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Prevalence and predictors of metabolically healthy obesity in severely obese Asian children

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BACKGROUND: Obese individuals who have little or no metabolic syndrome components are proposed to be "metabolically healthy obese (MHO)". This study aim to evaluate the prevalence of MHO and examine the predictors associated with MHO in a multi-ethnic Asian cohort of severely obese children.

METHODS: This study included a cross-sectional cohort of 406 Chinese, Malay and Indian children aged 5–20 years old with BMI for age ≥ 97th percentile. Metabolic syndrome (MS) and metabolic health (MH) definitions based on the presence or absence of metabolic abnormalities (High triglycerides, low HDL cholesterol, elevated blood pressure and high glucose) were used to define MHO in the cohort.

RESULTS: The prevalence of MHO is 63.5% by MS definition and 22.4% by MH definition. Maternal healthy metabolic status (OR: 2.47), age (OR: 0.83, 0.80), paternal obesity (OR: 0.48, 0.53), Malay (OR: 1.97) and Indian ethnicity (OR: 6.38, 3.21) (compared to Chinese ethnicity) are independent predictors for MHO phenotype based on different MHO definitions.

CONCLUSIONS: Adiposity measures are not associated with MHO phenotype, but instead younger age, maternal healthy metabolic status, absence of paternal obesity, Malay and Indian ethnicity are independent predictors for MHO phenotype in a multi-ethnic Asian cohort of severely obese children.

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IMPACT:

- The prevalence of metabolically healthy obese (MHO) in our multi-ethnic Asian cohort of severely obese children is 63.5% and 22.4%, respectively, based on different MHO definitions.
- Adiposity measures are not associated with the MHO phenotype. There are other factors that contribute to the metabolic phenotype in obese individuals.
- Younger age, maternal healthy metabolic status, absence of paternal obesity, Malay and Indian ethnicity are independent predictors for MHO phenotype.
- Parental influence is important in predicting metabolic health in obese individuals.

INTRODUCTION

The prevalence of obesity is increasing at an alarming rate worldwide, and a rising trend of childhood obesity is observed in many developed and developing countries.[1] According to World Health Organization (WHO), over 340 million children and adolescents were overweight or obese in 2016. An estimated 38.2 million children below age of 5 were overweight and obese in 2019, and half of these overweight and obese children lived in Asia.[2] In Singapore, the rate of obesity and overweight in children has increased from 11% in 2013 to 13% in 2017.[3] The global escalation of obesity is a major concern as excessive adiposity is the root cause of debilitating metabolic diseases including diabetes mellitus, hypertension and dyslipidemia that can potentially reduce the quality of life and life expectancy.[4]

Obesity is a heterogeneous condition, which contributes to a varying degree of mortality across obese individuals.[5] It appears that there is a subgroup of obese subjects who are protected from the metabolic and cardiovascular complications associated with obesity, and these subjects are described as "metabolically healthy obese (MHO)".[6–8] In general, MHO subjects demonstrated a more favourable metabolic profile such as lower fasting blood glucose level, lower fasting triglyceride level and lower blood pressure compared to their unhealthy counterparts who are referred to as "metabolically unhealthy obese (MUO)".[9] The prevalence of MHO in

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hildren varied from 7% to 87% in different studies,[8,10–14] and this is mainly attributed to the different definitions and parameters used to classify the children into MHO and MUO.[15–18] MHO individuals were found to be younger, with lower BMI for age percentile, lower waist to hip ratio and higher insulin sensitivity as compared to MUO individuals.[19,20] MHO subjects are also characterised with higher subcutaneous fat, lower visceral fat and less ectopic fat accumulation in liver and skeletal muscles,[9,21,22] and were found to have a more favourable inflammatory profile of lower concentrations of IL-6, CRP, TNF-α and higher levels of adiponectin as compared to MUO.[23,24]

The distinction between MHO and MUO will allow stratification and early targeted treatment to prevent the transition from MHO to MUO phenotype.[25–27] However, apart from the diverse definitions of MHO, the varying prevalence of MHO across different populations may have resulted from the influence of other factors such as ethnicity.[28–30] Hence, it is important to establish the prevalence and predictors of MHO within a certain population. To our knowledge, the prevalence of MHO is not well established in Singapore. This study aimed to evaluate (1) the prevalence of MHO using different criteria of metabolic abnormalities, and determine (2) the predictors associated with MHO phenotype in a multi-ethnic Asian cohort of severely obese children in Singapore.

MATERIALS AND METHODS

Study participants

The obese children and adolescents ($n = 406$) included in this study were from the OBesity in Singapore Children (OBiSC) study and they are of Chinese, Malay and Indian ethnicity. The participants were recruited from National University Hospital (NUH) and Health Promotion Board (HPB), Singapore. The recruitment criteria for these obese children and adolescents aged 5–20 years old were: (1) Obese before age of 10 years, (2) BMI for age ≥ 97th percentile, (3) No syndromic causes of obesity. Data such as age at onset of obesity, birthweight and history of breastfeeding were collected retrospectively from the participants through an interview that was conducted during their study visit. Parents of the obese children were also recruited. The study was performed in accordance with the Declaration of Helsinki and ethics approval was obtained from the Domain Specific Review Board of National Healthcare Group, Singapore (Reference number: 2015/00314). Written informed consent was obtained from all study participants. The study is registered under clinicaltrials.gov (NCT02418377).

Anthropometric and biochemical measurements

The standard anthropometric parameters including weight, height, waist and hip circumference were measured. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of height in metres (m), and BMI-standard deviation score (SDS) was adjusted for child's age and sex. Skinfold measurements were taken at triceps, biceps, subscapular and suprailiac using a skinfold caliper (Holtain). Total body fat percentage and percentage of fat in the left arm, right arm, left leg, right leg and trunk were assessed by bioelectrical impedance analysis (BIA) using Tanita body composition analyser (Model BC-418). Blood pressure was also measured (Carescape V100 Dinamap). Fasting blood samples were obtained and assayed for fasting glucose, fasting insulin, lipids, liver enzymes and plasma cytokines including IL-6 (Abcam) and TNF-α (ThermoScientific). Blood glucose was also measured at 2 h after the subjects underwent an oral glucose tolerance test (OGTT) by consuming a drink consisting of 75 g glucose. Homoeostatic model assessment to measure insulin resistance (HOMA-IR) was calculated as previously described.[31]

Classification of MHO and MUO children

There is currently no standardisation on the definition of metabolically healthy and unhealthy obese.[22,32,33] However, the reported studies seem to agree on the definition of MHO as obese individuals without metabolic abnormalities associated with excess adiposity. In this study, we classified the obese children into MHO and MUO according to two different definitions, metabolic syndrome (MS) and metabolic health (MH). The MS definition is adapted and modified from the International Diabetes Federation (IDF) consensus definition of metabolic syndrome in children and adolescents.[34] For the MS definition in this study, MHO is considered as being obese with less than two of the sub-conditions: (1) Fasting triglycerides ≥ 1.7 mmol/L or on hyperlipidemia medication, (2) High-density lipoprotein (HDL) cholesterol < 1.03 mmol/L for children under the age of 16, HDL < 1.03 mmol/L for male ≥ 16 years old and HDL < 1.29 mmol/L for female ≥ 16 years old, (3) Fasting glucose ≥ 5.6 mmol/L or glucose at 2 h OGTT ≥ 7.8 mmol/L or on diabetic medication, (4) Blood pressure ≥ 90th percentile based on age, sex and height or on hypertensive medication.[35] For the MH definition in this study, MHO is considered as being obese without any of the sub-conditions as mentioned above.

Parental obesity and metabolic status

Anthropometric parameters including weight, height, blood pressure, and biochemical tests for fasting glucose, fasting insulin and lipids were measured for parents recruited under the study. According to the WHO recommended standard for obesity in Asian population,[36] parental (maternal or paternal) obesity is defined as BMI ≥ 27.5 kg/m^2. Parental healthy metabolic status is defined as having none of the following metabolic conditions: (1) Dyslipidemia: Triglycerides ≥ 1.7 mmol/L or HDL < 1.03 mmol/L for male and HDL < 1.29 mmol/L for female or on hyperlipidemia medication, (2) Impaired fasting glucose or diabetes: fasting glucose ≥ 6 mmol/L or on diabetic medication, (3) Hypertension: Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or on hypertensive medication. For parents who did not participate in the study, self-reported obesity status and metabolic status were obtained as family history of obesity and family history of medical conditions respectively during the study visit interview with the obese children.

Statistical analysis

All analyses were performed using SPSS 26.0 with a level of significance set at 2-sided $P < 0.05$. Descriptive statistics for numerical and categorical variables were presented as mean ± standard deviation (mean ± SD) and proportion (%) respectively. Differences in clinical characteristics between MHO and MUO children were analysed by Student's *t*-test for continuous parameters and Chi-square for categorical parameters. General linear model was used to compare the differences in fat distribution between MHO and MUO children adjusting for age, sex, ethnicity and BMI-SDS. Multivariate logistic regression was performed to identify the predictors associated with the MHO phenotype. One-way ANOVA with Bonferroni correction was used to compare differences in clinical characteristics among the three ethnic groups.

RESULTS

Prevalence of metabolically healthy obese (MHO) children in Singapore

The prevalence of MHO by MS definition was 63.5% (95% CI 58.7–68.2%). The MHO children had significantly lower systolic blood pressure (118 ± 12 mmHg vs. 127 ± 11 mmHg), diastolic blood pressure (65 ± 8 mmHg vs. 69 ± 8 mmHg), triglycerides (1.15 ± 0.49 mmol/L vs. 1.82 ± 0.95 mmol/L), fasting glucose (4.78 ± 0.44 mmol/L vs. 5.02 ± 0.85 mmol/L) and higher HDL cholesterol level (1.15 ± 0.17 mmol/L vs. 1.03 ± 0.16 mmol/L) as compared to MUO children (Table 1). Moreover, the MHO children were significantly younger (13.6 ± 3.10 years vs. 14.6 ± 2.57years) and had significantly lower fasting insulin (24.1 ± 13.9 mU/L vs. 34.3 ± 30.1 mU/L), glucose at 2 h OGTT (5.93 ± 1.49 mmol/L vs. 6.92 ± 1.93 mmol/L), HOMA-IR (5.16 ± 3.36 vs. 7.83 ± 7.54), ALT level (41.7 ± 36.5 U/L vs. 52.7 ± 41.5 U/L) and GGT level (30.9 ± 17.2 U/L vs. 37.4 ± 23.2 U/L) as compared to MUO children.

The prevalence of MHO by MH definition was 22.4% (95% CI 18.3–26.5%) which is lower than the prevalence of MHO by MS definition. The MHO children had significantly lower systolic blood pressure (112 ± 10 mmHg vs. 124 ± 11 mmHg), diastolic blood pressure (62 ± 7 mmHg vs. 67 ± 8 mmHg), triglycerides (1.01 ± 0.31 mmol/L vs. 1.51 ± 0.82 mmol/L), fasting glucose (4.75 ± 0.35 mmol/L vs. 4.90 ± 0.69 mmol/L) and higher HDL cholesterol (1.23 ± 0.14 vs. 1.07 ± 0.17 mmol/L) as compared to MUO children (Table 1).

Table 1. Clinical characteristics of metabolically healthy and unhealthy obese children.

Parameters	MS definition			MH definition		
	MHO ($n = 258$)	MUO ($n = 148$)	*P*	MHO ($n = 91$)	MUO ($n = 315$)	*P*
Sex (%male/%female)	70.2/29.8	65.5/34.5	0.375	72.5/27.5	67.3/32.7	0.372
Ethnicity (%Chinese/%Malay/%Indian)	46.5/43.0/10.5	62.8/33.1/4.1	0.003	47.2/39.6/13.2	53.9/39.4/6.7	0.116
Age (years)	13.6 ± 3.10	14.6 ± 2.57	0.001	12.8 ± 3.51	14.3 ± 2.69	<0.0005
BMI (kg/m^2)	37.3 ± 7.04	37.0 ± 5.67	0.632	35.7 ± 6.54	37.6 ± 6.52	0.013
BMI-SDS	2.37 ± 0.37	2.31 ± 0.34	0.103	2.34 ± 0.38	2.35 ± 0.36	0.879
Body fat by BIA (%)	48.8 ± 11.2	47.5 ± 10.5	0.249	49.3 ± 12.2	48.1 ± 10.6	0.362
Waist to hip ratio	0.96 ± 0.07	0.95 ± 0.07	0.319	0.96 ± 0.07	0.95 ± 0.69	0.241
Systolic blood pressure (mmHg)	118 ± 12	127 ± 11	<0.0005	112 ± 10	124 ± 11	<0.0005
Diastolic blood pressure (mmHg)	65 ± 8	69 ± 8	<0.0005	62 ± 7	67 ± 8	<0.0005
Total cholesterol (mmol/L)	4.53 ± 0.87	4.69 ± 0.89	0.071	4.55 ± 0.80	4.60 ± 0.90	0.644
Triglycerides (mmol/L)	1.15 ± 0.49	1.82 ± 0.95	<0.0005	1.01 ± 0.31	1.51 ± 0.82	<0.0005
HDL cholesterol (mmol/L)	1.15 ± 0.17	1.03 ± 0.16	<0.0005	1.23 ± 0.14	1.07 ± 0.17	<0.0005
LDL cholesterol (mmol/L)	2.85 ± 0.78	2.85 ± 0.75	0.981	2.86 ± 0.74	2.85 ± 0.77	0.892
Fasting insulin (mU/L)	24.1 ± 13.9	34.3 ± 30.1	<0.0005	21.5 ± 12.5	29.7 ± 23.6	0.002
Fasting glucose (mmol/L)	4.78 ± 0.44	5.02 ± 0.85	<0.0005	4.75 ± 0.35	4.90 ± 0.69	0.047
Glucose at 2 h OGTT (mmol/L)	5.93 ± 1.49	6.92 ± 1.93	<0.0005	5.76 ± 0.87	6.42 ± 1.88	0.001
HOMA-IR	5.16 ± 3.36	7.83 ± 7.54	<0.0005	4.59 ± 2.86	6.58 ± 5.90	0.002
Alanine transaminase, ALT (U/L)	41.7 ± 36.5	52.7 ± 41.5	0.006	41.9 ± 31.8	46.8 ± 40.5	0.284
Aspartate transaminase, AST (U/L)	30.0 ± 18.9	33.8 ± 19.8	0.057	30.9 ± 14.9	31.5 ± 20.4	0.802
Gamma-glutamyl transferase, GGT (U/L)	30.9 ± 17.2	37.4 ± 23.2	0.001	30.4 ± 19.4	34.1 ± 19.9	0.116
Plasma IL-6 (pg/ml)*	1.58 ± 1.20	1.77 ± 1.25	0.278	1.65 ± 1.38	1.66 ± 1.16	0.979
Plasma TNF-α (pg/ml)*	1.69 ± 1.06	1.98 ± 2.66	0.277	1.53 ± 0.76	1.89 ± 2.07	0.240

Data presented as mean ± SD or proportion (%). Asterisk (*) indicates that the parameters were only measured in a subgroup ($n = 200$) of the obese children cohort. Student's *t*-test and Chi-square test were used to compare differences in continuous and categorical parameters, respectively, between MHO and MUO children.

Moreover, the MHO children were significantly younger (12.8 ± 3.51 years vs. 14.3 ± 2.69 years) and had significantly lower BMI (35.7 ± 6.54 vs. 37.6 ± 6.52 kg/m^2), fasting insulin (21.5 ± 12.5 mU/L vs. 29.7 ± 23.6 mU/L), glucose at 2 h OGTT (5.76 ± 0.87 mmol/L vs. 6.42 ± 1.88 mmol/L) and HOMA-IR (4.59 ± 2.86 vs. 6.58 ± 5.90) as compared to MUO children.

There were significant differences in ethnicity between MHO and MUO children for both MS and MH definition. Among the ethnic groups, there were significant differences in age, BMI, BMI-SDS, body fat by BIA, trunk fat by BIA, triglycerides, glucose at 2 h OGTT, levels of ALT and GGT (Table 2). In particular, Chinese subjects were found to be significantly older and had significantly lower BMI, BMI-SDS, body fat by BIA, trunk fat by BIA and higher levels of triglyceride, ALT, GGT and glucose at 2 h OGTT as compared to Malay and Indian subjects.

Fat distribution between metabolically healthy and unhealthy obese children

We compared the skinfold measurements and fat percentage (%) distribution measured by BIA between MHO and MUO children with adjustment for age, sex, ethnicity and BMI-SDS.

MHO children by MS definition were found to have significantly higher right leg fat (47.6 ± 11.7% vs. 46.5 ± 11.3%) and left leg fat (47.7 ± 12.2% vs. 46.5 ± 11.6%) as compared to MUO children (Table 3).

However, there were no significant differences in right leg fat (48.7 ± 12.6% vs. 46.8 ± 11.2%) and left leg fat (48.9 ± 13.1% vs. 46.8 ± 11.6%) between MHO and MUO children by MH definition (Table 3).

Predictors associated with metabolically healthy obese (MHO) phenotype

Maternal healthy metabolic status (OR: 2.47, 95% CI: 1.46–4.19), younger age (OR: 0.83, 95% CI: 0.74–0.92), absence of paternal obesity (OR: 0.48, 95% CI: 0.28–0.81), Malay (OR: 1.97, 95% CI: 1.12–3.47) and Indian ethnicity (OR: 6.38, 95% CI: 1.95–20.9) (with Chinese ethnicity as reference) are independent predictors for MHO phenotype by MS definition (Table 4).

Similarly, younger age (OR: 0.80, 95% CI: 0.71–0.89), absence of paternal obesity (OR: 0.53, 95% CI: 0.29–0.96) and Indian ethnicity (OR: 3.21, 95% CI: 1.18–8.72) (with Chinese ethnicity as reference) are independent predictors for MHO phenotype by MH definition (Table 4).

The clinical characteristics of the parents who participated in the study are shown in Supplementary Tables 1 and 2. The obesity and metabolic health status of the parents were tabulated based on the clinical data of parents who participated in the study and from the self-reported obesity and metabolic health status (obtained as family history of obesity and family history of medical conditions respectively during the study visit interview with the obese children) of parents who did not participate in the study (Supplementary Tables 3 and 4).

DISCUSSION

Our study demonstrated that the prevalence of MHO varies between different definitions of MHO (63.5% by MS definition and 22.4% by MH definition), and this is consistent with a review by Smith et al. that reported varying prevalence of MHO across different studies due to the use of more than 30 different definitions.[18] In this study, we defined MHO using the metabolic syndrome criteria by IDF (MS definition) and the absence of metabolic comorbidities associated with obesity, e.g. impaired glucose tolerance (IGT)/diabetes, elevated blood pressure and dyslipidemia (MH definition). While the use of metabolic syndrome criteria to define MHO is common among multiple studies,[7,10–14] the MS definition tends to overestimate the

Table 2. Clinical characteristics of obese children among different ethnic groups.

Parameters	Chinese ($n = 213$)	Malay ($n = 160$)	Indian ($n = 33$)	P
Sex (male/female)	69.5/30.5	66.9/33.1	69.7/30.3	0.855
Age (years)	14.4 ± 2.59[a]	13.4 ± 3.32[a]	13.8 ± 2.81	0.004
BMI (kg/m^2)	35.7 ± 5.85[a,b]	38.7 ± 6.66[a]	39.6 ± 8.09[b]	<0.0005
BMI-SDS	2.22 ± 0.35[a,b]	2.49 ± 0.32[a]	2.46 ± 0.39[b]	<0.0005
Body fat by BIA (%)	46.3 ± 10.5[a,b]	50.4 ± 10.9[a]	53.1 ± 11.5[b]	<0.0005
Waist to hip ratio	0.95 ± 0.07	0.96 ± 0.07	0.96 ± 0.06	0.765
Systolic blood pressure (mmHg)	122 ± 12	120 ± 12	119 ± 12	0.198
Diastolic blood pressure (mmHg)	67 ± 8	65 ± 8	67 ± 10	0.154
Total cholesterol (mmol/L)	4.68 ± 0.93	4.51 ± 0.82	4.41 ± 0.77	0.094
Triglycerides (mmol/L)	1.55 ± 0.87[a,b]	1.28 ± 0.62[a]	0.98 ± 0.35[b]	<0.005
HDL cholesterol (mmol/L)	1.11 ± 0.18	1.10 ± 0.18	1.11 ± 0.16	0.808
LDL cholesterol (mmol/L)	2.87 ± 0.81	2.83 ± 0.73	2.85 ± 0.67	0.848
Fasting insulin (mU/L)	28.5 ± 20.7	26.8 ± 24.2	28.4 ± 16.7	0.746
Fasting glucose (mmol/L)	4.93 ± 0.74	4.78 ± 0.51	4.85 ± 0.30	0.080
Glucose at 2 h OGTT (mmol/L)	6.48 ± 1.74[a]	6.03 ± 1.74[a]	6.12 ± 1.41	0.041
HOMA-IR	6.35 ± 5.34	5.83 ± 5.85	6.18 ± 3.62	0.655
Alanine transaminase, ALT (U/L)	52.3 ± 43.1[a,b]	39.7 ± 34.0[a]	31.8 ± 14.4[b]	0.001
Aspartate transaminase, AST (U/L)	33.3 ± 21.9	30.0 ± 16.7	25.8 ± 8.85	0.057
Gamma-glutamyl transferase, GGT (U/L)	35.8 ± 21.2[a]	31.7 ± 19.1	25.0 ± 8.61[a]	0.006
Plasma IL-6 (pg/ml)*	1.56 ± 1.24	1.69 ± 1.07	2.03 ± 1.53	0.255
Plasma TNF-α (pg/ml)*	1.55 ± 0.97	2.18 ± 2.70	1.66 ± 0.93	0.067

Data presented as mean ± SD or proportion (%). Asterisk (*) indicates that the parameters were only measured in a subgroup ($n = 200$) of the obese children cohort. One-way ANOVA with Bonferroni correction and Chi-square test were used to compare differences in continuous and categorical parameters among the three ethnic groups. Labelled means with the same letters "a" or "b" indicate significant pairwise comparison ($P < 0.05$) between the two groups.

Table 3. Fat distribution between MHO and MUO children.

Parameters	MS definition			MH definition		
	MHO ($n = 258$)	MUO ($n = 148$)	P	MHO ($n = 91$)	MUO ($n = 315$)	P
Skinfold biceps (mm)	29.3 ± 10.3	29.1 ± 10.1	0.627	29.3 ± 9.26	29.2 ± 10.5	0.656
Skinfold triceps (mm)	42.2 ± 10.2	42.8 ± 8.45	0.485	40.9 ± 9.10	42.8 ± 9.68	0.800
Skinfold subscapular (mm)	54.2 ± 14.9	55.3 ± 14.4	0.248	54.5 ± 15.1	54.6 ± 14.6	0.502
Skinfold suprailiac (mm)	53.9 ± 13.9	53.9 ± 13.2	0.606	53.5 ± 13.1	54.0 ± 13.8	0.719
Right leg fat %	47.6 ± 11.7	46.5 ± 11.3	0.044	48.7 ± 12.6	46.8 ± 11.2	0.221
Left leg fat %	47.7 ± 12.2	46.5 ± 11.6	0.035	48.9 ± 13.1	46.8 ± 11.6	0.188
Right arm fat %	43.5 ± 12.6	42.0 ± 11.5	0.653	44.0 ± 13.3	42.7 ± 11.9	0.797
Left arm fat %	43.0 ± 12.5	42.0 ± 11.6	0.661	43.1 ± 13.1	42.4 ± 11.9	0.767
Trunk fat %	47.8 ± 11.4	47.3 ± 11.3	0.904	46.1 ± 12.0	48.0 ± 11.2	0.170

Data presented as mean ± SD. General linear model was used to compare differences in parameters between MHO and MUO children with adjustment for age, sex, ethnicity and BMI-SDS.

prevalence of MHO, i.e. an obese individual with diabetes but without elevated blood pressure, triglycerides and HDL cholesterol levels would be considered MHO. Hence, we have included the MH definition which is more stringent as it excludes individuals with any of the metabolic morbidities associated with obesity, i.e. an obese individual with diabetes but without the elevated blood pressure and dyslipidemia would be considered MUO. In addition, studies have reported that MHO still have an increased risk of developing cardiovascular diseases compared to metabolically healthy normal-weight individuals,[37,38] and 40–70% of MHO transitioned to MUO within 3–10 years.[25–27] These may likely be attributed to the metabolic abnormalities that are already present in the MHO individuals due to the use of the less stringent metabolic syndrome criteria (MS definition) to define the MHO, and this can be circumvented through the use of more stringent criteria to define the MHO, e.g. MH definition. The varying prevalence of MHO highlight the need to develop a universally accepted standard to define MHO so as to better compare the prevalence and characteristics of MHO between different populations.[39]

As expected, MHO children showed a more favourable metabolic profile of lower lipid levels, lower liver enzymes, lower fasting glucose, lower blood pressure and higher insulin sensitivity as compared to MUO children.[19] However, there were no significant differences in adiposity measures such as BMI, BMI-SDS, body fat percentage, trunk fat percentage and waist to hip ratio, albeit adiposity measures have been reported to be predictors of MHO phenotype.[17,40] This suggests that while obesity is a risk factor for metabolic morbidities,[41,42] there may be other underlying factors and mechanisms that contribute to the metabolic health of an obese individual.

Our results showed that Chinese obese children had a lower prevalence of MHO as compared to Malay and Indian obese children, and this may be attributed to the higher age and higher

Table 4. Predictors associated with MHO phenotype.

Parameters	MS definition			MH definition		
	Odds ratio (OR)	95% confidence interval (CI)	*P*	Odds ratio (OR)	95% confidence interval (CI)	*P*
Age at onset of obesity (years)	0.96	0.88–1.04	0.287	0.96	0.88–1.06	0.442
Age (years)	0.83	0.74–0.92	<0.0005	0.80	0.71–0.89	<0.0005
Sex (female)	0.61	0.33–1.13	0.115	0.86	0.44–1.66	0.644
Ethnicity (Malay)	1.97	1.12–3.47	0.020	0.79	0.41–1.52	0.475
Ethnicity (Indian)	6.38	1.95–20.9	0.002	3.21	1.18–8.72	0.022
History of breastfeeding	0.98	0.57–1.69	0.944	1.09	0.56–2.10	0.805
Birthweight (kg)	0.77	0.48–1.22	0.258	0.86	0.49–1.51	0.589
BMI-SDS	1.36	0.46–3.99	0.577	0.65	0.20–2.19	0.489
Body fat by BIA (%)	0.99	0.96–1.03	0.571	1.00	0.97–1.04	0.932
Waist to hip ratio	0.54	0.01–30.1	0.763	2.89	0.03–301	0.654
Maternal healthy metabolic status	2.47	1.46–4.19	<0.0005	1.66	0.92–2.99	0.090
Paternal healthy metabolic status	0.99	0.59–1.64	0.952	1.75	0.99–3.11	0.056
Maternal obesity	1.63	0.95–2.79	0.074	1.65	0.90–3.05	0.107
Paternal obesity	0.48	0.28–0.81	0.007	0.53	0.29–0.96	0.037

Multivariate logistic regression was used to analyse the association between variables and MHO phenotype in obese children.

levels of triglyceride, glucose at 2 h OGTT, ALT and AST[43] observed among the Chinese obese children. Interestingly, the Chinese obese children had lower adiposity measures compared to Malay and Indian obese children, further indicating that adiposity is not the sole or main influencing factor of metabolic health in obese children. Our finding is consistent with an independent local study conducted in the Singapore adult population which showed that the impact of BMI on cardiovascular risk markers like insulin resistance appears greater in Chinese compared to Malay and Indians,[44] and may partly explain the rapid increase in the prevalence of diabetes and cardiovascular diseases (CVD) in our Chinese population despite lower levels of obesity.[45]

Adipose tissue inflammation is considered as one of the main factors involved in the pathogenesis of insulin resistance and cardiovascular complications,[46] and MHO individuals were shown to have reduced inflammatory profile compared to MUO individuals.[47] However, in this study, we did not observe any significant differences in plasma IL-6 and TNF-α levels between MHO and MUO children. Body fat distribution has also been implicated in the development of metabolic conditions.[48] Upper body fat and ectopic fat accumulation are associated with a greater risk of diabetes, hypertension, hyperlipidemia and CVD.[49–51] MUO children were found to have excess body fat, and visceral fat mass and lean fat mass derived by dual-energy X-ray absorptiometry (DXA) were predictors of MUO phenotype.[52] In this study, we found that our MHO children by MS definition had significantly higher leg fat percentage derived from BIA, and this concurs with the study by Appleton et al. that also found significantly higher leg fat percentage derived from DXA in MHO women.[27] The accumulation of fat at the lower part of the body (gluteofemoral region) has been shown to be protective against adverse cardiometabolic outcomes.[53] In particular, leg fat accumulation is inversely associated with risk of metabolic syndrome,[54] and has been reported to be predictive of CVD risk.[55] Hence, higher leg fat in our MHO children may explain their lower risk for metabolic and cardiovascular complications as compared to MUO children.

Apart from age, Malay and Chinese ethnicity, our data also showed that maternal health and paternal obesity are independent predictors of MHO phenotype. Offspring of mothers with metabolic conditions such as gestational diabetes mellitus (GDM) and hypertension during pregnancy were reported to have a higher risk of metabolic abnormalities.[56,57] In addition, paternal obesity is associated with less favourable cardiovascular risk factors in offspring.[58,59] These findings suggest that intergenerational influence may be important in conferring CVD risk among offspring and early intervention at the parental level may improve metabolic health in offspring.

Despite the notable findings in this study, there are several caveats that need to be discussed. Firstly, we were unable to establish the causal relationship between the predictors and MHO phenotype in our cross-sectional cohort of severely obese children. Secondly, only skinfold measurement and BIA were performed, and we did not assess ectopic and visceral fat distribution which are more directly associated with metabolic health.[50,51] Thirdly, only plasma IL-6 and plasma TNF-α levels were analysed, and there are other inflammatory cytokines such as hs-CRP that are not included in this study.[23] Lastly, pubertal status[60] and putative modifiable factors such as diet, physical activity and sleep pattern[61,62] were not available in this study. Hence, we are unable to evaluate the association between these factors and MHO phenotype.

In conclusion, our study demonstrated that the prevalence of MHO varies according to the different definitions of MHO, 63.5% by MS definition and 22.4% by MH definition. Adiposity measures are not associated with the MHO phenotype. Younger age, maternal healthy metabolic status, absence of paternal obesity, Malay and Indian ethnicity are independent predictors for MHO phenotype in a multi-ethnic Asian cohort of severely obese children.

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AUTHOR CONTRIBUTIONS

D.S.Q.O. and Y.S.L. made substantial contributions to conception and design. D.S.Q.O., Y.Y.L., C.W.L.H., V.T., V.K., K.Y.L., A.A.S. and Y.S.L. made substantial contributions to the acquisition of data. D.S.Q.O., S.G.O., O.M.H.L. and Y.H.C. made substantial contributions to the analysis and interpretation of data. D.S.Q.O., S.G.O. and Y.S.L. drafted the article and revised it critically for important intellectual content. All authors provided final approval for the version to be published.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Written informed consent was obtained from all study participants.

ADDITIONAL INFORMATION

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