiometry, and magnetic resonance imaging to collect information on body mass index, lean mass index, fat mass index, and abdominal visceral adipose tissue index. Indexes were standardized by height. Cardiac measures included right and left ventricular end-diastolic volume, left ventricular mass, and mass-to-volume ratio as a marker for concentricity. All body fat measures were positively associated with right and left ventricular end-diastolic volumes and left ventricular mass, with the strongest associations for lean mass index (all $P<0.05$). Obese children had a 1.12 standard deviation score (95% CI, 0.94–1.30) larger left ventricular mass and a 0.35 standard deviation score (95% CI, 0.14–0.57) higher left ventricular mass-to-volume ratio than normal weight children. Conditional on body mass index, higher lean mass index was associated with higher right and left ventricular end-diastolic volume and left ventricular mass, whereas higher fat mass measures were inversely associated with these cardiac measures (all $P<0.05$).

CONCLUSIONS: Higher childhood body mass index is associated with a larger right and left ventricular size. This association is influenced by higher lean mass. In childhood, lean mass may be a stronger determinant of heart growth than fat mass. Fat mass may influence cardiac structures at older ages.

Key Words: cardiac MRI ■ epidemiology ■ obesity ■ pediatrics

See Editorial by Christopher

Overweight and obesity are strongly associated with cardiovascular disease in adults.[1] Previous studies suggested that cardiac adaptations in response to overweight start already in childhood.[2] Higher childhood body mass index (BMI) is associated with adult left ventricular remodeling and larger left ventricular mass (LVM).[2] Left ventricular remodeling is generally categorized in eccentric and concentric remodeling. Eccentric remodeling, an increase in both left ventricular mass and volume, is associated with heart failure.[3] Concentric remodeling, in which the mass-to-volume ratio is increased, is also associated

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CLINICAL PERSPECTIVE

What Is New?

- Obese children have higher left ventricular mass and left ventricular mass-to-volume ratio than normal-weight children.
- Lean mass index is associated with relatively larger left and right cardiac measures.
- Fat mass index is associated with relatively smaller left and right cardiac measures.

What Are the Clinical Implications?

- In childhood, lean mass may be a stronger determinant of cardiac growth.
- Fat mass may may influence cardiac structure at later ages.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
cMRI	cardiac magnetic resonance imaging
LMVR	left ventricular mass-to-volume ratio
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVM	left ventricular mass
RVEDV	right ventricular end-diastolic volume
RVEF	right ventricular ejection fraction
SDS	standard deviation score

with stroke and coronary heart disease.[3] Concentric remodeling is, in general, thought to be caused by hypertension, but is also observed in obesity, independent of blood pressure.[4] Obesity is a condition associated with different and heterogeneous cardiovascular outcomes.[5] This may be because obesity is based on BMI, which does not distinguish between lean mass, subcutaneous fat mass, and visceral fat mass. The important role of body fat distribution is reflected by studies showing that visceral adipose tissue is more strongly associated with metabolic syndrome and hypertension than subcutaneous adipose tissue.[6] Body composition and, more specifically, fat distribution may also affect cardiac structure. Studies focused on body composition instead of BMI suggest that lean body mass is more strongly related to LVM than BMI or fat mass in adults.[7] Also, adiposity around the hips was associated with eccentric remodeling characterized by an increase in LVM and left ventricular end-diastolic volume (LVEDV), whereas central obesity was associated with concentric remodeling characterized by an increase in left ventricular mass-to-volume ratio (LMVR).[8] We have previously reported that body fat distribution was associated with cardiovascular risk factors in childhood.[9] To our knowledge, no studies have examined the associations of detailed general and abdominal adiposity measures with both right and left ventricular measures in childhood. Insight into the possible associations between body composition beyond BMI and cardiac measures in childhood could give clues to the primordial origins of cardiac disease.

We hypothesized that general and abdominal body fat distribution influence right and left cardiac measures from childhood onward. Therefore, in a population-based study among 2836 school-aged children, we examined the associations of general and abdominal body fat measures and being overweight with right and left ventricular structure and function based on cardiac magnetic resonance imaging (cMRI).

METHODS

Data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Design and Study Population

This study was embedded in the Generation R Study, a population-based, prospective cohort study from fetal life onward in Rotterdam, The Netherlands.[10] Response rate at birth was 61% (2002–2006).[10] Child ethnicity was classified by country of parents' birth, categorized as Dutch or non-Dutch.[10] The largest non-Dutch ethnicities are European, Turkish, Moroccan, Surinamese, Cape Verdian, and Dutch Antilles. The children's sex was obtained from midwife and hospital registries at birth. Childhood BMI, body composition, and cardiac measures were assessed during 2 visits at 10 years of age. Median time difference between the 2 visits was 1.1 (95% CI, 0–24.8) months. In total, 4135 singleton born children participated in the magnetic resonance imaging (MRI) studies. We obtained good-quality cMRI scans in 2836 children without cardiac abnormalities (see flowchart in Figure S1). Written informed consent was obtained from all parents of study participants. The study was approved by the local medical ethics committee.

General and Abdominal Body Fat Distribution Assessments

Trained staff at a dedicated research center measured the children's height and weight at 9.9 (95% CI, 9.5–11.8) years of age, according to specific research protocols. BMI (kg/m^2) and body surface area were calculated.[11] We obtained sex- and age-specific BMI standard deviation scores (SDSs) based on Dutch reference growth curves.[12] Childhood overweight status was defined according to age- and sex-specific cutoff points.[13]

Total body and regional fat and lean mass were measured using a dual-energy X-ray absorptiometry scanner (iDXA; GE-Lunar, 2008, Madison, WI) and analyzed using enCORE software version 12.6.[14] We divided total fat mass by height^4 to obtain a fat mass index uncorrelated with height, as confirmed by a log–log regression analysis.[15] Lean body mass was divided by height squared to obtain lean mass index. Correlations between general and specific body composition measures are presented in Table S1.

Visceral fat was obtained by MRI, as described previously, and in Data S1.[10,16] IDEAL IQ and LavaFlex acquisitions were used to obtain abdominal fat imaging. These were analyzed by Precision Image Analysis (Precision Image Analysis, Kirkland, WA) using sliceOmatic (TomoVision, Magog, QC, Canada) software. The visceral adipose tissue index uncorrelated with height was calculated as visceral adipose tissue / height^3.[15]

Cardiac Magnetic Resonance Imaging

As described previously, we acquired localizer images, followed by ECG gated breath-hold scans for 2 and 4-chamber views.[17] A short-axis steady-state free precession cine stack was then obtained over several end-expiration breath-holds. Offline image analyses were performed by Precision Image Analysis using QMASS software (Medis, Leiden, The Netherlands), following the guidelines of the Society for Cardiovascular Magnetic Resonance.[18] Papillary muscle was included in the ventricular cavity. Cardiac measurements included right ventricular end-diastolic volume (RVEDV), right ventricular ejection fraction (RVEF), LVEDV, left ventricular ejection fraction (LVEF), and LVM. We calculated LMVR as LVM/LVEDV, as a marker of concentric remodeling. We also obtained stroke volume and cardiac output. We used systemic vascular resistance as a proxy for afterload, which was calculated as mean arterial pressure divided by cardiac output. We added this measure to explore the associations between body composition and afterload, which may explain how adiposity is associated with cardiac remodeling through changes in cardiac hemodynamics and wall stress.

Blood Pressure Measurements

Childhood systolic and diastolic blood pressure were measured on the right brachial artery 4 times using a validated automatic sphygmomanometer (Accutorr Plus; Datascope, Fairfield, NJ). Mean values of the last 3 measurements were used in our analyses. Mean arterial pressure was calculated as 1/3 × systolic blood pressure + 2/3 × diastolic blood pressure.[19]

Statistical Analysis

First, we compared childhood characteristics between different childhood weight categories using one-way analysis of variance, Mann–Whitney *U* test, and chi-square test. Second, we used linear regression models to assess the associations of childhood general and abdominal body fat measures (BMI, lean mass index, fat mass index, and visceral adipose tissue index) with cardiac measures (RVEDV, RVEF, LVEDV, LVEF, LVM, LMVR, stroke volume, and systemic vascular resistance). Basic models were adjusted for age, sex, ethnicity, and time difference between the 2 visits. A second model was also adjusted for childhood blood pressure (blood pressure model). We used similar models to assess the associations of childhood overweight with LVM and LMVR. We created SDSs according to (observed value – mean) / SD, for all determinants and outcomes, to enable comparison of effect estimates. We did not observe a significant statistical interaction between child sex and being overweight or body composition in relation to cardiac measures. Finally, we used conditional regression analyses to assess whether the associations of general and abdominal body fat measures with cardiac outcomes were statistically independent of BMI.[20] For these models, we regressed each of the body composition measures on BMI to create standardized residuals, independent of BMI (scatterplots before and after residualization are shown in Figure S2). This approach enables analyses of body composition measures independent of BMI in relation to cardiac outcomes.[9,20] Because our outcomes are correlated, we considered Bonferroni correction for multiple testing too strict; in Table 2, we specify $P<0.01$ or $P<0.05$. Missing data of covariates were imputed using multiple imputations. Five data sets were created and analyzed together.[21] For multiple imputation, we used Fully Conditional Specification, an iterative of the Markov-chain Monte Carlo approach. For each variable, the fully conditional specification method fits a model using all other available variables in the model as predictors, and then imputes missing values for the specific variable being fit.[21] In the imputation model, we included all covariates. Furthermore, we also added the studied determinants and outcomes in the imputation model as prediction variables only; they were not imputed themselves.[22] These analyses were performed using the SPSS version 21.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

Subject Characteristics

Overweight and obese children had higher lean mass index, fat mass index, visceral adipose tissue index, and blood pressure than normal-weight children

Table 1. Characteristics of the Children in the Study

	Underweight, N=189 (6.7%)	Normal Weight, N=2149 (75.8%)	Overweight, N=412 (14.5%)	Obese, N=86 (3.0%)	*P* Value*
Age at magnetic resonance imaging, y	9.9 (9.4–11.8)	9.9 (9.5–11.8)	10.0 (9.5–11.8)	9.9 (9.5–11.7)	0.74
Male sex, N	99 (52.4)	1064 (49.5)	173 (42.0)	37 (43.0)	0.02
Non-Dutch ethnicity, N	71 (38.4)	728 (34.6)	226 (56.1)	56 (67.5)	<0.01
Height, cm	140.0 (7.1)	141.1 (6.4)	144.1 (6.9)	145.0 (6.6)	<0.01
Weight, kg	27.6 (22.2–34.7)	33.0 (26.0–43.4)	44.0 (35.2–56.8)	53.2 (43.2–72.3)	<0.01
Body mass index, kg/m^2	14.2 (12.7–14.9)	16.6 (14.7–19.4)	21.1 (19.6–23.8)	25.1 (23.7–31.1)	<0.01
Body surface area, m^2	1.02 (0.88–1.20)	1.13 (0.97–1.36)	1.33 (1.14–1.58)	1.48 (1.27–1.81)	<0.01
Lean mass index, kg/m^2	10.6 (9.0–11.8)	11.8 (10.2–13.6)	12.8 (11.3–14.7)	13.8 (11.4–16.3)	<0.01
Lean mass, kg	20.8 (15.8–26.1)	23.4 (18.2–30.2)	26.4 (20.4–33.7)	29.2 (23.0–37.5)	<0.01
Fat mass index, kg/m^4	1.43 (1.01–2.40)	2.04 (1.20–3.46)	3.69 (2.40–5.19)	5.02 (3.51–6.97)	<0.01
Fat mass, kg	5.5 (3.6–8.3)	8.0 (4.7–13.9)	15.7 (10.2–22.5)	22.3 (15.5–34.5)	<0.01
Visceral adipose tissue index, g/m^3	0.09 (0.05–0.17)	0.12 (0.06–0.25)	0.21 (0.09–0.40)	0.26 (0.12–0.53)	<0.01
Visceral adipose tissue, g	244 (133–496)	337 (162–696)	600 (266–1206)	853 (357–1648)	<0.01
Systolic blood pressure, mm Hg	99.1 (7.2)	102.4 (7.4)	107.3 (7.7)	112.3 (8.9)	<0.01
Diastolic blood pressure, mm Hg	57.4 (6.3)	58.5 (6.3)	59.4 (6.2)	61.5 (7.6)	<0.01
Right ventricular end-diastolic volume, mL	87.9 (15.7)	98.7 (18.5)	110.0 (21.3)	114.5 (19.8)	<0.01
Right ejection fraction, %	58.6 (5.2)	58.3 (4.9)	57.5 (4.7)	57.6 (4.4)	<0.01
Left ventricular end-diastolic volume, mL	88.3 (14.0)	99.2 (16.5)	109.3 (19.3)	115.1 (18.7)	<0.01
Left ventricular ejection fraction, %	58.6 (4.6)	58.4 (4.6)	58.4 (4.6)	58.3 (4.7)	0.97
Left ventricular mass, g	42.5 (9.1)	48.2 (9.8)	54.3 (9.9)	59.0 (11.0)	<0.01
Left ventricular mass-to-volume ratio	0.48 (0.08)	0.49 (0.08)	0.50 (0.08)	0.52 (0.08)	<0.01
Left ventricular stroke volume, mL	51.6 (9.2)	57.9 (10.2)	63.9 (11.8)	67.0 (11.3)	<0.01
Cardiac output, mL/min	3.8 (0.8)	4.2 (0.9)	4.7 (1.0)	5.0 (1.0)	<0.01
Heart rate, bpm	74 (13)	73 (13)	74 (12)	75 (12)	0.17
Systemic vascular resistance, mm Hg/min/mL	19.6 (4.0)	18.2 (3.9)	16.9 (4.3)	16.3 (3.7)	<0.01

Data expressed as mean (standard deviation), median (95% CI), or number (%), on the basis of original, nonimputed data.
*Derived from analysis of variance, Mann–Whitney *U* test, or chi-square test.

(Table 1). Also, cardiac volume, mass, mass-to-volume ratio, and stroke volume were highest in obese children. RVEF was lower in overweight and obese children, but no difference was observed for LVEF. Systemic vascular resistance was lowest in obese children.

General and Abdominal Body Fat Distribution and Cardiac Measures

BMI was positively associated with RVEDV, LVEDV, and LVM, with the strongest association between BMI and LVEDV (a 1-SD increase in BMI was associated with 0.41 SDS [95% CI, 0.38–0.44] higher LVEDV) (Table 2). The strength of the association of BMI with LMVR was smaller (difference: 0.07 SDS [95% CI, 0.04–0.11] per increase of 1 SD in BMI). BMI was inversely associated with systemic vascular resistance (difference: −0.20 SDS [95% CI, −0.24 to −0.17]). The associations of lean mass index with all cardiac measures were stronger than those for BMI, and the strongest associations were with LVEDV (difference: 0.51 SDS [95% CI, 0.48–0.54]). Fat mass index and visceral adipose tissue index were also positively associated with RVEDV, LVEDV, LVM, and LMVR, and inversely associated with systemic vascular resistance. Most associations attenuated only slightly after adjustment for blood pressure (Table S2). Associations with RVEF, LVEF, and stroke volume are shown in Table S3. Children with obesity had a 1.12-SDS (95% CI, 0.94–1.30) higher LVM and a 0.35-SDS (95% CI, 0.14–0.57) higher LVMR than normal-weight children (Table S4).

Body Fat Distribution and Cardiac Measures

The associations of general and abdominal body fat mass measures with cardiac measures independent

Table 2. Associations of General and Abdominal Body Fat Mass Measures With Cardiac Measures (N=2836)

Body fat mass measure in SDS	Cardiac Measures in SDS				
	Right Ventricular End-Diastolic Volume	Left Ventricular End-Diastolic Volume	Left Ventricular Mass	Left Ventricular Mass-to-Volume Ratio	Systemic Vascular Resistance
Body mass index	0.39 (0.36–0.42)*	0.41 (0.38– 0.44)*	0.39 (0.36– 0.42)*	0.07 (0.04–0.11)*	−0.20 (−0.24 to −0.17)*
Lean mass index	0.50 (0.47–0.53)*	0.51 (0.48– 0.54)*	0.47 (0.44–0.52)*	0.06 (0.02–0.10)*	−0.24 (−0.27 to −0.20)*
Fat mass index	0.15 (0.11–0.19)*	0.17 (0.13–0.20)*	0.19 (0.15–0.23)*	0.07 (0.03–0.11)*	−0.09 (−0.13 to −0.05)*
Visceral adipose tissue index	0.09 (0.05–0.12)*	0.09 (0.06–0.13)*	0.12 (0.09–0.16)*	0.09 (0.06–0.13)*	−0.07 (−0.11 to −0.03)*

Data expressed as linear regression coefficients (95% CI). The estimates represent differences in SDS of the cardiac measures per SDS of childhood general and abdominal body fat measure (determinants). Models are adjusted for child age, sex, ethnicity, and time difference between measurement of body fat mass measures and cardiac magnetic resonance imaging. Models also adjusted for blood pressure are shown in Table S2. SDS indicates standard deviation score.
*$P<0.01$.

of BMI are shown in Figure. Children who had a higher lean mass index had larger RVEDV and LVEDV (all $P<0.05$; FigurA), whereas those who had a higher fat mass index or visceral adipose tissue index had smaller RVEDV and LVEDV (all $P<0.05$). Similar results were observed for LVM (FigurB), but no associations were observed with LMVR (FigurB). Children with higher lean mass index had lower systemic vascular resistance, independent of BMI, whereas higher fat mass index or visceral adipose tissue index was associated with higher systemic vascular resistance (FigurC). Higher lean mass index was associated with lower RVEF and LVEF, whereas higher fat mass index and visceral adipose tissue index were associated with higher RVEF and LVEF (all $P<0.05$; Figure S3).

DISCUSSION

In this population-based cohort study, we observed that overweight and obesity were associated with left and right cardiac measures. General and abdominal fat mass were across their full spectrum associated with higher RVEDV, LVEDV, LVM, and LMVR, and with lower systemic vascular resistance. Obese children have higher LVM and LMVR. The association of higher BMI with larger cardiac measures seems to be driven mainly by the increase in lean mass index.

Interpretation of Main Results

Studies in adults on the associations of adiposity with cardiac structure and function showed that obesity is associated with higher RVEDV, LVEDV, and LVM.[23,24] Obesity or BMI cannot distinguish between lean and adipose body mass, which are both increased in overweight and obese subjects.[25,26] The exact mechanisms that could explain the associations between obesity and cardiac disease remain unclear. An major role seems to be reserved for the cardiometabolic changes associated with obesity and visceral adipose tissue.[27] In adults, abdominal fat mass is associated with cardiovascular disease.[28] Visceral adiposity, but not subcutaneous adiposity, was found to be associated with LVM and LMVR, independent of weight.[27] Another study showed that adiposity of the hip region was associated with eccentric remodeling of the left ventricle, and visceral adiposity was associated with concentric remodeling.[8] Thus far, it remains unclear by which mechanisms general and abdominal fat mass affect cardiac structure and function in childhood.

In this cross-sectional study we have examined the associations of childhood general and abdominal fat mass with cardiac structure and function. We observed that all general and abdominal fat mass measures were associated with larger RVEDV, LVEDV, and LVM, independently of blood pressure. However, independently of BMI, only higher lean mass index was associated with an increase in RVEDV, LVEDV, and LVM, whereas higher fat mass index and visceral adiposity index were associated with lower RVEDV, LVEDV, and LVM. Our results are in line with previous studies suggesting that obesity was associated with increase in LVEDV and LVM in both adults and children.[29,30] One study suggested that lean body mass was the main determinant of LVM in childhood, not total body fat or blood pressure.[31] 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.[32] Thus, the higher RVEDV, LVEDV, and LVM that can be observed in children who are overweight are mainly determined by the increase in lean mass and not by higher fat mass or higher blood pressure.

Measures of concentric remodeling, in which the LMVR is increased, add information additional to left ventricular hypertrophy on prediction of cardiovascular events.[3,33] Concentric remodeling is often thought

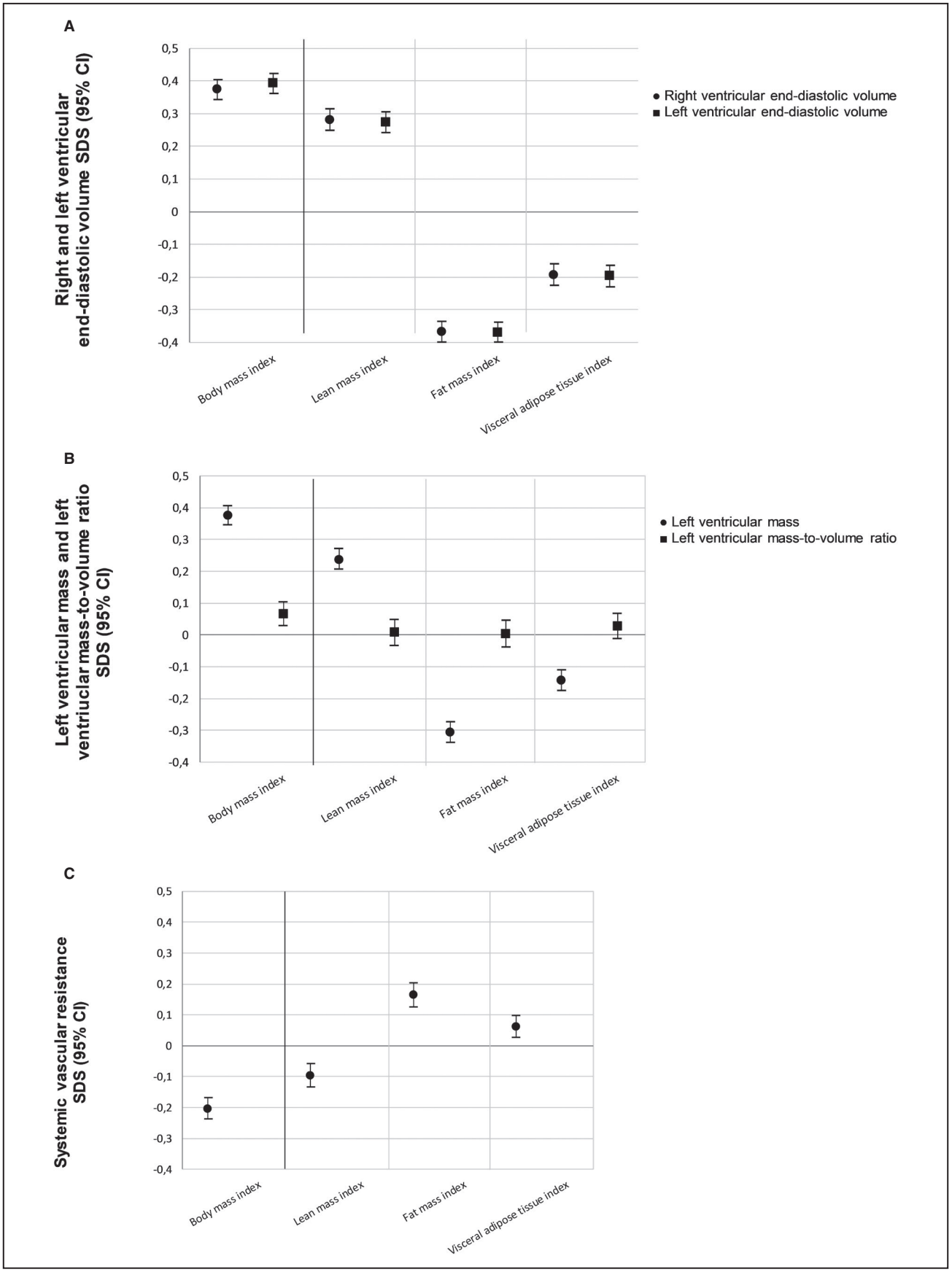
A
Right and left ventricular end-diastolic volume SDS (95% CI)
0,5
0,4
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
-0,4
Body mass index
Lean mass index
Fat mass index
Visceral adipose tissue index
Right ventricular end-diastolic volume
Left ventricular end-diastolic volume
B
Left ventricular mass and left ventriuclar mass-to-volume ratio SDS (95% CI)
Left ventricular mass
Left ventricular mass-to-volume ratio
C
Systemic vascular resistance SDS (95% CI)

Figure. Associations of general and abdominal body fat mass measures with cardiac measures, independent of body mass index.

A, Represents differences in right and left ventricular end-diastolic volume per standardized residual change of general or abdominal fat mass measure conditional on body mass index. **B**, Represents differences in left ventricular mass and left ventricular mass-to-volume ratio per standardized residual change of general or abdominal fat mass measure conditional on body mass index. **C**, Represents differences in systemic vascular resistance per standardized residual change of general or abdominal fat mass measure conditional on body mass index. SDS indicates standard deviation score. Values are expressed as standardized regression coefficients (95% CI) from conditional analyses with body mass index as exposure. The estimates represent the differences in cardiac measures per standardized residual change of general or abdominal fat mass measure conditional on body mass index. Models are adjusted for child age, sex, ethnicity, time difference between measurement of body composition and cardiac magnetic resonance imaging, and childhood systolic and diastolic blood pressure.

to be caused by pressure overload and increased wall stress, as observed in individuals with hypertension.[34] However, obese individuals have concentric remodeling, independent of blood pressure.[35] Concentric remodeling has also been observed in obese children.[36] Abdominal adiposity may play a major mechanistic role. A previous study showed that, although increased hip fat in adults was associated with eccentric remodeling, more abdominal fat was associated with concentric remodeling.[8] That study also showed that increased hip fat was associated with lower systemic vascular resistance, whereas abdominal fat was associated with relatively higher systemic vascular resistance.[8] These varied hemodynamic findings may relate to differences in arterial compliance; central obesity is associated with higher arterial stiffness, whereas hip fat is associated with lower arterial stiffness.[8] We also observed lower systemic vascular resistance with increasing BMI, and that both fat mass index and visceral adipose tissue index were associated with relatively higher systemic vascular resistance. However, neither fat mass index nor visceral adipose tissue index was associated with increased LMVR, independently of BMI. When combined, these observations could indicate that hemodynamic changes related to total fat increase afterload and may lead to remodeling later in life. Other mechanisms leading from increased visceral adipose tissue to concentric remodeling may play a role. Visceral adiposity can elicit endocrine and immune responses that affect cardiovascular structure and function directly and through worsening of other cardiovascular and metabolic risk factors.[24] A study in adults showed that LMVR was not only associated with abdominal adiposity, but also with insulin resistance and biomarkers of inflammation, independent of BMI.[37] Because we did not yet observe an independent association of visceral adipose tissue index with LMVR, it is possible that these changes take place after longer exposure to adverse abdominal fat deposition.

Obesity is not only associated with cardiac structure, but also with function. Studies in adults and children showed changes in strain in obese individuals, indicating subclinical damage, but no changes in RVEF or LVEF were observed.[29,38] In line with these studies, we observed no associations between BMI and LVEF. However, we did observe that BMI was associated with lower RVEF. One other study has reported a relation between childhood body size and lower RVEF.[39] A study in adults showed that increased visceral adipose tissue index was associated with lower LVEF.[27] In obese adults, especially when sleep apnea is present, the right cardiac function can be affected.[4] However, we consider it as unlikely that sleep apnea or pulmonary hypertension could have been a factor in our study with relatively healthy 10-year-old children. The associations and mechanisms connecting obesity and visceral adiposity with RVEF and LVEF require further study.

In our study, childhood body composition was associated with small changes in cardiac structure. In adults, cardiac hypertrophy and concentric remodeling are associated with increased cardiovascular disease and mortality.[33] It remains unclear how childhood cardiac structure relates to adult cardiac structure. However, previous research has suggested that childhood body size is associated with adult cardiac structure, independent of adult body size.[2] Also, cardiac structure has been shown to track from childhood to adulthood.[40] These findings suggest that body composition across the full spectrum in childhood is associated with cardiac adaptations and subsequently predispose an individual for later cardiovascular disease. More research is needed to disentangle the mechanisms linking childhood body composition with adult cardiac structure and cardiovascular disease. To disentangle physiologic from pathologic remodeling in childhood, there may be a role for other imaging techniques, such as 3-dimensional imaging of the ventricles or strain imaging. Strain imaging could provide more information on cardiac function and hold prognostic information.[41] Three-dimensional imaging could give better insight into cardiac remodeling patterns.[42] Because weight loss in adults can have beneficial effects on cardiac structure, the adverse changes in childhood cardiac structure and geometry could also be reversible.[43] It is important to better understand the mechanisms behind the associations between obesity,

body composition, and cardiac remodeling, and how this progresses from early life onward. This could eventually help to reduce the burden of cardiovascular disease in future generations.

Methodological Considerations

The main strengths of this study are its population-based design and the large number of body composition measurements and cardiac imaging available. Using dual-energy X-ray absorptiometry, MRI, and cMRI, we were able to study the associations of specific body composition measures on both the right and the left ventricle, but there some limitations. Not all children participating in our studies had successful cMRIs. Poor-quality cardiac MRI scans were often caused by logistical or participant constraints. This could lead to bias if obesity is related to the success rate of cMRI. We did not observe any association of BMI with success rate of cMRI in our nonresponse analyses (results not shown). In our study, BMI and dual-energy X-ray absorptiometry measurements were performed at a different timepoint than the MRI scans. However, the majority of children (65%) had the 2 visits within 2 months, when there was more time between the measurements, so the body composition at the time of the cMRI may have changed. We adjusted our analyses for the time difference, so this measurement error could have led to some attenuation of the effect estimates. In our population, 17.5% of the children were overweight or obese, as compared with 75.8% of the normal-weight children. This relatively lower number could have favored associations within the normal-weight category; however, we did not observe an interaction between our determinants and outcomes and the weight categories. Although we adjusted for some confounders, residual confounding may be of concern, as with any observational study. We did not have information on physical activity and fitness, or on diet, and thus these factors could have influenced the associations observed.

CONCLUSIONS

Higher childhood BMI is associated with both larger right and left ventricular sizes. Our findings suggest that these associations are mainly influenced by higher lean mass. In childhood, lean mass may be a stronger determinant of heart growth than fat mass.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

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Supplemental Material

Data S1.

Supplemental Methods

Magnetic Resonance Imaging

Abdominal adiposity Magnetic Resonance Imaging

MRI scanning was performed on a wide-bore GE Discovery MR 750 3T scanner (General Electric, Milwaukee, MI, USA). Briefly, children were introduced with the scanning environment through the use of a simulated scanning session. Three abdominal fat scans were acquired. A fat scan centered at the liver was performed using an axial volume and a proton-density weighted 3-point DIXON technique (IDEAL IQ). A second fat scan followed using an axial volume comprising the lower liver, abdomen and part of the upper pelvis using a proton density weighted 2-point DIXON acquisition (LavaFlex). Finally, a high resolution free-breathing coronally acquired scan centered at the head of the femurs was performed using a T1-weighted 2-point DIXON technique (LavaFlex). For both IDEAL IQ and LavaFlex measurements, water, fat, in-phase and out-of-phase 3D volumes were reconstructed. The obtained fat scans were analyzed by the Precision Image Analysis company (PIA, Kirkland, Washington, United States), using the sliceOmatic (TomoVision, Magog, Canada) software package. All extraneous structures and any image artifacts were removed manually.(16) Total visceral fat volumes ranged from the dome of the liver to the superior part of the femoral head. Fat masses were obtained by multiplying the total volumes by the specific gravity of adipose tissue, 0.9 g/ml. VAT index (VATI) uncorrelated with height was calculated as: $VAT/height^3$, confirmed by a log-log regression analysis.(15)

Figure S1. Flow chart of participants included in the analysis.

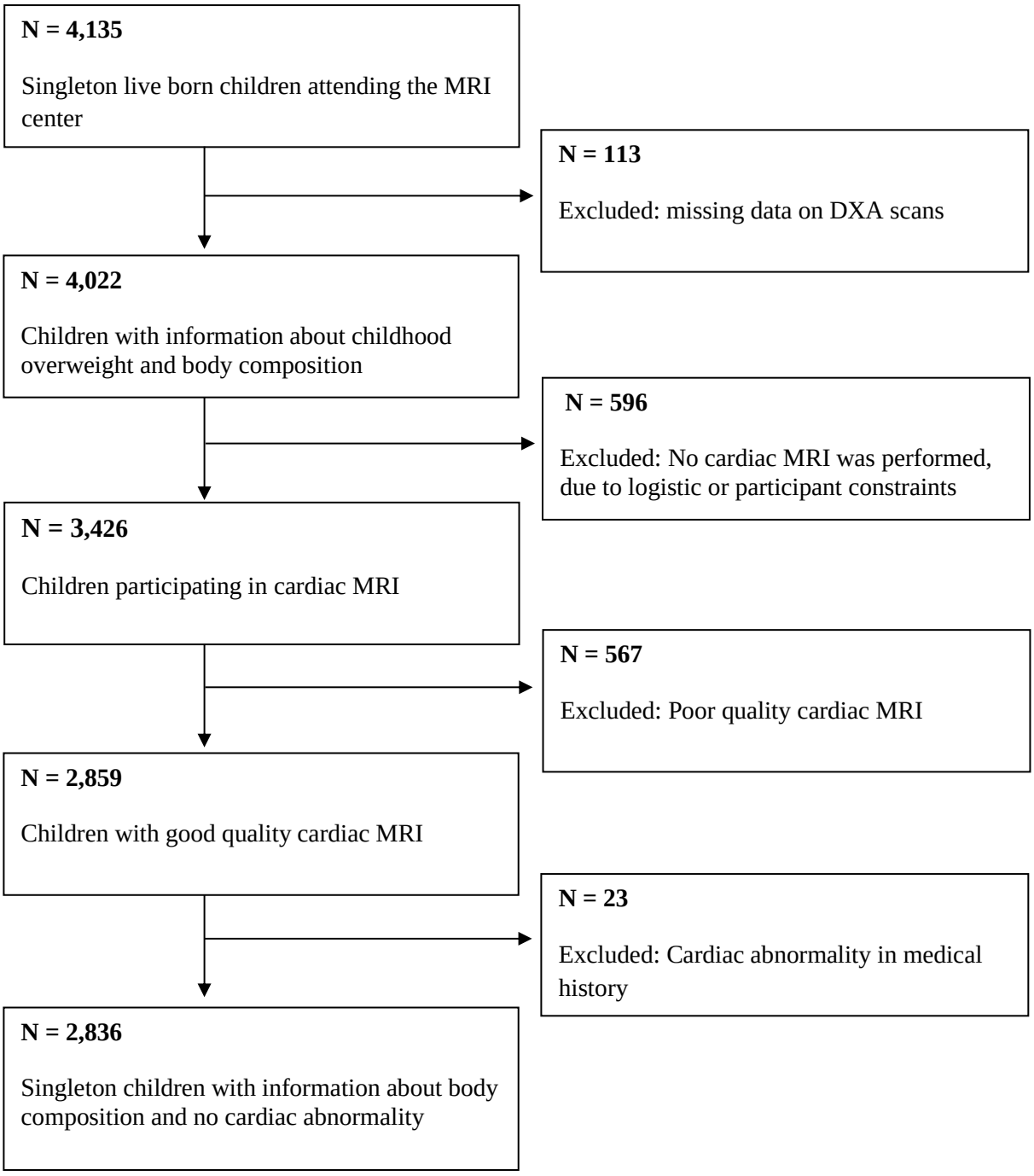
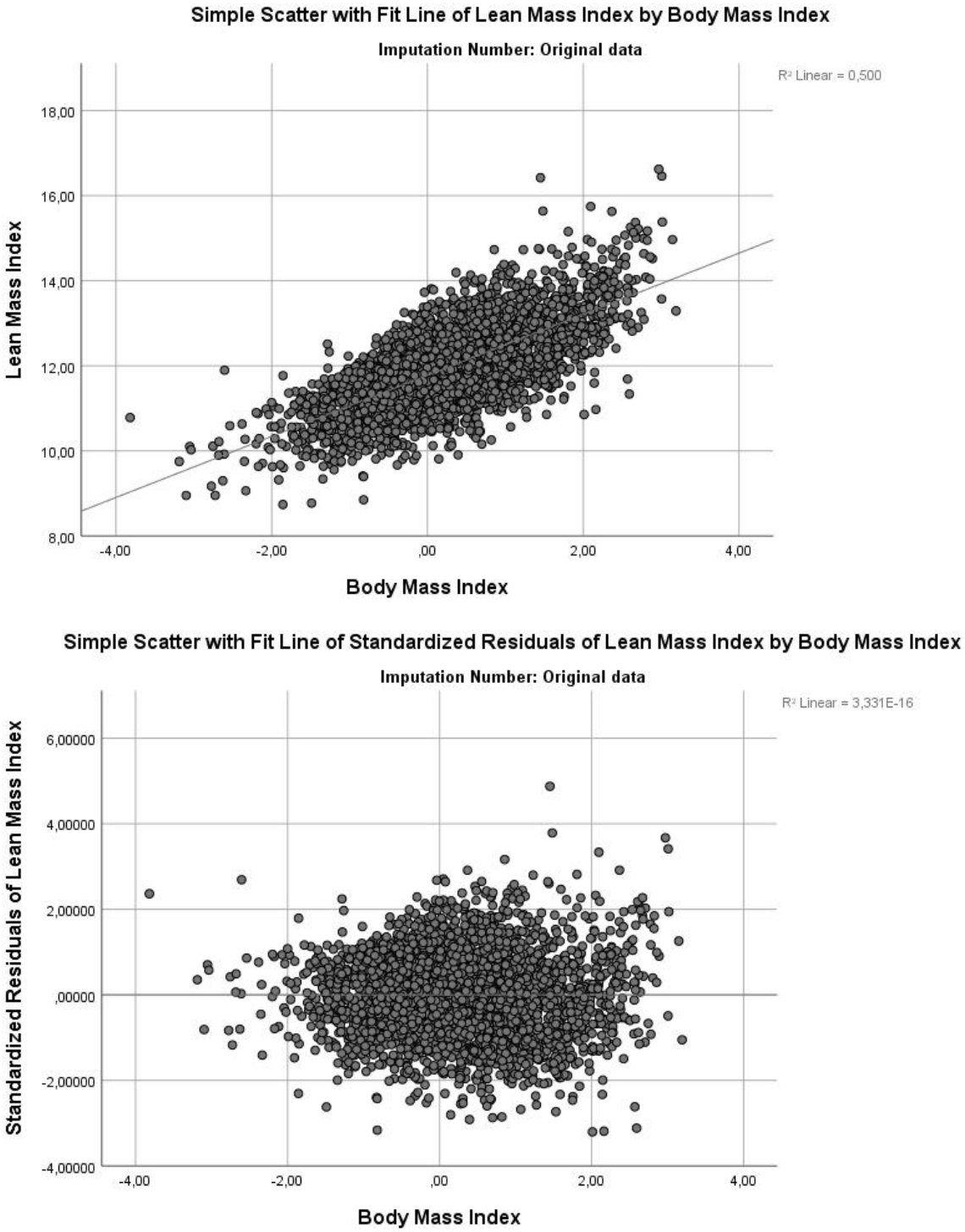
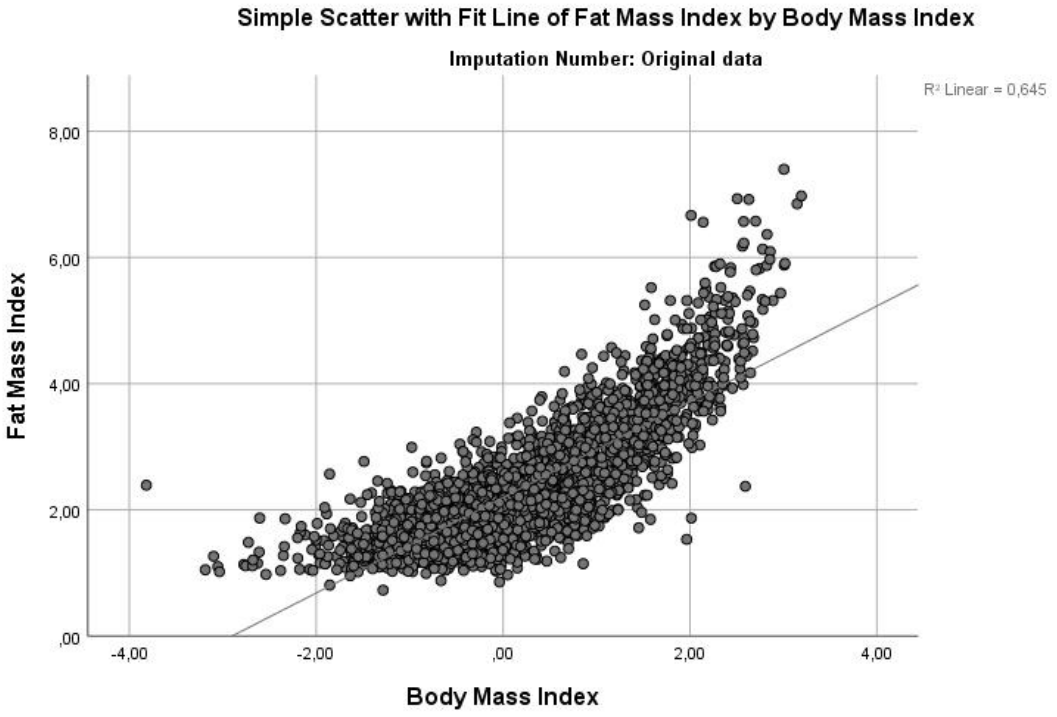


Figure S2. Simple scatter plots of BMI with body composition measures before and after residualization.




Simple Scatter with Fit Line of Fat Mass Index by Body Mass Index
Imputation Number: Original data
R² Linear = 0,645
Fat Mass Index
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4,00
2,00
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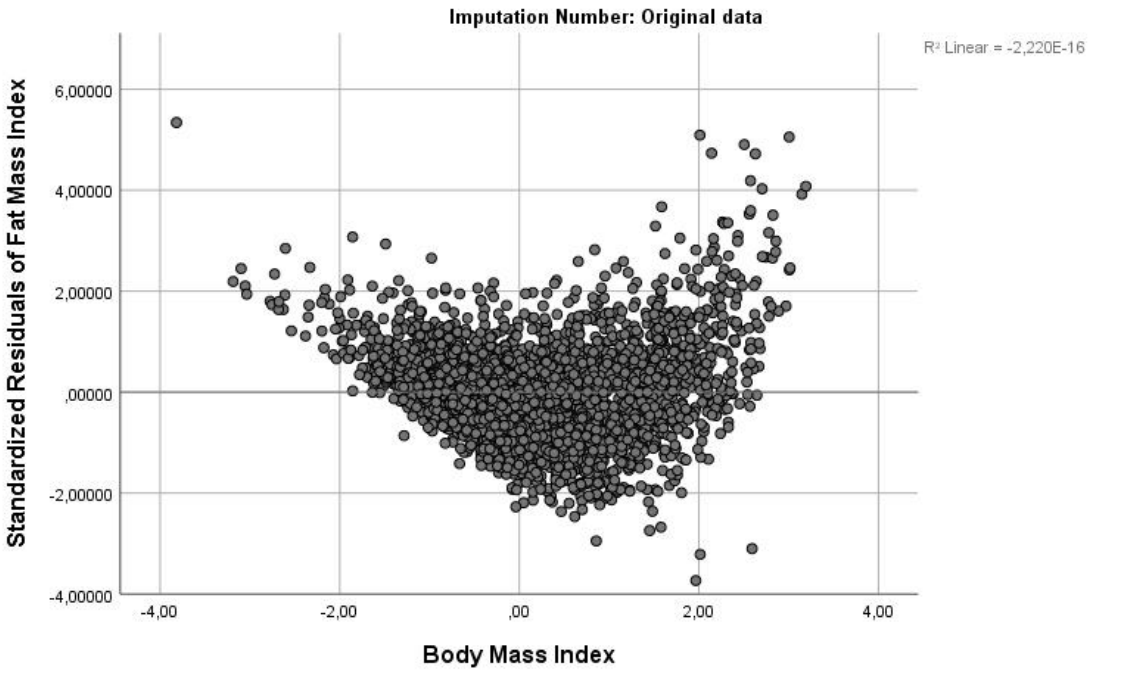
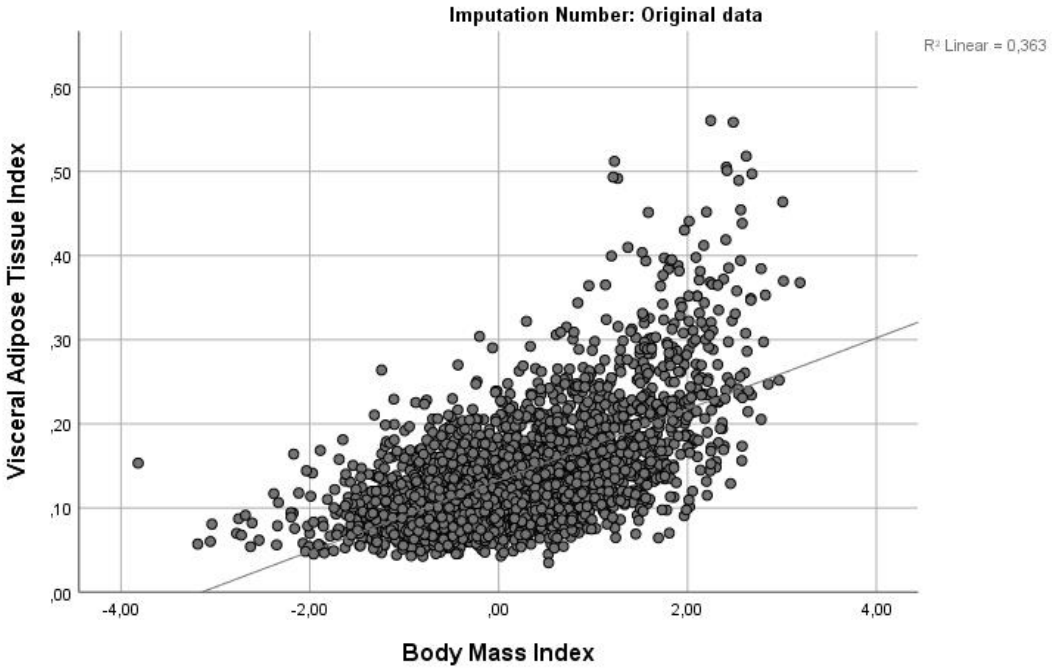
-4,00
-2,00
,00
2,00
4,00
Body Mass Index


Simple Scatter with Fit Line of Standardized Residuals of Fat Mass Index by Body Mass Index
Imputation Number: Original data
R² Linear = -2,220E-16
Standardized Residuals of Fat Mass Index
6,00000
4,00000
2,00000
,00000
-2,00000
-4,00000
-4,00
-2,00
,00
2,00
4,00
Body Mass Index

Simple Scatter with Fit Line of Visceral Adipose Tissue Index by Body Mass Index



Simple Scatter with Fit Line of Standardized Residuals of Visceral Adipose Tissue Index by Body Mass Index

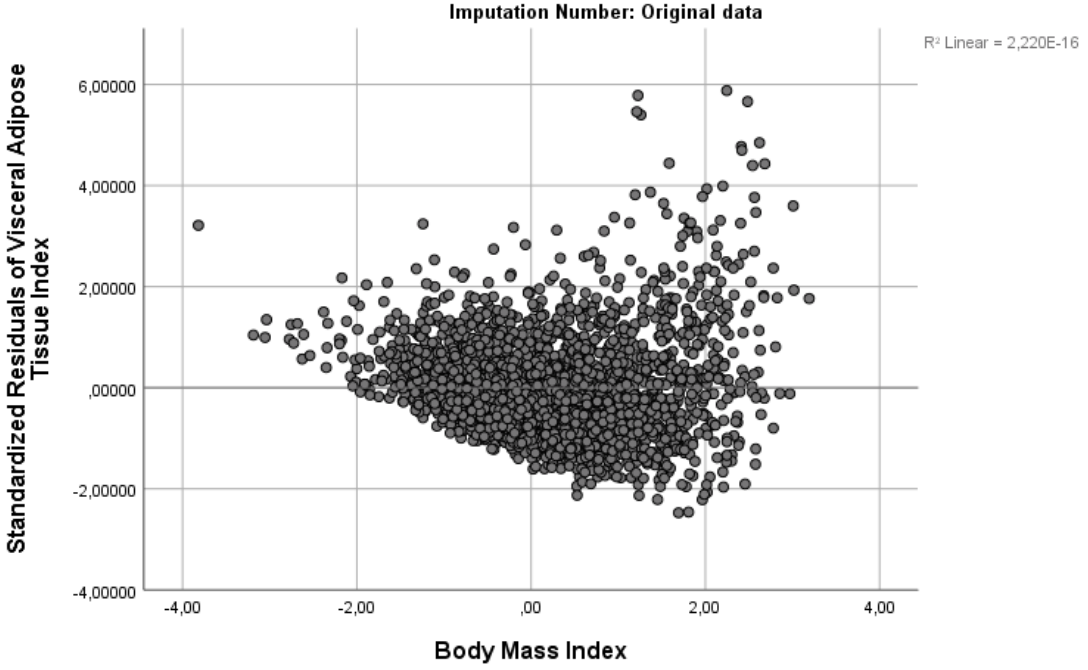
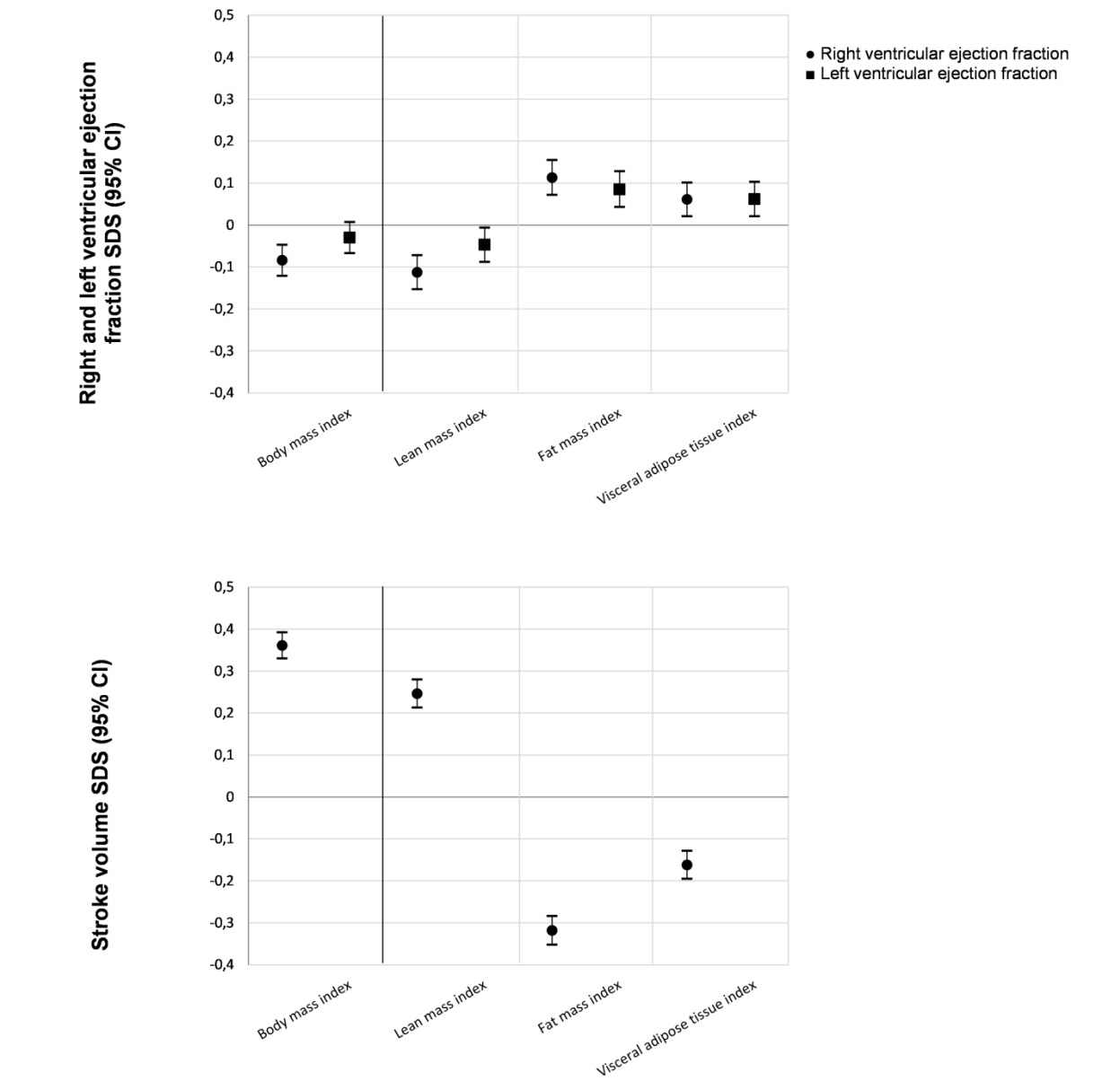


Figure S3. Associations of body mass index, and body composition and abdominal fat mass measures independent of body mass index, with cardiac function measures.



SDS, standard deviation score; CI, confidence interval; Values are standardized regression coefficients (95% CI) from conditional analyses. The estimates represent the differences in cardiac measures per standardized residual change of body composition or abdominal adiposity measure, conditional on body mass index. Models are adjusted for child age; sex; ethnicity; time difference between measurement of body composition and cMRI; and childhood systolic and diastolic blood pressure.

Table S1. Correlation coefficients between general and abdominal body fat mass measures.

	Height	Weight	Body mass index	Lean body mass index	Fat mass index index	Visceral adipose tissue index
Height	NA					
Weight	0.671**	NA				
Body mass index	0.215**	0.861**	NA			
Lean body mass index	0.195**	0.634**	0.707**	NA		
Fat mass index index	-0.042*	0.607**	0.803**	0.291**	NA	
Visceral adipose tissue index	-0.043*	0.452**	0.602**	0.230**	0.730**	NA

Values are Pearson correlation coefficients.

*P-value <0.05; **P-value <0.01.

Table S2. Associations of general and abdominal body fat mass measures with cardiac measures, blood pressure model (N=2,836).

	Cardiac measures in SDS				
Body fat mass measures in SDS	**Right ventricular end-diastolic volume**	**Left ventricular end-diastolic volume**	**Left ventricular mass**	**Left ventricular mass-to-volume ratio**	**Systemic vascular resistance**
Body mass index	0.37 (0.34, 0.40)**	0.39 (0.36, 0.42)**	0.38 (0.35, 0.41)**	0.07 (0.03, 0.10)**	-0.20 (-0.24, -0.17)**
Lean mass index	0.48 (0.45, 0.51)**	0.49 (0.46, 0.52)**	0.45 (0.42, 0.48)**	0.06 (0.02, 0.10)**	-0.22 (-0.26, -0.19)**
Fat mass index	0.15 (0.11, 0.18)**	0.16 (0.13, 0.21)**	0.18 (0.15, 0.22)**	0.06 (0.02, 0.10)**	-0.10 (-0.14, -0.06)**
Visceral adipose tissue index	0.08 (0.04, 0.11)**	0.08 (0.05, 0.12)**	0.11 (0.07, 0.14)**	0.05 (0.02, 0.09)**	-0.08 (-0.12, -0.04)**

N, number; SDS, standard deviation scores;

Values are linear regression coefficients (95% confidence interval). The estimates represent differences in cardiac measures per SDS of childhood general and abdominal body fat mass measure (determinants). Models are adjusted for child age; sex; ethnicity; time difference between measurement of body fat mass measures and cMRI; and childhood systolic and diastolic blood pressure.

* $p<0.05$; ** $p<0.01$.

Table S3. Associations of general and abdominal body fat mass measures with cardiac function measures (N=2,836).

	Cardiac measures in SDS			Cardiac measures in SDS blood pressure model		
Body fat mass measures in SDS	**Right ventricular ejection fraction**	**Left ventricular ejection fraction**	**Stroke volume**	**Right ventricular ejection fraction[a]**	**Left ventricular ejection fraction[a]**	**Stroke volume[a]**
Body mass index	-0.08 (-0.12, -0.05)**	-0.02 (-0.06, 0.01)	0.38(0.35, 0.41) **	-0.08 (-0.12, -0.05)**	-0.03 (-0.07, 0.01)	0.36 (0.33, 0.39) **
Lean mass index	-0.14 (-0.18, -0.10)**	-0.04 (-0.08, -0.01)*	0.47 (0.44, 0.50) **	-0.14 (-0.18, -0.10)**	-0.06 (-0.10, -0.02)**	0.45 (0.41, 0.48) **
Fat mass index	-0.02 (-0.06, 0.02)	0.02 (-0.02, 0.06)	0.16 (0.13, 0.20) **	-0.02 (-0.06, 0.02)	0.02 (-0.02, 0.06)	0.16 (0.13, 0.20) **
Visceral adipose tissue index	-0.05 (-0.08, -0.01)*	-0.01 (-0.05, 0.03)	0.10 (0.07, 0.14) **	0.00 (-0.04, 0.04)	0.03 (-0.01, 0.07)	0.09 (0.06, 0.13) **

N, number; SDS, standard deviation scores;

Values are linear regression coefficients (95% confidence interval). The estimates represent differences in SDS of the cardiac measures per SDS of childhood general and abdominal body fat mass measure (determinants). Models are adjusted for child age; sex; ethnicity; and time difference between measurement of body fat mass measures and cMRI.

[a] Models additionally adjusted for systolic and diastolic blood pressure.

* $p<0.05$; ** $p<0.01$

Table S4. Associations of childhood overweight with left ventricular mass and mass-to-volume ratio (N=2,836).

		Cardiac measures in SDS	
		Left ventricular mass	**Left ventricular mass-to-volume ratio**
Weight status	**N**		
Underweight	189	-0.54 (-0.67, -0.42)**	-0.06 (-0.20, 0.09)
Normal weight	2149	*Reference*	*Reference*
Overweight	412	0.64 (0.55, 0.73)**	0.15 (0.04, 0.26)**
Obesity	86	1.12 (0.94, 1.30)**	0.35 (0.14, 0.57)**

N, number; SDS, standard deviation scores;

Values are linear regression coefficients (95% confidence interval). The estimates represent differences in SDS of the cardiac measures compared to the reference category (normal weight). Models are adjusted for child age; sex; ethnicity; time difference between measurement of body fat mass measures and cMRI; systolic and diastolic blood pressure.

* $p<0.05$; ** $p<0.01$