Cardiorespiratory Fitness and Adiposity in Metabolically Healthy Overweight and Obese Youth

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KEY WORDS: metabolic syndrome, hepatic steatosis, body fat distribution, obesity, physical activity

ABBREVIATIONS: ALT—alanine aminotransferase
AST—aspartate aminotransferase
CI—confidence interval
HDL—high-density lipoprotein
MHO—metabolic healthy overweight
OR—odds ratio

Drs Sénéchal and McGavock conceptualized and designed the study, carried out the analysis, and wrote the manuscript as submitted; Dr Wicklow conceptualized and designed the study, carried out the analysis, and wrote the manuscript as submitted; Dr Wittmeier and Ms Eskicioglu reviewed and revised the manuscript; Dr Venugopal designed and coordinated and supervised the data collection, and critically reviewed the manuscript; and all authors approved the final version of the manuscript as submitted.

WHAT’S KNOWN ON THIS SUBJECT: Obesity is associated with cardiometabolic risk factors and chronic conditions, such as type 2 diabetes. However, a proportion of overweight and obese youth remain free from cardiometabolic risk factors and are considered metabolically healthy.

WHAT THIS STUDY ADDS: This study provides insight into the determinants of cardiometabolic risk factors and the concept in health promotion of “fitness versus fatness.” Hepatic lipid accumulation and not fitness level appears to drive cardiometabolic risk factor clustering among overweight and obese youth.

abstract

OBJECTIVE: Controversy exists surrounding the contribution of fitness and adiposity as determinants of the Metabolically Healthy Overweight (MHO) phenotype in youth. This study investigated the independent contribution of cardiorespiratory fitness and adiposity to the MHO phenotype among overweight and obese youth.

METHODS: This cross-sectional study included 108 overweight and obese youth classified as MHO (no cardiometabolic risk factors) or non-MHO (≥1 cardiometabolic risk factor), based on age- and gender-specific cut-points for fasting glucose, triglycerides, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, and hepatic steatosis.

RESULTS: Twenty-five percent of overweight and obese youth were classified as MHO. This phenotype was associated with lower BMI z-score (BMI z-score: 1.8 ± 0.3 vs 2.1 ± 0.4, P = .02) and waist circumference (99.7 ± 13.2 vs 106.1 ± 13.7 cm, P = .04) compared with non-MHO youth. When matched for fitness level and stratified by BMI z-score (1.6 ± 0.3 vs 2.4 ± 0.2), the prevalence of MHO was fourfold higher in the low BMI z-score group (27% vs 7%, P = .03). Multiple logistic regression analyses revealed that the best predictor of MHO was the absence of hepatic steatosis even after adjusting for waist circumference (odds ratio 0.57, 95% confidence interval 0.40–0.80) or BMI z-score (odds ratio 0.59, 95% confidence interval 0.43–0.80).

CONCLUSIONS: The MHO phenotype was present in 25% of overweight and obese youth and is strongly associated with lower levels of adiposity, and the absence of hepatic steatosis, but not with cardiorespiratory fitness. Pediatrics 2013;132:e85–e92
Obesity is associated with a clustering of cardiometabolic risk factors, including hypertension, insulin resistance, inflammation, and dyslipidemia.\(^1\) However, cardiometabolic risk factor clustering is not an obligatory consequence of obesity. In fact, 18% to 44% of obese individuals are free from cardiometabolic risk factors.\(^2\)\(^,\)\(^3\) The absence of cardiometabolic risk factor clustering in obese individuals is associated with lower measures of adiposity, including lower total fat mass,\(^4\) abdominal obesity,\(^5\)\(^,\)\(^6\) measures of adiposity including the proportion of girls,\(^7\)\(^,\)\(^8\) and the absence of ectopic lipid accumulation.\(^9\)

Surprisingly, little attention has been paid to the modifiable factors as determinants of this “Metabolically Healthy Overweight” (MHO) phenotype.\(^10\)\(^,\)\(^11\) This is particularly important, as the identification of modifiable behaviors associated with the MHO phenotype could provide information to guide interventions aimed at preventing obesity-related chronic disease among overweight youth.

Cardiorespiratory fitness is a modifiable factor that is protective against overweight status and visceral obesity in youth.\(^12\) However, the importance of cardiometabolic fitness as a protective determinant of metabolic risk factor clustering in youth is controversial.\(^10\)\(^,\)\(^13\)

Some studies suggest that high cardiometabolic fitness confers significant protection from cardiometabolic risk factor clustering in youth is controversial.\(^10\)\(^,\)\(^13\) Other studies suggest that the association between fitness and cardiometabolic risk factor clustering is confounded by differences in adiposity levels.\(^16\)\^-\(^18\)

To the best of our knowledge, no study has been designed specifically to delineate the individual contribution of cardiometabolic fitness and adiposity as risk factors for the MHO phenotype among youth.

In light of these issues, we designed a series of observational matching studies to dissect the independent contribution of cardiometabolic fitness and adiposity to the MHO phenotype among overweight and obese youth. Our primary working hypothesis was that high cardiometabolic fitness would be associated with an increased likelihood of MHO after controlling for adiposity. Our secondary hypothesis was that a lower level of hepatic steatosis would mediate the association between cardiometabolic fitness and the MHO phenotype.

**METHODS**

**Study Design and Participants**

We recruited 210 youth, 13 to 18 years old, through public advertisements for a series of studies in our laboratory. Sixteen youth were excluded from the analysis because they were not overweight (BMI percentile <85th), according to the International Obesity Task Force,\(^19\) and 4 were excluded because they were ≥19 years of age. Eighty-two participants were also excluded from the analysis as they (1) had missing data for cardiometabolic risk factors (n = 63) and therefore could not be categorized for the primary outcome (MHO), (2) did not provide a valid cardiometabolic fitness test (ie, respiratory exchange ratio < 1.1) (n = 9), or (3) had impaired fasting glucose or were diagnosed with type 2 diabetes after screening (n = 10). Participants excluded from the analyses had similar characteristics to those who remained in the analysis, including the proportion of girls (58.7% vs 56.4%), mean age (15.4 ± 1.7 vs 15.2 ± 1.5 years), and mean BMI z-score (2.0 ± 0.4 vs 2.1 ± 0.5). All 108 remaining participants and parents provided written informed consent and assent. The study was approved by the University of Manitoba Biomedical Research Ethics Board and performed according to the Declaration of Helsinki.

Exclusion criteria included a diagnosis of type 2 diabetes, treatment with antipsychotics or corticosteroids, orthopedic injury or illness preventing participation in the exercise test, and enrollment in a weight loss program within the previous 6 months. A standard 2-hour 75-g oral glucose tolerance test was used to screen for type 2 diabetes.

**Primary Outcome Variable**

*MHO*

There are several definitions for classifying an individual as MHO, including “normal” insulin sensitivity, “low” insulin resistance (measured by homeostatic model assessment), and the absence of any cardiometabolic risk factors.\(^8\) To facilitate comparisons with other studies, we classified youth as MHO if they did not present a clinically relevant elevation in any of the following cardiometabolic risk factors: serum triglycerides, glucose, systolic and diastolic blood pressure, hepatic triglyceride content, or an abnormally low high-density lipoprotein (HDL)-cholesterol. The age- and gender-specific cut-points used for the MHO classification have been published elsewhere\(^20\) and can be found in Supplemental Table 5.

We also included a definition of the metabolic syndrome as an ancillary outcome. Metabolic syndrome was defined according to the age- and gender-specific cut-points for the following risk factors: serum triglycerides, HDL cholesterol, fasting glucose, systolic or diastolic blood pressure, and hepatic triglyceride content (≥5.5% fat/water). The cut-points used to define metabolic syndrome (Supplemental Table 5) are established in the literature and represent the cut-points used in adults.\(^20\)\^-\(^22\)

We replaced waist circumference with hepatic triglyceride content for 2 reasons: (1) 81.5% of youth in this cohort presented with a waist circumference
above age and gender-specific thresholds for the metabolic syndrome,20 and (2) we have previously shown that hepatic steatosis is a robust predictor of metabolic syndrome and type 2 diabetes in youth.21 Overweight youth with hepatic steatosis is a robust predictor of the metabolic syndrome,20 and we have previously shown that he-
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BMI z-score instead of percent body fat, as BMI z-score facilitates comparisons across age and gender, and similar scores are not currently available for percent body fat. Nonparametric analyses were performed to compare non-normally distributed cardiometabolic risk factors between matched groups. Data management and statistical analyses were performed by using SAS version 9.1 (SAS Institute, Cary, NC). P ≤ .05 was considered statistically significant.

**RESULTS**

**Participant Characteristics**

Of the 108 overweight and obese youth (mean age 15.2 ± 1.5 years) studied, 56.4% (61/102) were white and 67.6% (73/108) were girls. On average, each participant displayed 1.4 ± 1.1 of the clinically elevated cardiometabolic risk factors and had a VO₂peak of 26.0 mL/kg per minute. Nearly 25% (n = 27/108) of overweight and obese youth did not have a single cardiometabolic risk factor, and therefore were classified as MHO. Among those with at least 1 risk factor, 43.2% (n = 35/81) had 1 risk factor, 33.3% (27/81) had 2 risk factors, and 23.4% (19/81) had ≥3 risk factors and met criteria for the metabolic syndrome. Compared with youth with at least 1 metabolic risk factor, youth classified as MHO displayed a lower BMI (P = .01), BMI z-score (P = .02), and waist circumference (P = .04) (Table 1). No significant differences in body weight (MHO: 85.4 ± 14.5 kg versus non-MHO: 91.0 ± 16.8 kg; P = .39), percent body fat (MHO: 36.4 ± 6.0 versus non-MHO: 38.6 ± 5.8%; P = .09), or total fat mass (MHO: 31.5 ± 8.1 versus non-MHO: 35.5 ± 10.3 kg; P = .09) were observed between the groups.

Compared with those with at least 1 cardiometabolic risk factor, MHO youth displayed lower serum triglycerides (P = .001), higher HDL cholesterol (P = .01), lower systolic blood pressure (P = .007), and lower hepatic triglyceride content (P = .001) (Table 2). Physical activity and cardiorespiratory fitness were not significantly different between MHO and youth with at least 1 cardiometabolic risk factor (P > .05).

**Matched Comparisons**

When matched for cardiorespiratory fitness (25.9 ± 6.4 vs 25.7 ± 0.6 mL/kg per minute), but stratified by BMI z-score (1.6 ± 0.3 vs 2.4 ± 0.2), the prevalence of MHO was fourfold lower (Fig 1) and the prevalence of metabolic syndrome was fourfold higher in youth with a higher BMI z-score. In contrast, when stratified by cardiorespiratory fitness (21.3 ± 2.8 vs 31.5 ± 3.6 mL/kg per minute), rates of MHO (30% vs 30%, P = 1.00) and metabolic syndrome (23% vs 17%, P = .52) were not different between overweight youth matched for BMI z-score (1.9 ± 0.3 vs 1.9 ± 0.4), despite a 10-mL/kg per minute difference in cardiorespiratory fitness. When stratified according the BMI z-score, differences in metabolic syndrome were driven largely by differences in systolic blood pressure and hepatic steatosis (Table 3).

**Regression Analyses**

Bivariate analyses revealed that cardiorespiratory fitness was negatively associated with several measures of adiposity, including body weight, BMI z-score, waist circumference, percent body fat, and total fat mass (P < .01). Cardiorespiratory fitness was significantly associated with ALT, AST, and ALT, AST, and ALP.

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**Table 1** Comparison of the Body Composition of MHO and Obese Youth and Non-MHO and Obese Youth

<table>
<thead>
<tr>
<th>Variables</th>
<th>MHO</th>
<th>Non-MHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>81</td>
</tr>
<tr>
<td>Age, y</td>
<td>15.4 ± 1.4</td>
<td>15.1 ± 1.6</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>17 (83)</td>
<td>56 (69.1)</td>
</tr>
<tr>
<td>Boys</td>
<td>10 (37)</td>
<td>25 (30.9)</td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (44.4)</td>
<td>49 (60.4)</td>
</tr>
<tr>
<td>First Nation</td>
<td>4 (14.8)</td>
<td>8 (9.8)</td>
</tr>
<tr>
<td>Others</td>
<td>11 (40.7)</td>
<td>24 (29.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.4 ± 14.5</td>
<td>91.0 ± 16.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.5 ± 3.8</td>
<td>33.0 ± 4.9*</td>
</tr>
<tr>
<td>BMI, z-score</td>
<td>1.8 ± 0.3</td>
<td>2.1 ± 0.4*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>99.7 ± 13.2</td>
<td>106.1 ± 13.7*</td>
</tr>
<tr>
<td>Total body fat, %</td>
<td>36.4 ± 6.0</td>
<td>38.6 ± 5.8</td>
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<tr>
<td>Total fat mass, kg</td>
<td>31.5 ± 8.1</td>
<td>35.5 ± 10.3</td>
</tr>
<tr>
<td>Visceral fat mass, cm³</td>
<td>68.6 ± 57.6</td>
<td>68.2 ± 62.0</td>
</tr>
<tr>
<td>Subcutaneous fat mass, cm³</td>
<td>237.6 ± 175.4</td>
<td>250.2 ± 206.6</td>
</tr>
<tr>
<td>Total fat-free mass, kg</td>
<td>52.6 ± 9.6</td>
<td>53.1 ± 9.0</td>
</tr>
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</table>

Data are described as means and SDs. * Significantly different from the MHO group. P ≤ .05.

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**Table 2** Comparison of the Cardiometabolic Risk Factors and Fitness of MHO and Obese Youth and Non-MHO and Obese Youth

<table>
<thead>
<tr>
<th>Variables</th>
<th>MHO</th>
<th>Non-MHO</th>
</tr>
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<tbody>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.9 ± 0.3</td>
<td>1.4 ± 0.6*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.4 ± 0.2</td>
<td>1.0 ± 0.2*</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.7 ± 0.3</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110.2 ± 8.9</td>
<td>118.0 ± 13.7*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>65.6 ± 7.1</td>
<td>64.5 ± 8.6</td>
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<tr>
<td>AST, U/L</td>
<td>20.5 ± 8.8</td>
<td>24.0 ± 8.7</td>
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<tr>
<td>ALT, U/L</td>
<td>18.7 ± 10.6</td>
<td>26.0 ± 20.1</td>
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<tr>
<td>Hepatic triglyceride content, %</td>
<td>2.3 ± 1.5</td>
<td>8.1 ± 11.3*</td>
</tr>
<tr>
<td>No. of MetS criteria</td>
<td>0</td>
<td>1.9 ± 0.9*</td>
</tr>
<tr>
<td>Physical activity, steps/day</td>
<td>6632 ± 2839</td>
<td>5392 ± 2763</td>
</tr>
<tr>
<td>Cardiorespiratory fitness, L/min</td>
<td>2.3 ± 0.6</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Cardiorespiratory fitness, ml·kg⁻¹·min⁻¹</td>
<td>27.2 ± 5.5</td>
<td>25.2 ± 4.7</td>
</tr>
<tr>
<td>Cardiorespiratory fitness, ml·FFM⁻¹·min⁻¹</td>
<td>44.0 ± 5.8</td>
<td>42.7 ± 5.7</td>
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Data are described as means and SDs. FFM, fat-free mass; MetS, metabolic syndrome. * Significantly different from the MHO group. P ≤ .05.
hepatic triglyceride content after adjusting for age, gender, and race/ethnicity. After adjusting for body weight, cardiorespiratory fitness was not significantly associated with any cardiometabolic risk factors. Total fat mass and BMI z-score were both associated with HDL cholesterol, systolic blood pressure, ALT, hepatic triglyceride content, and the presence and number of cardiometabolic risk factors (P < .05).

Multiple logistic regression analysis revealed the single best predictor of the MHO phenotype was the absence of hepatic steatosis, even after adjusting for waist circumference (OR 0.57, 95% CI 0.40–0.80) and BMI z-score (OR 0.59, 95% CI 0.43–0.80). The odds of hepatic steatosis were 4.45 times higher (95% CI 1.10–19.56) in the lowest quartile of cardiorespiratory fitness relative to fat-free mass independent of age, gender, race/ethnicity, and visceral fat mass (Table 4). This association disappeared after adjusting for BMI z-score. Moreover, cardiorespiratory fitness was not associated with the metabolic syndrome (P > .05).

**DISCUSSION**

The series of matched comparisons performed in this study provide important insight into the determinants of cardiometabolic risk factor clustering among overweight and obese youth. They also expand on the controversy of “fitness versus fatness” presented in previous pediatric studies. First, we found that a significant proportion (~25%) of overweight and obese youth did not present a single cardiometabolic risk factor, despite high adiposity levels (BMI z-score ranging from 1.02 to 2.87). Second, we found that hepatic triglyceride content, BMI z-score, and waist circumference are the dominant predictors of cardiometabolic risk factor clustering in overweight youth. Third, after adjusting for measures of adiposity, we found that cardiorespiratory fitness was not associated with the presence of MHO or metabolic syndrome components among overweight and obese youth. Collectively, these data suggest that risk factors other than cardiorespiratory fitness are driving the increased cardiometabolic risk factor clustering observed among overweight and obese youth.

The risk of metabolic syndrome increases 1.6-fold for every 0.5 increment in BMI z-score in children and adolescents. The limited studies performed in cohorts of exclusively overweight and obese youth suggest that ectopic fat and body fat distribution also contribute to the variance in cardiometabolic risk factor clustering. Studies of cardiometabolic risk factor clustering in overweight and obese youth frequently fail to include measures of modifiable lifestyle factors in their study design. Therefore, it remained unclear if differences in either physical activity or fitness contribute to the MHO phenotype. The data presented here support the concept that BMI z-score and hepatic lipid content are critical determinants of the MHO phenotype in overweight and obese youth. Furthermore, the lack of an association...
TABLE 4 Logistic Regression of Hepatic Steatosis and Presence of MHO and Obese Status Across Quartile of CRF

<table>
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<th>Models</th>
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<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
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<tr>
<td>Model 1 Quartile 1 CRF, mL FFMM (^{-1} ) min (^{-1} )</td>
<td>3.30</td>
<td>0.83–13.06</td>
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<td>Model 2 Quartile 1 CRF, mL FFMM (^{-1} ) min (^{-1} )</td>
<td>4.45</td>
<td>1.10–19.56</td>
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<tr>
<td>Model 3 Quartile 1 CRF, mL FFMM (^{-1} ) min (^{-1} )</td>
<td>2.44</td>
<td>0.51–11.56</td>
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</table>

CRF, cardiorespiratory fitness; FFM, fat-free mass; Model 1, adjusted for age, gender, and race/ethnicity; Model 2, adjusted for age, gender, race/ethnicity, and visceral fat; Model 3, adjusted for age, gender, race/ethnicity, visceral fat, and BMI z-score. ref, reference.

between MHO and cardiorespiratory fitness, despite a very large difference between groups, suggests that any association between fitness and risk factor clustering among overweight and obese youth is likely mediated through differences in BMI and/or hepatic triglyceride content.

The lack of an association between cardiorespiratory fitness and the MHO phenotype contradicts other studies of overweight youth.14,37 These studies demonstrated that youth with high cardiorespiratory fitness were more likely to be insulin sensitive and less likely to present with the metabolic syndrome. These observations were made without adjusting for key confounding variables, in particular age and adiposity.14 In fact, when differences in adiposity are controlled for, differences in fitness between MHO youth and peers with metabolic syndrome often disappear.16 Using a reciprocal matching approach, we were able to demonstrate that any positive association between cardiorespiratory fitness and the MHO phenotype is mediated by differences in adiposity and hepatic steatosis. Furthermore, in a multivariate logistic regression analysis, the most significant predictors of the MHO phenotype were measures of adiposity. Collectively, these data reinforce the importance of adiposity and hepatic lipid content as predictors of the MHO phenotype.

To the best of our knowledge, this is the most comprehensive study to compare various measures of adiposity as predictors of the MHO phenotype in overweight and obese youth. Although some studies have documented a dominant role of hepatic steatosis,38 others have suggested that visceral fat is a more important predictor of MHO.39 We have previously demonstrated that in overweight and obese youth, hepatic steatosis is a better predictor of metabolic syndrome and glucose tolerance than visceral fat mass.21 The data presented here suggest that the absence of hepatic lipid content and a low BMI z-score are the 2 dominant measures of the MHO phenotype in youth. The factors that contribute to the development of hepatic steatosis and subsequently cardiometabolic risk factor clustering among overweight and obese youth remain poorly understood. Other modifiable lifestyle factors, including diet, sleep, and sedentary behavior, as well as nonmodifiable risk factors, such as ethnicity, may play a role and should be included in future studies.

Some limitations need to be acknowledged. First, the combination of overweight and obese youth for the analysis and the absence of waist circumference into the MHO definition restrict the clinical use of these results. Second, the population consisted of a relatively healthy cohort of overweight youth, making it difficult to extrapolate these findings to clinical populations of severely obese youth, who are at greater risk of chronic disease. Third, we may have been underpowered to test for an association between fitness and the MHO phenotype. However, to observe a significant difference in cardiorespiratory fitness between the groups, we would require a sample of 274 adolescents, assuming a power of 0.80 and an α of 0.05. Finally, we did not adjust for Tanner staging, which may contribute to some of the differences between groups. If differences in puberty did exist between groups, they would be minimal, considering the similarities in age and gender between the groups.

In conclusion, among overweight and obese youth, high cardiorespiratory fitness is not associated with being “metabolically healthy.” In contrast, a lower BMI z-score and lower hepatic triglyceride content decrease the likelihood of presenting with cardiometabolic risk factor clustering. Future studies are needed to pinpoint thresholds of BMI z-score or hepatic triglyceride content that are associated with an increased likelihood of progression from the metabolically healthy phenotype to the presence of cardiometabolic risk factor clustering.

ACKNOWLEDGMENTS

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