Changes in Body Size Phenotypes From Childhood to Adulthood and the Associated Cardiometabolic Outcomes, a Prospective Cohort Study

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Abstract

Background: Cardiometabolic outcomes associated with changes between body size phenotypes (defined by body mass index [BMI] together with metabolic status) over time have attracted attention recently. It remains unclear how metabolic health change from childhood to adulthood across different BMI categories and how such dynamic changes from childhood to adulthood might affect risk of cardiometabolic outcomes in adulthood. Therefore, we aimed to examine the effects of changes in body size phenotypes between childhood and adulthood on risks of diabetes and left ventricular hypertrophy (LVH) in adulthood.

Methods: We included 3,351 individuals who participated as both children and adults in the Bogalusa Heart Study. The mean follow-up period was 36 years. Body size phenotypes for both children and adults were defined by harmonized criteria.

Results: Compared with participants with persistently metabolically healthy normal weight (MHNW) from childhood to adulthood, MHNW children who became metabolically unhealthy in adulthood had increased diabetes burden and LVH risk in adulthood; Metabolically unhealthy normal weight (MUNW) children who became MHNW or metabolically healthy obese (MHO) as adults and individuals with persistent MHO from childhood to adulthood were not at increased risks of diabetes or LVH. The risks were increased if MHO during childhood transitioned to metabolically unhealthy obesity (MUO) by adulthood or MUO stayed from childhood to adulthood. MUO children who became MHO or MHNW as adults had decreased diabetes burden and LVH risk in adulthood.

Conclusions: Individuals maintained MHO from childhood to adulthood and MUNW children who became MHO as adults had a diabetes burden and LVH risk similar to individuals with persistent MHNW. Progression to metabolically unhealthy status and maintenance of metabolically unhealthy status, regardless of childhood BMI status, were associated with increased cardiometabolic outcomes.

Background

Over the past several decades, childhood obesity, an established risk factor for diabetes and cardiovascular disease (CVD) [1, 2], has increased dramatically and become a worldwide epidemic [3]. Forecasts suggest that this obesity epidemic may reverse the current welcome trend of declining rates of CVD mortality. Given that the potential increasing demand for weight management care may exceed the supply of health care services, it begs the question of whether stratifying obese individuals based on their metabolic health status could prioritize allocation of clinical resources for those most at risk of poor cardiometabolic outcomes. Hereto, the concept of metabolically healthy obesity (MHO), which is characterized by possessing none of the traditional metabolic disorders despite being obese, has been proposed for both children and adults [4, 5].

Larger studies, including meta-analyses, reported that MHO was associated with a risk of diabetes and CVD intermediate between metabolically healthy normal weight (MHNW) and metabolically unhealthy

obesity (MUO) [6], which is characterized by metabolic disturbances as a consequence of obesity [4]. Recently, emerging evidence shows that MHO represents a temporally intermediate stage on the pathway to cardiometabolic risk, with 30–52% of MHO individuals transitioning to MUO phenotype during follow-up and then having higher odds of diabetes and CVD [7–10]. However, changes in metabolic health status over time and the associated risk of cardiometabolic outcomes have been conducted only in adult populations [7]. Since the developmental origins of health and disease hypothesis posits that exposures in early life, even in utero, are associated with risk of chronic diseases in adulthood and later life, a necessary extension of this work that has not previously been examined would be to assess how metabolic health change from childhood to adulthood across different BMI categories and how such dynamic changes from childhood to adulthood affect risk of cardiometabolic outcomes in adulthood.

Metabolic health profile is also relevant for individuals without obesity. Although the largest study showed that a normal body mass index (BMI) associates with the lowest all-cause mortality [11], a subset of normal-weight individuals have metabolic abnormalities, the so-called metabolically unhealthy normal weight (MUNW) phenotype, whose diabetes and CVD risk is similar to that recorded in MUO individuals [6]. The evolution of the MUNW from childhood to adulthood and the related cardiometabolic outcomes remain unclear.

Hence, we utilize data from the Bogalusa Heart Study (BHS), which initially involved children has followed participants into mid-life, to examine the associations of BMI categories and metabolic health status and their transition from childhood to adulthood with cardiometabolic outcomes in adulthood.

Methods

Study design and participants

The BHS is a series of long-term studies begun in 1973 focusing on understanding the early natural history of CVD since childhood [12]. Between 1973 and 2016, 9 cross-sectional surveys of children aged 3 to 18 years and 11 surveys of adults aged 19 to 58 years, who had been previously examined as children were conducted in the semirural biracial (65% white and 35% black) community of Bogalusa, Louisiana. This panel design of repeated cross-sectional examinations conducted approximately every 3 to 4 years, resulted in serial observations from childhood to adulthood. Participants who had a baseline examination during childhood and underwent a follow-up examination as an adult were included in the present analysis. Children with underweight (BMI < 5th percentile), diabetes, or having a follow-up period < 5 years were excluded. A total of 3,351 children (2,126 whites and 1,225 blacks; 46.6% male; age 4–18 years at baseline) who had been examined for BMI, systolic/diastolic blood pressure (BP), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) at least once in childhood (baseline) and at least once in adulthood (follow-up) were included in the analysis exploring the association of childhood obesity/metabolic phenotypes and shifts in obesity/metabolic phenotypes from childhood to adulthood with diabetes risk in adulthood. Among these participants, 1,639 adults (44.2% men; age 24–57 years at follow up) had echocardiography conducted to measure left ventricular

hypertrophy (LVH) and thus were included in the analysis exploring the association of shifts in obesity/metabolic phenotypes from childhood to adulthood with LVH risk in adulthood. There was no difference in the baseline characteristics between children who had and did not have adult echocardiography measurements (data not shown).

Written informed consent was obtained from parents or guardians in childhood and from the participants themselves in adulthood. Study protocols were approved by the Institutional Review Board of the Tulane University Health Sciences Center in accordance with the principles of the Declaration of Helsinki as revised in 2008.

Clinical measurements

All participants in each survey were asked to complete a structured questionnaire which collected information on demographics, parental history of diabetes, medical history and use of medications, and smoking and drinking habits.

Standardized protocols were followed by trained and certified personnel across all surveys. Participants were instructed to fast for 12 hours before the screening. For each participant, replicate measurements of height and weight were obtained, and the mean values were used for analysis. BMI was calculated as weight in kilograms divided by height in meters squared. BP was measured between 8:00 AM and 10:00 AM on the right arm with appropriate cuff in a relaxed sitting position by 2 trained technicians (triplicate each), using calibrated mercury sphygmomanometers. The 6 readings were averaged. For both children and adults, the first Korotkoff phase was used for systolic BP; The fifth Korotkoff (K5) phase was used for diastolic BP. Diastolic BP at the fourth Korotkoff (K4) phase was also recorded for all children. For children with the K5 being very low (< 20 mm Hg), the K4 was used as diastolic BP [13].

Biochemical laboratory measurements

Between 1973 and 1986, total cholesterol (TC) and TG were determined with Technicon Auto Analyzer II (Technicon Instrument Corp, Tarrytown, NY) according to the laboratory manual of the Lipid Research Clinics Program. From 1987, these variables were measured using an Abbott VP instrument (Abbott Laboratories, Abbott Park, Ill) by enzymatic procedures. Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention (CDC). Measurements on CDC-assigned quality control samples showed no consistent bias over time within or between surveys. Serum lipoprotein cholesterol were analyzed by using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures. Between 1978 and 1991, FPG was determined with a glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Since 1992, FPG has been measured enzymatically as part of a multi-chemistry profile.

Echocardiography

Left ventricular mass (LVM) was measured by 2-dimensional M-mode echocardiography with 2.25- and 3.5-MHz transducers following American Society of Echocardiography recommendations [14]. Parasternal long- and short-axis views were used for measuring LV end-diastolic and end-systolic measurements in duplicate, and the mean was calculated. LVM was calculated from a necropsy-validated formula on the basis of a thick-wall prolate ellipsoidal geometry [15]. The index of LVM to height^{2.7} (g/m^{2.7}) (LVMI) was used to adjust for body size.

Classification of adiposity and metabolic status in childhood and adulthood

For the definition of childhood weight status, BMI percentile for age and sex was calculated according to CDC reference charts. Children with BMI $\geq$ 85th but $<$ 95th percentile were classified as overweight, and those $\geq$ 95th percentile as obese. Weight status in children were also defined using the BMI cut off points recommended by the World Health Organization (WHO). In adulthood, overweight was defined as BMI between 25 and 29.9 kg/m² and obesity as BMI $\geq$ 30 kg/m².

In the consensus criteria suggested by Damanhoury et al. [5], childhood metabolic status (metabolically healthy, no risk factor, and metabolically unhealthy, one or more risk factors) was based on the following four cardiovascular risk factors: systolic/diastolic BP $\geq$ 90th percentile for sex, age, and height using the 2004 child BP Tables, TG $\geq$ 150 mg/dL, HDL-C $<$ 40 mg/dL, and FPG $\geq$ 100 mg/dL. In the harmonized definition suggested by Lavie et al.[4], adulthood metabolic status (metabolically healthy, no risk factor, and metabolically unhealthy, one or more risk factors) was based on the following four cardiovascular risk factors: systolic/diastolic BP $\geq$ 130/85 mmHg or using antihypertensive drugs, TG $\geq$ 150 mg/dL, HDL-C $<$ 40 mg/dL in men and $<$ 50 mg/dL in women, and FPG $\geq$ 100 mg/dL or using antidiabetic drugs.

According to their BMI and metabolic status, both children and adults were divided into four body size phenotypes according to harmonized definitions [4, 5]: MHNW defined as normal weight/overweight and healthy metabolic status, MUNW defined as normal weight/overweight and unhealthy metabolic status, MHO defined as obesity and healthy metabolic status, MAO defined as obesity and unhealthy metabolic status.

Definition of study outcomes

Diabetes in adulthood was defined based on FPG $\geq$ 7.0 mmol/L (126 mg/dL) or use of insulin or oral antidiabetic medications [16]. In a sensitivity analysis, diabetes was also defined based on FPG $\geq$ 7.0 mmol/L or HbA1c $\geq$ 6.5% (48mmol/mol) or use of insulin or oral antidiabetic medications [16]. LVH in adulthood was defined as LVMI $>$ 46.7 g/m^{2.7} in women and $>$ 49.2 g/m^{2.7} in men [17].

Statistical Analysis

All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). The differences in baseline and follow-up variables between groups were tested using generalized linear models (for continuous) and χ^2 or Fisher exact tests (for categorical). Bonferroni correction was applied

to adjust P values for multiple comparisons. Poisson regression with robust errors variance were used to examine the associations of childhood body size phenotypes with adult cardiometabolic outcomes. Four models were applied: Model 1 was unadjusted; Model 2 was adjusted for baseline age, sex, race, and follow-up year; Model 3 was further adjusted for baseline LDL-cholesterol; Model 4 was additionally adjusted for parental history of diabetes, smoking and drinking status, and use of anti-diabetic, anti-hypertensive and lipid-lowering agents. We chose these covariates because of their significant correlations with body size phenotypes or as relevant factors associated with outcomes. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by using logistic regression models to examine the associations between child-adult body size phenotypes and cardiometabolic outcomes in adulthood. Significance was accepted at a two-tailed $P < 0.05$.

Results

The baseline (childhood) and follow-up (adulthood) characteristics of the study population by childhood obesity and metabolic status are shown in Table 1.

Table 1

Baseline and follow-up characteristics of study participants according to baseline body size phenotypes

	MHNW	MUNW	MHO	MUO
N	1544	1375	141	291
Men (%)	45.2	47.4	41.8	51.9
Whites (%)	61.9	66.5 [†]	53.9	61.9
Childhood				
Age (years)	9.78 ± 3.23 ^{*†‡}	9.33 ± 3.01 ^{†‡}	8.18 ± 2.83	8.67 ± 3.0
BMI (kg/m ²)	16.75 ± 2.58 ^{†‡}	16.80 ± 2.43 ^{†‡}	20.80 ± 4.94 [‡]	22.16 ± 4.80
SBP (mmHg)	97.54 ± 9.37 ^{*‡}	100.85 ± 10.87 [‡]	98.85 ± 8.74 [‡]	106.49 ± 11.02
DBP (mmHg)	50.84 ± 9.39 ^{*‡}	51.86 ± 9.83 [‡]	51.82 ± 7.5	53.50 ± 9.52
TC (mg/dl)	163.1 ± 27.75 ^{†‡}	162.83 ± 29.19 ^{†‡}	169.87 ± 28.48	169.08 ± 33.24
TG (mg/dl)	58.87 ± 21.14 ^{*‡}	72.2 ± 37.86 ^{†‡}	61.91 ± 24.59 [‡]	88.10 ± 53.96
LDL-C (mg/dl)	85.48 ± 21.57 ^{*†‡}	92.29 ± 24.19 [‡]	91.97 ± 24.29 [‡]	100.61 ± 31.13
HDL-C (mg/dl)	71.17 ± 17.71 ^{*‡}	61.58 ± 22.55 ^{†‡}	70.14 ± 18.06 [‡]	56.57 ± 23.63
FPG (mmol/l)	84.53 ± 8.63 ^{*‡}	88.68 ± 12.27 [†]	83.84 ± 8.02 [‡]	87.64 ± 10.04
Adulthood				
Age (years)	35.13 ± 11.83	36.10 ± 11.73 [†]	32.69 ± 11.06	35.76 ± 11.18
BMI (kg/m ²)	26.73 ± 6.32 ^{*†‡}	27.67 ± 6.3 ^{†‡}	37.09 ± 8.70	38.26 ± 8.19
SBP (mmHg)	115.72 ± 14.21 ^{*‡}	118.78 ± 14.83 [‡]	116.7 ± 14.01 [‡]	123.07 ± 16.67

Values are means (standard deviations) or percentages.

*P < 0.05 compared with MUNW;

† P < 0.05 compared with MHO;

‡ P < 0.05 compared with MUO.

BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.

	MHNW	MUNW	MHO	MUO
DBP (mmHg)	70.88 ± 11.5*‡	72.73 ± 11.98‡	72.54 ± 12.87‡	76.50 ± 12.76
TC (mg/dl)	183.09 ± 37.43	186.69 ± 39.71	182.45 ± 38.69	188.10 ± 40.86
TG (mg/dl)	103.96 ± 75.46*‡	130.39 ± 104.69‡	109.90 ± 71.21‡	151.64 ± 120.93
LDL-C (mg/dl)	112.51 ± 33.31*‡	116.30 ± 34.12	114.19 ± 36.21	118.99 ± 36.10
HDL-C (mg/dl)	53.23 ± 15.31*‡	48.54 ± 15.28‡	49.82 ± 14.44‡	44.11 ± 15.36
FPG (mmol/l)	90.62 ± 27.67*‡	93.48 ± 30.89‡	98.63 ± 38.53	105.18 ± 44.55
Values are means (standard deviations) or percentages.				
*P < 0.05 compared with MUNW;				
† P < 0.05 compared with MHO;				
‡ P < 0.05 compared with MUO.				
BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.				

At baseline, of the 3,351 children free of existing diabetes and not underweight, 141 (4.2%), 1,375 (41%), and 291 (8.7%) children were MHO, MUNW, and MUO, respectively. Over a mean follow up of 26 years (range 5–43 years) there were 224 incident cases of diabetes. Over a mean follow up of 36 years (range 17 to 43 years) there were 185 incident cases of LVH. Longitudinal risks of diabetes and LVH by childhood body size phenotypes are presented in Table 2. For the outcome of diabetes in adulthood, relative risks were 1.51 (1.11–2.05) for MUNW children, 2.54 (1.52–4.25) for MHO children, and 3.54 (2.49–5.03) for MUO children, compared with MHNW children. Additional adjustment for age sex, race, and follow-up year (model 2) led to similar results. Results remained statistically significant even when further adjusted for baseline LDL-cholesterol (model 3), parental history of diabetes, drinking and smoking status, and BP-lowering and lipid-lowering medication use (model 4).

Table 2

Relative risks (RR) and 95% confidence intervals (CI) for adult diabetes and left ventricular hypertrophy according to childhood body size phenotypes

Outcome and childhood phenotype	Model 1	Model 2	Model 3	Model 4
Diabetes				
MHNW	1	1	1	1
MUNW	1.51 (1.11–2.05)	1.37 (1.01–1.84)	1.34 (1.00–1.81)	1.36 (1.01–1.85)
MHO	2.54 (1.52–4.25)	2.97 (1.81–4.16)	2.89 (1.77–4.72)	2.35 (1.42–3.89)
MUO	3.54 (2.49–5.03)	3.27 (2.30–4.63)	3.09 (2.17–4.39)	2.45 (1.70–3.54)
Left ventricular hypertrophy				
MHNW	1	1	1	1
MUNW	1.37 (1.08–1.72)	1.46 (1.16–1.83)	1.49 (1.18–1.87)	1.41 (1.13–1.78)
MHO	2.42 (1.66–3.52)	2.51 (1.74–3.62)	2.58 (1.79–3.70)	2.49 (1.72–3.63)
MUO	3.18 (2.48–4.07)	3.30 (2.60–4.19)	3.42 (2.69–4.34)	2.97 (2.32–3.81)
MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.				
Model 1 was unadjusted.				
Model 2 was adjusted for childhood age, sex, race, and follow-up year.				
Model 3 was adjusted for variables in model 2 plus baseline LDL-cholesterol.				
Model 4 was adjusted for variables in model 3 plus parental history of diabetes, smoking and drinking status, and use of anti-hypertensive and lipid-lowering agents.				

For the outcome of LVH in adulthood, compared to MHNW phenotype, all other childhood body size phenotypes were at significantly higher risks of developing LVH in all the 4 models (Table 2). The relative risk with 95% confidence interval of the development of LVH in adulthood for MUNW, MHO, and MUO children was 1.41 (1.13–1.78), 2.49 (1.72–3.63), and 2.97 (2.32–3.81), respectively, after adjusting for baseline age, sex, race, follow-up year, baseline LDL-cholesterol, parental history of diabetes, drinking and smoking status, and use of anti-diabetic, anti-hypertensive, and lipid-lowering agents (model 4).

Table 3 reports the evolution of body size phenotypes from childhood to adulthood. Substantial dynamic changes in body size phenotypes during the period from childhood to adulthood were observed, with

38.9% of the MHNW, 22% of MHO, 43.1% of MUNW, and 77% of MUO participants maintaining their baseline body size phenotypes. Of the 141 children with MHO phenotype, 31 (22%) became normal-weight/overweight as adults, 24 (77%) of whom were metabolically healthy, and 79 (56%) became MUO as adults. Of the 1,375 children with MUNW phenotype, 413 (30%) became obese as adults, 369 (89%) of whom were metabolically unhealthy, and 370 (27%) became MHNW as adults. Of note, within children who were metabolically healthy at baseline, the development of metabolically unhealthy conditions in adulthood was more frequent in obese (baseline MHO, 61%, n = 86) compared with normal-weight/overweight (baseline MHNW, 56%, n = 864) participants; 61% of those with MHNW in childhood became obese or metabolically unhealthy in adulthood.

Table 3
Changes in body size phenotypes from childhood to adulthood

Childhood	Adulthood			
	MHNW	MUNW	MHO	MUO
MHNW	600 (38.9)	528 (34.2)	80 (5.2)	336 (21.7)
MUNW	370 (26.9)	592 (43.1)	44 (3.2)	369 (26.8)
MHO	24 (17.0)	7 (5.0)	31 (22.0)	79 (56.0)
MUO	18 (6.2)	21 (7.2)	28 (9.6)	224 (77.0)
Values are numbers (percentages).				
MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.				

Given the transient nature of the body size phenotypes over time, we assessed incident outcomes associated with maintaining or changing body size phenotypes from childhood to adulthood. Incident diabetes according to childhood and adulthood body size phenotypes are displayed in Fig. 1. Compared with participants staying MHNW phenotype from childhood to adulthood, participants with MHNW phenotype in childhood who developed metabolic unhealthy conditions in adulthood (5.1% for MUNW and 12.5% for MUO) suffered an increased burden of incident diabetes (all $P < 0.05$). Incident diabetes was increased in the MUNW who remained stable (5.6%) or progressed to the MUO phenotype as adults (16.3%); in contrast, no diabetes burden among MUNW children who become MHNW or MHO as adults was noted. In the MHO who remained stable or improved (became MHNW as adults) from childhood through adulthood, no incident diabetes was noted, which was similar to those who were consistently MHNW phenotype from childhood to adulthood. In contrast, participants who had MHO phenotype in childhood but became MUO as adults bore the greatest burden of incident diabetes (20.3%), which was similar to that in participants maintaining MUO phenotype from childhood through adulthood (19.6%). The burden was reduced in MUO children who had improved body size phenotypes in adulthood.

With respect to the analysis of LVH outcome (1,639 subjects), the categorizing of participants on the basis of body size phenotypes in childhood and adulthood resulted in limited sample size in some subgroups (Table 4). Therefore, we collapsed some subgroups into a single group (Table 5). In the unadjusted model, compared with participants who had a consistently MHNW from childhood through adulthood, children who were initially MHNW but developed obesity or metabolically unhealthy conditions in adulthood had an increased risk of adult LVH (OR 2.88, 95% CI 1.46–5.66); MUNW children who remained or progressed to MHO/MUO in adulthood were at 4.17-fold risk for adult LVH; MHO children who remained (MHO) or improved (MHNW) through adulthood did not have an increased adult LVH risk (2.90, 0.72–11.7). In contrast, MHO children who developed metabolically unhealthy conditions in adulthood had over 10 times the risk of adult LVH (10.36, 4.38–24.48); the greatest LVH risk was noted in participants displaying a stable MUO phenotype from childhood through adulthood (14.05, 6.78–29.12); LVH risk was significantly decreased in MUO children who improved in adulthood (5.64, 6.78–29.12). Adjustment for other potential confounding variables did not eliminate the associations.

Table 4

Changes in body size phenotypes from childhood to adulthood among 1,639 participants who had echocardiography measurement in adulthood

Childhood	Adulthood			
	MHNW	MUNW	MHO	MUO
MHNW	155 (21.2)	279 (38.3)	50 (6.9)	245 (33.6)
MUNW	100 (14.5)	298 (43.1)	30 (4.3)	263 (38.1)
MHO	7 (10.6)	1 (1.5)	11 (16.7)	47 (71.2)
MUO	6 (3.9)	10 (6.5)	9 (5.9)	128 (83.7)
Values are numbers (percentages).				
MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.				

Table 5

Associations between shifts in body size phenotypes between childhood and adulthood and the risk of left ventricular hypertrophy in adulthood.

	Model 1	Model 2	Model 3	Model 4
Stable MHNW	1	1	1	1
Progressing MHNW	2.88 (1.46–5.66)	2.48 (1.25–4.93)	2.51 (1.26–4.98)	2.23 (1.12–4.44)
MUNW to MHNW	0.60 (0.18–1.98)	0.65 (0.20–2.14)	0.67 (0.20–2.22)	0.67 (0.20–2.23)
Stable MUNW or MUNW to MHO/MUO	4.17 (2.14–8.14)	4.04 (2.05–7.95)	4.21 (2.13–8.29)	3.55 (1.79–7.03)
Stable/improved MHO	2.90 (0.72–11.71)	3.04 (0.73–12.69)	3.23 (0.77–13.52)	3.21 (0.77–13.37)
MHO to MUNW/MUO	10.36 (4.38–24.48)	10.05 (4.16–24.32)	10.50 (4.34–25.41)	9.13 (3.75–22.23)
Improved MUO	5.64 (1.91–16.65)	6.14 (2.03–18.58)	6.08 (2.00–18.51)	5.35 (1.74–16.47)
Stable MUO	14.05 (6.78–29.12)	14.20 (6.76–29.84)	15.70 (7.42–33.21)	12.43 (5.81–26.56)
Values are odds ratios (95% confidence intervals) from logistic regression analyses.				
MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.				
Progression includes an increase in body mass index category and/or development of metabolic unhealth. Improvement includes a reduction in body mass index category and/or metabolic unhealth.				
Model 1 was unadjusted.				
Model 2 was adjusted for childhood age, sex, and race.				
Model 3 was adjusted for variables in model 2 plus baseline LDL-cholesterol.				
Model 4 was adjusted for variables in model 3 plus parental history of diabetes, smoking and drinking status, and use of anti-diabetic, anti-hypertensive, and lipid-lowering agents.				

Similar estimates were noted in analyses in which childhood weight status was assessed by WHO cut off points and diabetes were defined as having FPG ≥ 7.0 mmol/l or HbA1c $\geq 6.5\%$ (48mmol/mol) or use of insulin or oral antidiabetic medications (data not shown).

Discussion

This is, as far as we are aware, the first report to describe the association between shifts in body size phenotypes from childhood to adulthood and cardiometabolic outcomes in adulthood. We found that the

maintenance or development of metabolic disorders in adults, regardless of their childhood BMI status, conferred significantly increased diabetes burden and LVH risk in adulthood. However, maintenance of metabolic health from childhood to adulthood, regardless of childhood BMI status, and childhood MUNW phenotype having a resolution of metabolic disorder in adulthood were not at increased risks of diabetes or LVH. We also found that MUO children who had improved metabolic health, including MHO and MHNW, in adulthood had decreased risks of diabetes and LVH. Although we acknowledge that the observational nature of the current study precludes making clinical recommendations, the findings could have clinical relevance in that efforts to prevent persistence of childhood metabolic disorders into adulthood and the resolution of metabolic disorders in adulthood might translate to reductions in later cardiometabolic outcomes.

The MHO phenotype has sparked interest as a body size phenotype that can be used in risk stratification [18–20]. Evidence has indicated the prognostic value of MHO phenotype for later-life cardiometabolic disease and mortality [18–20]. Conflicting results have been observed regarding cardiovascular outcomes [18–20], and thus raise questions as to the clinical and public health relevance of MHO and challenge the conceptual definition of MHO. Efforts to understand the cardiometabolic consequences of MHO, seeking to end the controversy about MHO, are ongoing, but a fundamental question remains unanswered regarding risks of cardiometabolic outcomes resulting from longitudinal changes between body size phenotypes. Of the few studies that examined change in body size phenotypes over time, most focused on the transition from MHO to MUO or maintenance of the MHO phenotype and the associated cardiometabolic outcomes [7–10, 21]. Further, all of these studies were conducted in middle-aged/older persons or high-risk populations [7, 21]. Moreover, conflicting results regarding CVD risk impacts of maintenance of MHO were noted in these studies [7, 21]. To date, there has been little examination of the cardiometabolic consequences of all possible transitions of body size phenotypes from an initial state, including recovery from obesity and/or metabolically unhealthy conditions, weight gain and metabolic deterioration from a healthy state, or maintenance of the initial state, in a population who were followed from childhood into adulthood. Answering this particular research question is important because early-life exposure to obesity and/or metabolically unhealthy conditions may have a persistent impact on later-life body size phenotype and associated disease risk [22, 23].

We addressed this fundamental knowledge gap in the present study. We found that 22% of the MHO children retained the MHO phenotype as adults. The participants with persistent MHO from childhood to adulthood subsequently exhibited risks for diabetes and LVH similar to participants presenting a consistent MHNW phenotype from childhood to adulthood, thus supporting the concept of MHO. We also found that over one-half of the MHO children developed incident metabolic disorders in adulthood, highlighting the fluidity of MHO over time, which is in line with studies conducted in adults that reported about 30–52% of participants transitioning from MHO into MUO over 10–20 years of follow-up [7, 21, 24]. In the present study, when outcomes were assessed in relation only to baseline status, the MHO experienced elevated risks of developing diabetes and LVH in adulthood compared with MHNW subjects. The increased risks of diabetes and LVH were attributable to those who transitioned to MUO from initial MHO. These findings imply that only considering baseline metabolic health status in prospective studies

may mischaracterize the cardiometabolic risk as well as that MHO children might benefit from early intervention, such as improving diet quality and increasing physical activity, to prevent or delay incident metabolic disorders in the period between childhood and adulthood.

In the present study, participants with MUNW in childhood who improved to MHNW in adulthood had lower risks of diabetes and LVH than participants with a consistent MUNW phenotype. In addition, most MUO children remained MUO as adults and subsequently were at greatest risk of cardiometabolic outcomes. MUO children who improved to MHO or MHNW had a decreased diabetes burden and LVH risk. These findings indicate that a longer exposure to the metabolically unhealthy status is associated with higher disease risk. The diabetes burden and LVH risks among MUNW children who became MHNW in adulthood were not significantly different from those who had a consistent MHNW phenotype from childhood to adulthood, suggesting that MUNW children are not destined to have metabolic disorders in adulthood, and the effects of metabolic disorders in childhood on later-life cardiometabolic outcomes can be reversed if metabolically healthy status is achieved by adulthood. This finding is consistent with those from other studies demonstrating that disease risk is reduced if elevated cardiovascular risk factors during childhood resolve by adulthood [25, 26].

Of note, we found that MUNW children who became MHO as adults were not at increased risks of diabetes and LVH compared to those who maintained MHNW from childhood to adulthood. Mechanisms for this transition remain unknown. It is increasingly recognized that MUNW may have a lipodystrophy-like phenotype, characterized by impaired adipogenesis, insulin resistance, hypertriglyceridemia, and hepatic steatosis [27, 28]. According to the overflow hypothesis, adipose tissue acts as a reservoir of free fatty acids and prevents their overflow into insulin-sensitive tissues contributing to insulin resistance. Alterations in fatty acid trafficking leads to abnormalities in lipid storage and consequent ectopic fat deposition, promoting metabolic disorders and the resultant cardiometabolic outcomes [29]. Thus, expansion of adipose tissue may improve fatty acid trafficking and lower risk for cardiometabolic outcomes. Further studies to examine the potential mechanisms for the transition from MUNW to MHO are warranted.

The strengths of our study include a well-characterized cohort with carefully prospectively collected follow-up data from childhood to adulthood. In addition, this study used harmonized definitions to define MHO and MUO for both adults and children, which will facilitate direct comparisons between studies. Furthermore, this study is one of the first to investigate all possible transitions of body size phenotypes from childhood to adulthood and the associated cardiometabolic outcomes.

Limitations of the present study require careful consideration. First, a standard 75-g oral glucose tolerance test was not performed, which might result in an underestimation of the prevalence of diabetes. Second, major CVD events in adulthood, such as coronary heart disease and heart failure were not available in the data. Nevertheless, a subclinical outcome such as LVH is strongly predictive of later life major CVD events. Third, the sample is based in a semirural community of African and European ancestry; therefore, the results may not be generalizable to other groups not studied. Finally, this is an

observational study, although it represents our best evidence to date, the findings are subject to residual confounding, such as physical activity and cardiorespiratory fitness, and measurement error, as with all observational studies.

In summary, MHO children who maintained MHO in adulthood and MUNW children who became MHO as adults had a diabetes burden and LVH risk in adulthood similar to participants who maintained MHNW from childhood to adulthood. Progression to metabolically unhealthy status and maintenance of metabolically unhealthy status, regardless of childhood BMI status, were associated with increased diabetes burden and LVH risk. Together, data presented in this longitudinal observational study support encouraging children to maintain healthy habits, irrespective of their weight status. Distinguishing MHO from MUO can help to prioritize risk management and avoid a one-size-fits-all approach in managing obesity.

Abbreviations

CVD, cardiovascular disease; MHO, metabolically healthy obesity; MHNW, metabolically healthy normal weight; MUO, metabolically unhealthy obesity; BMI, body mass index; MUNW, metabolically unhealthy normal weight; BHS, Bogalusa Heart Study; BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; LVH, left ventricular hypertrophy; CDC, Centers for Disease Control; LVM, Left ventricular mass; WHO, World Health Organization.

Declarations

Authors' contributions

All authors were responsible for acquisition or interpretation of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. TTD. and LAB came up with the conception and design of the study, did the statistical analysis, were responsible for drafting of the manuscript. WC, and VF contributed to interpretation of results, commented on drafts, and approved the final version. LAB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability

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

Ethics approval and consent to participate

Study protocols were approved by the Institutional Review Board of the Tulane University Health Sciences. Written informed consent was obtained from parents or guardians in childhood and from the participants themselves in adulthood.

Consent for publication

Not applicable.

Conflict of interests

The authors declare no conflict of interests.

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Figures

Figure 1

Incident cases of diabetes in relation to changes in body size phenotypes between childhood and adulthood. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.