

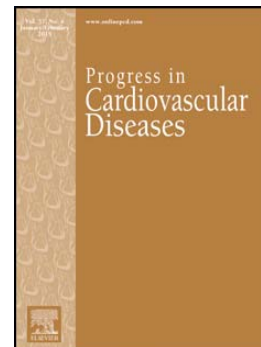
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Role of Fitness in the Metabolically Healthy But Obese Phenotype: A Review and Update

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ABSTRACT

Despite the strong and consistent evidence supporting that a high physical fitness (PF) level at any age is a major predictor of a healthier metabolic profile, major studies focused on the metabolically healthy but obese (MHO) phenotype have ignored the role of PF when examining this phenotype and its prognosis. Particularly, the role of its main health-related components such as higher cardiorespiratory fitness (CRF) and muscular fitness in the MHO phenotype need to be reviewed in depth. The present review aimed to: 1) contribute to the characterization of the MHO phenotype by examining whether MHO individuals are fitter than metabolically abnormal obese (MAO) individuals in terms of CRF and other PF components; 2) review the role of CRF and other PF components in the prognosis of MHO. The studies reviewed suggest that a higher CRF level should be considered a characteristic of the MHO phenotype. Likewise, CRF seems to play a key role in the prognosis of the MHO individuals, yet this statement is based on a single study and future studies need to confirm or contrast these findings. Comparability of studies is difficult due to the different definitions used for MHO; consequently, the present review makes a proposal for harmonizing this definition in adults and in youth. Obesity is still related to an important number of comorbidities; therefore, the public health message remains to fight against both obesity and low CRF in both adult and pediatric populations.

KEYWORDS

Physical fitness, cardiorespiratory fitness, muscular strength, metabolically healthy but obese, metabolically abnormal obese, prognosis, mortality.

ABBREVIATIONS

CVD: Cardiovascular disease

CRF: Cardiorespiratory fitness

MHO: Metabolically healthy but obese

PF: Physical fitness

MS: Muscular strength

MAO: Metabolically abnormal obese

BMI: Body mass index

VO₂max: maximal oxygen consumption

VO₂peak: peak oxygen consumption

SD: Standard deviation

HE clamp: Hyperinsulinemic-euglycemic clamp

NS: Not significant

ES: Effect size

CI: Confidence interval

FFM: Fat free mass

WC: Waist circumference

ATP III: Adult Treatment Panel III

1RM: 1 repetition maximum

BF%: Body fat percentage

HDL-C: High-density lipoprotein cholesterol

Introduction

Strong and consistent evidence supports that a higher cardiorespiratory fitness (CRF) level at any age is a major predictor of a healthier metabolic profile, as well as a lower risk for incident cardiovascular disease (CVD) and CVD mortality¹⁻⁴. Based on this evidence, it would be expected that epidemiological studies and reviews focusing on metabolic syndrome and/or CVD would account for CRF in their analyses or if CRF data are not available, would at least mention it as a limitation. The same would apply when studying the metabolically healthy but obese (MHO) phenotype, a condition in which obesity coexists with a fully healthy metabolic profile. MHO is present in 10-30% of obese adults⁵ and in 6-36% of obese children/adolescents^{6,7}, with prevalence differences largely due to different definitions of MHO. Unfortunately, many of the major studies on this topic ignored the critical impact of CRF. As an example, Primeau et al.⁸ reviewed the existing literature and reported a number of characteristics of the MHO phenotype, including lower visceral fat accumulation, higher birth weight, adipose cell size, and gene expression-encoding markers of adipose cell differentiation; however, CRF was not mentioned. Likewise, Kramer et al.⁹ conducted a systematic review and meta-analysis about the prognosis of individuals who are MHO, but again, the potential role of CRF in this prognosis was ignored. Another recent high profile study by Bell and colleagues indicated that a high percentage of those with MHO usually lose their metabolic health over time, much more so than do leaner subjects who are also metabolically healthy¹⁰; however, we have argued that this analysis also did not assess physical activity much less CRF¹¹. On the other hand, the latest literature on this topic does acknowledge that CRF levels should be considered and that CRF could play a central role in the risk of mortality in MHO individuals¹²⁻¹⁴. Moreover, a recent review specifically explored the role of CRF when comparing *healthy obese* with

unhealthy lean, and concluded that greater emphasis should be placed on improving CRF rather than weight loss *per se* in the primary and secondary prevention of CVD, at least in patients with overweight and class I obesity (body mass index, BMI 25–35 kg/m²)¹⁵.

Although available information is promising, whether a higher CRF is a characteristic in MHO individuals has not been specifically reviewed. In order to address this question we searched for studies assessing both CRF and the MHO phenotype in adults as well as in youth up to March 31st 2015. We decided to extend the search to other health-related physical fitness (PF) components, such as muscular strength (MS), flexibility and balance. Particularly, there is accumulating evidence supporting that MS is an emerging predictor for CVD mortality, independently of traditional risk factors such as obesity and hypertension, and also independently of CRF^{16–19}; however, its role in the MHO phenotype is unknown. Likewise, there is a need for an update on the potential role of PF on the prognosis of MHO individuals. The present review specifically aimed to: 1) contribute to the characterization of the MHO phenotype by examining whether MHO individuals are fitter than metabolically abnormal obese (MAO) individuals in terms of CRF and other PF components; 2) review the role of CRF and other PF components in the prognosis of MHO.

Are MHO individuals fitter than their MAO peers? Current evidence from cross-sectional data

Overall description of the studies reviewed

We found 12 studies in which any of the components of PF were compared between MHO and MAO. The most relevant information from each of these studies is presented in **Table 1**. In addition, a summary of the characteristics of these studies is shown in **Table 2**. Surprisingly, 75% of the studies focused exclusively on women²⁰⁻²⁸ and only 25% focused on both women and men (no study was focused only in men)²⁹⁻³¹. Likewise, all studies^{20-28,30,31} but one²⁹ were conducted in adults or older adults. These two observations inform us that the output and conclusion derived from this review would mainly apply to adult or older adult women.

Most of studies were conducted in Canada (n=6)^{21,22,27-30} or in USA (n=2)^{20,31}, with both comprising two thirds (50%+17%=67%) of the studies published on this topic. The concept of MHO, as indicated by its name, refers to obese individuals. However, 5 out of the 12 studies (42%) also included overweight participants and analyzed them together with the obese participants^{21,25-27,29}, so that the results reported in these studies are referring to metabolically healthy but overweight or obese individuals. The definition of MHO differed across studies and could be summarized into 2 groups: 1) those based on meeting 0 or 1 (including or excluding waist circumference) of the metabolic syndrome criteria internationally accepted (yet with slight modifications in some studies)³², which was used in 75% of the studies^{22-26,28,30,31}; and/or 2) markers of insulin sensitivity (mainly using top/bottom tertiles/quartiles of the hyperinsulinemic-euglycemic clamp), which was used in 33% of the studies^{20,21,27,28}.

Although our effort was to search studies assessing any PF component, we found that CRF was the most studied, with 100% of the studies including a measure of CRF, only 2 studies additionally assessing MS^{23,27} and one of them, additionally assessing other components of PF, such as flexibility, balance and agility²³. CRF was assessed mainly using an incremental test in a cycle ergometer (58% of the studies)^{21,24–29}, followed by treadmill testing (25%)^{20,30,31}, and expressed as measured/estimated maximal oxygen consumption (VO₂max or VO₂peak; 83% of the studies).

Differences in CRF between MHO and MAO

In order to make the results from the reviewed studies comparable, we computed standardized mean differences; specifically, we computed Cohen's *d* from the data provided in each study (i.e. N, means and standard deviations or standard errors of the mean)³³. This information has been included in **Table 1**, so that the exact numbers are reported, and has also been graphically illustrated in **Figure 1**. Most of the Cohen's *d* values (i.e. MHO *minus* MAO) and their confidence intervals were positive, which suggests that overall CRF was higher in MHO than in MAO. In two thirds of the studies (n=8, 67%), the confidence intervals did not include zero, indicating that the differences between MHO and MAO were mostly significant. According to Cohen's effect size, a Cohen's *d* value of less than 0.25 is considered trivial, 0.25–0.5 small, 0.5–0.8 moderate, and greater than 0.8 large³⁴. With a few exceptions in which the difference was large (i.e. Cohen's equal to 1)^{22,24} or very small (i.e. Cohen's equal to roughly 0.1)²⁶, the studies reviewed suggest that the differences observed between MHO and MAO (in favor to MHO) were of small-to-moderate size (see shaded region in **Figure 1**)^{20,21,23,25,27–31}. In our opinion, this small-to-moderate effect size is a reasonable and expected estimate, since other environmental factors as well as genetic factors additionally contribute to explain the variance in the metabolic profile of obese

individuals^{8,12-14}. In our previous study³¹, we observed that the differences in CRF between MHO and MAO were consistent and highly significant when obesity was defined according to BMI (N=5649 obese women and men) or body fat percentage - BF%- (N=12859 obese women and men) (**Figure 2**). It is important to highlight that the mean CRF levels represented in Figure 2 (and also the standardized mean differences shown in **Table 1** and **Figure 1**) are adjusted for a complete set of potential confounders (see **Figure 2**'s legend), while most (with only one exception²⁵) of the mean differences (Cohen's *d* values) from the rest of studies presented in **Table 1** and **Figure 1** were not adjusted for any potential confounder^{21,22,24,26-30,35} or just for age²³. *In summary*, these findings support the notion that a higher CRF should be considered as one more trait of the MHO phenotype. This conclusion is supported by recent data from intervention studies, in which Dalleck et al.³⁶ implemented a community-based exercise intervention program and observed that those participants who improved their CRF levels had higher chances to transition from MAO to MHO. For the first time, this study provides causal evidence supporting that the healthier metabolic profile of MHO can be partially achieved from their improved CRF level. In this context, it is important to highlight that transitioning from MHO to MAO is more likely to occur as age increases^{5,37}, future intervention studies should take into account that older people are at a higher risk of MAO.

Differences in MS and other PF components between MHO and MAO

We found very little information about how other components of PF might differ between MHO and MAO. Two studies focused on MS and reported mixed findings. Messier et al.²⁷ observed that when MS is expressed in relative terms (i.e. 1 repetition maximum in leg press divided by kg of body mass or kg of lean body mass) MHO had a borderline significantly higher MS than MAO [Cohen's *d* (confidence interval)=0.5

(0.0,0.9)], whereas this trend was opposite when MS was expressed in absolute terms (i.e. 1 repetition maximum in leg press). Aparicio et al.²³ assessed MS by means of the 30s chair stand test (relative strength, i.e. score depends on participant's body weight) and handgrip strength test (absolute strength). They found that MHO had a higher relative MS than MAO, yet this difference was not significant [Cohen's d (confidence interval)=0.3 (-0.2,0.9)]; whereas no difference was observed in absolute MS [Cohen's d (confidence interval)=0.0 (-0.6,0.6)]. This finding, in line with previous literature, suggests that the association between MS and cardio-metabolic risk markedly differs when strength is expressed in relative or absolute terms³⁸.

Finally, only Aparicio et al.²³ have studied other components of PF in relation to MHO, and concluded that MHO had a significantly better static balance and dynamic balance/agility than MAO [Cohen's d (confidence interval)=0.6 (0.0,1.2) and 0.9 (0.3,1.5) respectively]; while no difference was observed for flexibility tests. *In summary*, these findings suggest that MHO might have a better relative MS and dynamic balance/agility than MAO, however the limited number of studies call for caution when interpreting these findings.

Does PF influence the prognosis of MHO? Current evidence from prospective longitudinal data

From a public health and clinical point of view, the most relevant question is related to the prognosis of MHO individuals when compared with MAO individuals and also when compared with normal-weight individuals. The present review identified only one study, conducted by our group, that explored the role of CRF (no study examining other PF components) in relation with the prognosis of MHO³¹. In that study, we observed

that when models were not adjusted for CRF, the results suggested that obesity *per se* (either MHO or MAO) was associated with higher risk of all-cause, CVD and cancer mortality. However, the conclusion was modified when CRF was entered into the model, resulting in no difference in the prognosis between MHO and metabolically healthy normal-fat individuals. In addition, once CRF was accounted for and an accurate measure of adiposity was used, our results further supported that the MHO phenotype is a benign condition, with a better prognosis (30–50% lower risk) for mortality and morbidity than MAO individuals. The meta-analysis of Kramer et al.⁹ concluded that there is no healthy pattern of increased weight, which is in agreement with our findings when CRF was not accounted for, but in disagreement with the CRF-adjusted findings. A recent and large-cohort study provided evidence supporting that MHO is associated with a low risk for myocardial infarction, but obesity *per se* (with or without metabolic abnormalities) is associated³⁹, suggesting that different prognosis might exist for different manifestations of CVD. The authors acknowledged as a limitation the lack of CRF data in their study. Unfortunately, to the best of our knowledge (including information from systematically reviews⁹), no other previous study on this topic has considered the role of CRF in the prognosis of MHO individuals, which should be studied in the future. *In summary*, these findings suggest that CRF might play a key role in the prognosis of MHO individuals, yet these findings are based on a single study and need therefore to be confirmed or contrasted in future studies. Clearly, substantial data, including in the analysis of studies on the “obesity paradox” (at least in coronary heart disease and heart failure), point out that CRF markedly alters the relationship between measures of adiposity and subsequent prognosis^{40–44}.

Nevertheless, although more emphasis should be placed on improving CRF¹⁵, obesity is still related with poorer mental health, social relationships, osteoarthritis and chronic pain, among others⁴⁵. The public health message therefore is still to focus on prevention and treatment of obesity, but also against low levels of CRF⁴.

Proposal of a harmonized definition of the MHO and MAO phenotypes

While reviewing the existing literature on MHO individuals, it became clear that a harmonized definition of the MHO was highly needed. A standardized definition of MHO would increase the comparability of the data, allowing accurate meta-analyses in the future. Based on several facts, we hereby propose a harmonized definition of the MHO and MAO phenotypes (**Table 3**).

Future directions

In addition to the need of a harmonized MHO definition, several future directions for research have been identified in this review: 1) More investigation is needed for a better understanding of the interrelationship between MHO and cardiorespiratory fit obese phenotypes⁴⁶; 2) Whether the differences in PF between MHO and MAO differ by gender and whether the role of PF in the prognosis of MHO differ by gender is unknown and need to be addressed; 3) There is a need for further study on the role of PF, including both CRF and MS, in relation to the MHO phenotype (only 1 study found).

Conclusions

The studies reviewed suggest that a higher CRF level should be considered a characteristic of the MHO phenotype. Likewise, CRF seems to play a key role in the prognosis of the MHO individuals, yet this statement is based on a single study and future studies are needed to confirm or contrast these findings. In a perfect world, all individuals would be fit and metabolically healthy at any weight.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Table 1. Studies examining the differences in physical fitness (i.e. cardiorespiratory fitness and other fitness components) between metabolically healthy but obese and metabolically abnormal obese.

Studies with a sample size < 100						
Reference	Age (y=mean±SD)	Sample size (country)	Fitness assessment method	MHO/MAO definition	Diff. MHO-MAO	Conclusion
Brochu et al. (2001) ²⁰	MHO= 58.0 ± 6.3 MAO= 58.6 ± 5.9	43 obese postmenopausal women (USA) MHO=17 MAO=26	CRF: VO ₂ peak was measured by a gas analyzer during an incremental (grade increasing) treadmill test	Insulin sensitivity: MHO if HE clamp (M values) higher than 8.0 mg/min/kg lean body mass; MAO otherwise.	NS (+) ES(CI)=0.4 (-0.2,1.0)	MHO had higher VO ₂ peak compared with their MAO peers, yet this difference was not significant.
Karelis et al. (2005) ²¹	MHO= 56.7 ± 6.7 MAO= 59.2 ± 5.1	44 obese* postmenopausal women (Canada) MHO=22 MAO=22	CRF: VO ₂ peak was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test.	Insulin sensitivity: MHO if belonging to quartile 4 th of HE clamp (M/FFM ≥12.6) and MAO if belonging to quartile 1 st of HE clamp (M/FFM <9.3).	NS (+) ES(CI)=0.4 (-0.2,1.0)	MHO had higher VO ₂ peak compared with their MAO peers, yet this difference was not significant.
Bouchard et al. (2011) ²²	MHO= 60.7 ± 1.4 MAO= 58.2 ± 1.2	86 obese women (Canada) MHO=18 MAO=68	CRF was assessed by the 6-min walk test.	Metabolic syndrome: MHO if meeting 0 or 1 of the 5 risk factors (WC included) proposed by the ATP III ⁴⁷ ; MAO otherwise.	+ ES(CI)=1.1 (0.6,1.5)	MHO had a significantly higher CRF level than their MAO peers, as indicated by a higher performance in the 6-min walk test.

Aparicio et al. (2013) ²³	All sample = 52.49 ± 0.58	49 obese women (Morocco) MHO=14 MAO=35	CRF was assessed by the 6-min walk test. MS was assessed by the 30-s chair stand and handgrip strength test. Flexibility was assessed by the back scratch and the chair-sit-and-reach tests. Static Balance/agility was assessed by 30-s bling flamingo and dynamic balance/agility by 8-foot up-and-go test.	Metabolic syndrome: MHO if meeting 0 or 1 of the 4 risk factors (WC excluded) proposed by international consensus, i.e. Alberti et al. (2009) ³² ; MAO otherwise.	+ CRF:ES(CI)=0.6 (0.0,1.2) Balance-static:ES(CI)=0.6 (0.0,1.2) Balance-agility: ES(CI)=0.9 (0.3,1.5) NS (+) MS-lower body (relative strength): ES(CI)=0.3 (-0.2,0.9) MS-upper body (absolute strength):ES(CI)=0.0 (-0.6,0.6) Flex-lower body :ES(CI)=0.1 (-0.5,0.7) Flex-upper body :ES(CI)=0.2 (-0.4,0.7)	MHO group performed significantly better than MAO in CRF, static balance and dynamic balance/agility tests. There were not significant differences between groups in MS and flexibility tests.
Poelkens et al. (2014) ²⁴	MHO= 50.0 ± 5.0 MAO= 52.0 ± 7.0	20 obese women (The Netherlands) MHO=10 MAO=10	CRF: VO ₂ max was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test.	Metabolic syndrome: MHO if having a high WC but 0 of the resting 4 risk factors proposed by international consensus, i.e. Alberti et al. (2009) ³² ; MAO otherwise.	+ ES(CI)=1.0 (0.0,2.0)	MHO had significantly higher VO ₂ max compared with their MAO peers. In addition, VO ₂ max was the strongest predictor of being MHO out of a large number of candidate factors studied (e.g. body fat distribution,

						adiponectin, c-reactive protein, TNF- α).	
Yu et al. (2013) ²⁵	All sample= 61.1 \pm 3.1	98 postmenopausal overweight/obese** women (China) MHO=84 MAO=14	CRF: VO ₂ max was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test.	Metabolic syndrome: MHO if meeting 0 or 1 of the 4 risk factors (WC excluded) proposed by international consensus, i.e. Alberti et al. (2009) ³² (with only one cut-point slightly different, i.e. 6.1 instead of 5.6 mmol/L for glucose); MAO otherwise.	+	ES(CI)=0.7(0.3,1.2)	MHO had significantly higher VO ₂ max than their MAO peers.
Wiklund et al. (2014) ²⁶	MHO= 39.7 \pm 7.6 MAO= 44.1 \pm 6.1	78 premenopausal overweight/obese women (Finland) MHO=42 MAO=36	CRF: VO ₂ max was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test.	Metabolic syndrome: MHO if having a high WC but 0 of the resting 4 risk factors proposed by international consensus, i.e. Alberti et al. (2009) ³² ; MAO if meeting 3 to 5 risk factors.	NS (+)	ES(CI)=0.1(-0.4,0.5)	MHO had higher VO ₂ max compared with their MAO peers, yet this difference was not significant.
Studies with a sample size between 100 and 200							
Messier et al. (2008) ²⁷	All sample= 57.7 \pm 4.8	127 obese* postmenopausal women (Canada) MHO=42 MAO=42	CRF: VO ₂ max was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test. MS: Maximal leg-press strength was assessed by 1RM.	Insulin sensitivity: MHO if belonging to tertile 3 rd of HE clamp (M/kg lean body >12.9) and MAO if belonging to tertile 1 st of HE clamp (M/ kg lean body <10.9).	+	CRF: ES(CI)=0.6 (0.1,1.0) MS lower body (relative strength):	MHO had significantly higher VO ₂ max compared with their MAO peers. When MS was expressed in relative terms (i.e. divided by kg of lean body mass), MHO had

					ES(CI)=0.5(0.0,0.9)	borderline significantly higher MS than their MAO. The trend was opposite when MS was expressed in absolute terms (i.e. 1RM values).
Messier V et al. (2010) ²⁸	57.3 ± 4.8	113 obese postmenopausal women (Canada) Sample size of the MHO and MAO groups differed depending on the MHO definition used (5 different)	CRF: VO ₂ max was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test.	5 different definitions were used in this study. Presented here the most similar and comparable with the literature. Inulin sensitivity: MHO defined as the upper quartile of HE clamp and MAO as the lower quartile. Metabolic syndrome: MHO defined as having 0–1 of the risk factors proposed by international consensus, i.e. Alberti et al. (2009) ³² , but with the additional inclusion of HOMA and C-reactive protein.	+ When using the HE clamp definition: ES(CI)=0.6(0.1,1.1) NS (+) When using the metabolic syndrome definition. ES(CI)=0.4(0.0,0.7)	MHO had higher VO ₂ max than their MAO peers, being this difference significant when MHO was defined based on HE clamp and borderline significant when MHO was defined based on the metabolic syndrome criteria.
Sénéchal et al. (2013) ²⁹	15.2 ± 1.5	108 overweight/obese adolescent girls and boys (Canada) MHO=27 MAO=81	CRF: VO ₂ max was measured by a gas analyzer during an incremental (Watts increasing) cycle ergometer test.	Metabolic syndrome: MHO if meeting 0 of the 4 risk factors (WC excluded) proposed by Jolliffe et al. ⁴⁸ for use in youth, which are based on sex-and-age specific cut-points interpolated from the adults' criteria (with the additional inclusion of hepatic triglyceride content); MAO otherwise.	NS (+) ES(CI)=0.4(0.0,0.8)	MHO had higher VO ₂ max compared with their MAO peers, yet this difference was borderline non-significant.
Dalzell et al. (2014) ³⁰	MHO=51 ± 8 MAO=	134 obese women and men (Canada) MHO=55	CRF: VO ₂ peak was measured by a gas analyzer during an incremental (grade increasing)	Metabolic syndrome: MHO if meeting 0 or 1 of the 4 risk factors (WC excluded) proposed	NS (+) ES(CI)=0.4(0.1,0.8)	MHO had significantly higher VO ₂ peak compared with their MAO peers.

	54 ± 9	MAO=79	treadmill test.	by international consensus, i.e. Alberti et al. (2009) ³² ; MAO otherwise.		
Studies with a sample size >200						
Ortega et al. (2013) ³¹	44.2 ± 9.9	When obesity was defined based on BMI, 5649 obese women and men (USA) MHO=1738 MAO=3911	CRF: VO ₂ max was estimated from an incremental (grade increasing) treadmill test.	Metabolic syndrome: MHO if meeting 0 or 1 of the 4 risk factors (WC excluded) proposed by international consensus, i.e. Alberti et al. (2009) ³² ; MAO otherwise.	+	MHO had significantly higher VO ₂ max than their MAO peers both when obesity was defined using BMI or BF%.
		When obesity was defined based on BF%, 12859 obese men and women MHO=5959 MAO=6900			+	BF%-obesity: ES(CI)=0.3(0.3,0.4)

* In these 2 studies, the inclusion criterion was BMI>27kg/m², so that this sample should be considered as a mixture of overweight and obese participants.

** In this study overweight was defined as ≥23kg/m² which is the standard cut-point for overweight in Asian population.

Abbreviations used in the table (ordered by first appearance): SD, standard deviation; MHO, metabolically healthy but obese; MAO, metabolically abnormal obese; CRF, cardiorespiratory fitness; VO₂max or VO₂peak, maximal or peak oxygen consumption; HE clamp, hyperinsulinemic-euglycemic clamp; NS (+) indicates that fitness level was higher in MHO than in MAO, but the difference was not significant; + indicate that fitness level was significantly (P<0.05) higher in MHO than in MAO; ES indicates Effect size, i.e. Cohen's *d*; CI, confidence interval of the Cohen's *d*; FFM, fat-free mass; MS, muscular strength; WC, waist circumference; ATP III, Adult Treatment Panel III; 1RM, 1 repetition maximum; BMI, body mass index; BF%, body fat percentage.

Table 2. Summary of the characteristics of the studies reviewed.

	Number of studies (N=12)	%
Gender of participants		
Only female participants	9	75
Female and male participants analyzed together	3	25
Age of participants		
Adult-elderly	11	92
Youth	1	8
Number of participants		
< 100 participants	7	58
Between 100 and 200 participants	4	33
> 200 participants (i.e. N=5649 / 12859 for BMI-obesity / BF%-obesity)	1	8
Participants' country		
Canada	6	50
USA	2	17
The Netherlands	1	8
Finland	1	8
Morocco	1	8
China	1	8
Weight status of the MHO and MAO participants		
Including only obese participants	7	58
Including a combination of overweight and obese participants	5	42
Definition of MHO		
Based on metabolic syndrome criteria (with slight modifications)	9	75
Based on insulin sensitivity (HE clamp)	4	33
Fitness variables studied		
Cardiorespiratory fitness	12	100
Muscular strength	2	17
Others: flexibility, balance and agility	1	8
Method/test used to assess fitness		
Studies with cycle ergometer protocol	7	58
Studies with treadmill protocol	3	25
Studies with others test (i.e. 6 min walk)	2	17
Indicator of cardiorespiratory fitness level		
VO ₂ max or VO ₂ peak	10	83
Performance (distance in m) in the 6 min walk test	2	17

MHO, metabolically healthy but obese; MAO, metabolically abnormal obese; HE clamp, hyperinsulinemic-euglycemic clamp.

Table 3. Harmonizing the definition of Metabolically Healthy but Obese in adults and youth.

The present proposal for harmonizing the MHO definition in adults is based on two facts:

Fact 1: Most of previous studies have used definitions of MHO based on metabolic syndrome criteria²²⁻³¹, but using different definitions of metabolic syndrome. Nowadays there is a widely and internationally accepted definition of the metabolic syndrome criteria³², which is a consensus from major International Organizations, i.e. the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity .

Recommendation 1: To link the harmonized definition of MHO in adults to this consensus effort already done for metabolic syndrome.

Fact 2: As indicated by its name, MHO individuals are already obese and consequently most of them meet the metabolic syndrome criterion of high waist circumference^{23,31}, specifically 80 to 95% of them, depending on the cut-points used (102/88cm *versus* 94/80cm³²).

Recommendation 2: In accordance previous literature^{8,23,25,30,31,49}, we suggest to exclude waist circumference among the criteria to be considered for MHO.

Definition of MHO in adults

Based on the two facts and recommendations indicated above, a person would be classified as MHO if meeting 0 or 1* of the remaining metabolic syndrome criteria (i.e. after excluding waist circumference), which would be the following³²:

Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mmHg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL (5.6 mmol/L)

Definition of MAO in adults

A person would be classified as MAO if meeting 2 to 4 of the criteria indicated above.

The present proposal for harmonizing the MHO definition in youth is based on two facts:

Fact 1: The literature available about MHO in youth is much less than in adults, and its definition complicated, since abnormalities in the metabolic profile became more frequent in adulthood. Nevertheless, Jolliffe and Janssen developed age- and gender-specific cut-points to define metabolic syndrome in adolescents aged 12 to 19 years⁴⁸. These cut-points are based on mathematical models so that they are equivalent to those proposed for adults by the IDF and the ATP-III. Other definitions for metabolic syndrome in youth have been proposed, but they are not gender- and age-specific which can be a problem due to the marked physiological changes occurring during puberty and growth in general.

Recommendation 1: To link the harmonized definition of MHO in youth to this consensus effort already done for metabolic syndrome⁴⁸, which is equivalent to the adult criteria mentioned above³².

Fact 2: As indicated above in adults, most of obese adolescents would meet the criterion of high waist circumference.

Recommendation 2: In accordance previous literature in youth^{29,50,51}, we suggest to exclude waist circumference among the criteria to be considered for MHO.

Definition of MHO in youth

Based on the two facts and recommendations indicated above, a young person would be classified as MHO if meeting 0* of the remaining metabolic syndrome criteria (i.e. after excluding waist circumference).

Definition of MAO in youth

A person would be classified as MAO if meeting 1 to 4 of the criteria indicated above.

MHO, Metabolically Healthy but Obese; HDL-C, high-density lipoprotein cholesterol; MAO, Metabolically Abnormal Obese; IDF, International Diabetes Federation; ATP III, Adult Treatment Panel III.

* In adults, some studies defined MHO as meeting 0 of these criteria and some others as meeting 0 or 1 of these criteria; we propose to use 0 or 1, because it has been more used in the literature, allowing comparison with more previous studies. In youth, our proposal is to define MHO as meeting 0 of this criteria (i.e. a more strict definition), since young people have overall healthier metabolic profile than adults.

†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose of ω -3 fatty acids presumes high triglycerides.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

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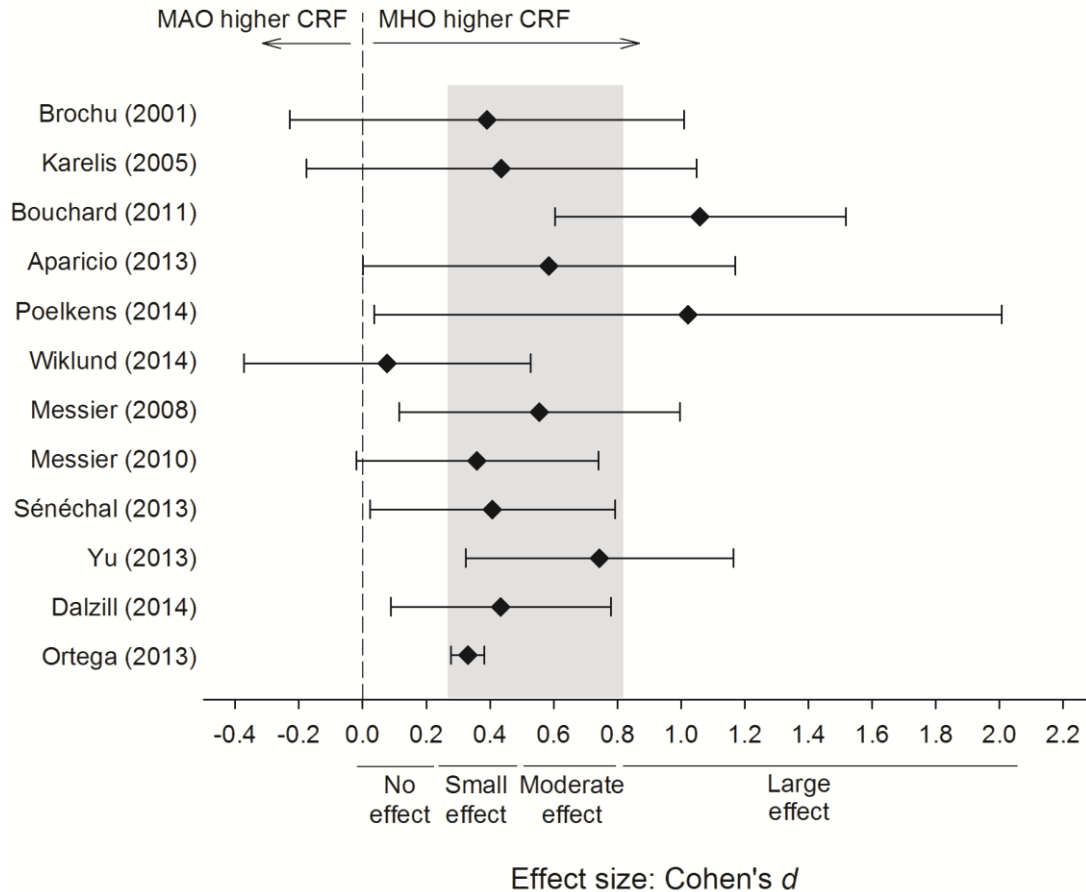


Figure 1. Standardized mean differences (effect size: Cohen's *d*) between metabolically healthy but obese (MHO) and metabolically abnormal obese (MAO). Error bars represent means and 95% confidence intervals.

Effect size: Cohen's *d* was computed from the data provided in each study (i.e. *N*, mean and standard deviation or standard error of the mean). According to Cohen's effect size, an Cohen's *d* value of less than 0.25 is considered trivial, 0.25–0.5 small, 0.5–0.8 moderate, and greater than 0.8 large³⁴.

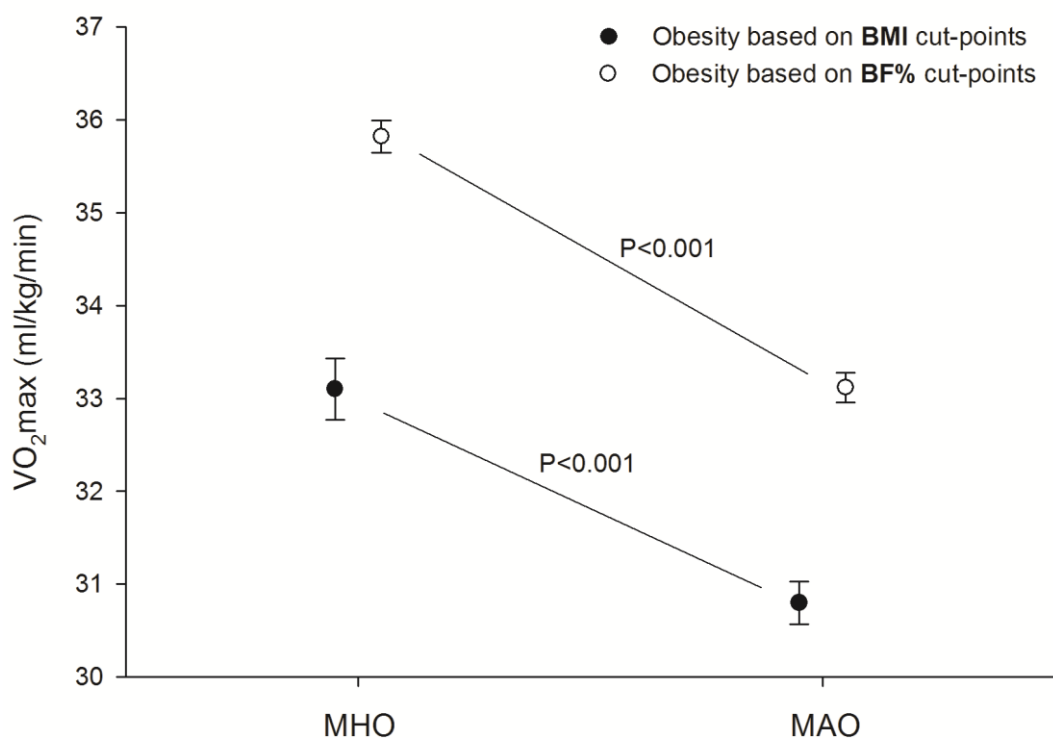


Figure 2. Differences in cardiorespiratory fitness (maximal oxygen consumption, $VO_2\max$) between metabolically healthy but obese (MHO) and metabolically abnormal obese (MAO), when obesity was defined according to body mass index (BMI, $N=5649$) and percent body fat (BF%, $N=12859$).

The circled points and error bars represent adjusted means and 95% confidence intervals, respectively. The model (one-way analysis of covariance) was adjusted for age, sex, examination year, smoking, and alcohol consumption. Figure created from the Aerobics Center Longitudinal Study (ACLS) data published by Ortega et al.³¹