

# Can we identify metabolically healthy but obese individuals (MHO)?

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## SUMMARY

**Objectives:** A unique subset of obese individuals termed, Metabolically Healthy but Obese (MHO), has been described in the literature. However, there is no agreed upon method to identify MHO individuals for research protocols or in clinical practice. Therefore, we examined a large cohort of obese older women to attempt to develop a first set of clinical markers that may identify MHO individuals.

**Methods:** We studied 154 obese postmenopausal women (age: 57.0  $\pm$  5.3 years and BMI: 34.3  $\pm$  5.5 kg/m<sup>2</sup>). Selection criteria for MHO individuals were partially based on the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) for lipid profiles (triglycerides:  $\leq$ 1.7 mmol/l, total cholesterol:  $\leq$ 5.2 mmol/l, HDL-cholesterol:  $\geq$ 1.3 mmol/l and LDL-cholesterol:  $\leq$ 2.6 mmol/l) and from the study of Brochu *et al.* (2001) for insulin sensitivity (HOMA  $\leq$ 1.95). When 4 out of 5 criteria are met, we suggest that a diagnosis of the MHO individual could be made.

**Results:** Based on the proposed criteria, 19 out of 154 (12.3%) postmenopausal women subjects were identified as MHO. By design, MHO individuals showed a favourable lipid profile and higher insulin sensitivity values.

**Conclusion:** We suggest a potential new set of clinical markers to identify MHO individuals. Identifying MHO individuals could have important implications for therapeutic medical decision making, subject characterization in research protocols and in medical education.

**Key-words:** Obesity · Metabolic syndrome · Insulin resistance · Lipid profile.

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## RÉSUMÉ

### Pouvons-nous identifier les individus obèses sans anomalie métabolique (MHO) ?

**Objectifs :** Un sous-ensemble d'individus nommés, obèses mais ne présentant pas d'anomalies métaboliques, MHO, (Metabolically Healthy Obese), a été décrit dans la littérature. Il n'existe pas encore de définition permettant d'identifier cette population. Nous avons examiné une cohorte de femmes obèses dans le but de développer un premier ensemble de marqueurs cliniques afin d'identifier les individus MHO.

**Méthodes :** Étude transversale sur 154 femmes post-ménopausées obèses (âge :  $\pm$  57,0 5,3 ans et BMI : 34,3  $\pm$  5,5 kg/m<sup>2</sup>). Les critères de sélection pour les individus MHO sont partiellement basés sur le consensus Américain pour le traitement des dyslipidémies (NCEP ATP III) pour le profil lipidique (triglycérides :  $\leq$ 1,7 mmol/l, cholestérol total :  $\leq$ 5,2 mmol/l, HDL-cholestérol :  $\geq$ 1,3 mmol/l et LDL-cholestérol :  $\leq$ 2,6 mmol/l) et sur l'étude de Brochu et col (2001) pour la sensibilité à l'insuline (HOMA  $\leq$ 1,95). Quand 4 sur 5 critères sont présents, nous proposons de considérer un individu obèse comme étant MHO.

**Résultats :** Avec les critères proposés, 19 sur 154 (12,3%) femmes en post ménopause sont identifiées comme MHO et présentent par définition un profil lipidique favorable ainsi qu'une haute sensibilité à l'insuline.

**Conclusion :** Nous suggérons un ensemble de marqueurs cliniques pour identifier des individus de MHO. L'identification des individus de MHO pourrait avoir des implications importantes dans la pratique clinique et dans des protocoles de recherches ainsi que dans l'éducation médicale.

**Mots-clés :** Obésité · Syndrome métabolique · Résistance d'insuline · Cholestérol-total · Cholestérol LDL · Triglycérides.

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There has been considerable interest recently in the establishment of clinical criteria to identify individuals who are potentially at risk for metabolic and cardiovascular complications. For example, much attention has been paid to the establishment of criteria to identify individuals having the metabolic syndrome [1]. This clustering of risky phenotypes (central body fat, hypertension, dyslipidemia, etc), in which insulin resistance may play a central role, predisposes individuals to an increased risk of cardiovascular disease and type 2 diabetes mellitus [1].

Although scientific efforts have been directed toward characterizing individuals having the metabolic syndrome and/or disease-related endpoints, the clinical utility of identifying “healthy characteristics” in obese individuals has received less attention. In other words, is there clinical utility in identifying individuals who, despite having an outward appearance of a potentially risky condition (i.e., obesity), may actually be quite healthy from a metabolic standpoint? Interestingly, a unique subset of obese individuals has been described in the literature that appears to be “protected” from development of metabolic disturbances associated with obesity [2, 3]. These individuals, termed “Metabolically Healthy, but Obese” (MHO), despite having large quantities of fat mass, exhibit a healthy metabolic profile including remarkably high levels of insulin sensitivity and a favorable lipid profile [4].

To our knowledge, there is no agreed upon method to identify MHO individuals for research protocols or in clinical practice. This is not a trivial argument. It is conceivable that these patients require different medical management and that inclusion of MHO individuals in research protocols with individuals possessing metabolic complications of obesity may confound data interpretation. We have recently raised this issue in a limited data set [5]. Therefore, we considered it timely to potentially provide simple clinical metabolic criteria to identify MHO individuals in a large data set of older postmenopausal women.

## Research design and methods

### Subjects

The population was selected from a series of studies conducted between 2000 and 2004. We extracted data on all subjects undergoing identical baseline phenotyping measurements. One hundred and fifty four postmenopausal obese women met these criteria. This population included a retrospective series of 77 previously published patients and 77 new prospective patients.

### Body Composition and Blood Pressure

Body weight was measured using an electronic scale (Balance Industrielles, Montreal, Canada) and standing height was measured using a wall stadiometer (Perspective

Enterprises, Michigan, USA). Fat-free mass and fat mass were evaluated by Dual Energy X-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, USA). Waist circumference was measured with a flexible steel metric tape at the nearest 0.5 cm. Blood pressure was determined as the average of the last four readings of five (at 1/min) in the left arm, after subjects rested quietly for 10 min, using a Dinamap automatic machine (Welch Allyn Inc., San Diego, USA).

### Blood Samples

After an overnight fast (12 h), venous blood samples were collected for the measurement of plasma concentrations of total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose and insulin. Plasma was analyzed on the day of collection. Analyses were done on the COBAS INTEGRA 400 (Roche Diagnostic, Montreal, Canada) analyzer for total cholesterol, HDL-cholesterol, triglycerides and glucose. Total-cholesterol, HDL-cholesterol and triglycerides were used in the Friedewald formula [6] to calculate LDL-cholesterol concentration. Insulin levels were determined by automated radioimmunoassay (Medicorp, Montreal, Canada). Homeostasis model assessment (HOMA) was calculated according to the formula of Matthews *et al.* [7].

### Establishment of MHO criteria

We have attempted to establish several criteria to classify individuals as MHO based on several literature sources. First, we have proposed lipid cut-points that are partially based on the National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III) [8]. These cut-points include: triglycerides:  $\Omega 1.7$  mmol/l, total cholesterol:  $\Omega 5.2$  mmol/l, HDL-cholesterol:  $\Omega 1.3$  mmol/l and LDL-cholesterol:  $\Omega 2.6$  mmol/l. These cut-points for the lipid profile were chosen to define a very low risk population [1]. Second, we sought a measure of insulin sensitivity given its central importance in the metabolic syndrome. The detailed study of Brochu *et al.* [4] measured euglycemic-hyperinsulinemic clamps in older obese women and suggested that a value exceeding 8 ml/kg/FFM was a cut-point for MHO individuals. However, because clamp methodology is not practical from a clinical standpoint, we extracted baseline values for insulin and glucose to propose a cut-point based on HOMA ( $\Omega 1.95$ ). We would suggest that when 4 out of 5 criteria are met, a diagnosis of the MHO individual could be made. Fasting plasma glucose and blood pressure were not included in these selection criteria because diabetics and hypertensive individuals were excluded from studies from which these individuals were selected. Waist circumference was also excluded as a potential marker because most obese individuals have large waist circumferences; and thus this phenotype becomes non-discriminatory in the identification of MHO individuals.

## Statistical Analysis

The data are expressed as the mean  $\pm$  SD. Unpaired t-tests were performed to analyze mean differences between two groups. Significance was accepted at  $P < 0.05$ .

## Results

Nineteen out of 154 (12.3%) postmenopausal women subjects met 4 out of 5 proposed criteria and were thus identified as MHO. As shown in *Table I* there was no significant difference in clinical parameters between MHO and at risk obese individuals. *Table II* shows the proposed markers with their defining levels. MHO individuals had significantly lower values for HOMA, triglycerides, total-cholesterol and LDL-cholesterol as well as significantly higher values for HDL-cholesterol than at risk individuals. When we examined the at risk obese group, we found that ~25% met 3/5 criteria; ~47% met 2/5 criteria, ~20% met 1/5 criteria and ~7% met 0/5 criteria.

## Conclusion

Metabolically healthy, but obese individuals are a unique subset of individuals that have recently attracted new attention in the literature [4]. It is presently unclear as to how to identify these persons. Using several sources of criteria, we suggest a potential new set of clinical markers to identify MHO individuals. Previous work has identified MHO individuals based exclusively on a glucose disposal rate greater than 8 mg/kg/fat-free mass, using the hyperinsulinemic-euglycemic clamp technology [4]. How-

**Table I**  
Physical characteristics of MHO and at risk obese postmenopausal women.

Parameters	MHO (n = 19)	At risk (n = 135)
Age (years)	56.9 $\pm$ 5.9	57.0 $\pm$ 5.3
Height (m)	1.63 $\pm$ 0.05	1.61 $\pm$ 0.06
Weight (kg)	89.6 $\pm$ 16.4	89.1 $\pm$ 15.8
Body Mass Index	33.5 $\pm$ 5.2	34.4 $\pm$ 5.5
Fat Mass (kg)	41.4 $\pm$ 8.7	40.8 $\pm$ 10.2
Fat Free Mass (kg)	44.7 $\pm$ 6.6	45.4 $\pm$ 6.0
Waist Circumference (cm) (n = 8/60)	91.5 $\pm$ 5.9	98.5 $\pm$ 9.7
Systolic Blood Pressure (mm Hg)	129.4 $\pm$ 19.3	126.7 $\pm$ 15.9
Diastolic Blood Pressure (mm Hg)	75.3 $\pm$ 10.8	72.8 $\pm$ 9.9

Values are means  $\pm$  SD.

**Table II**  
Metabolic markers that identify metabolically healthy but obese individuals.

Metabolic markers	Defining level	MHO (n = 19)	At risk (n = 135)
HOMA Index (n = 16/118)	$\geq 1.95$	2.30 $\pm$ 1.2*	3.26 $\pm$ 1.8
Triglycerides (mmol/l)	$\geq 1.7$	1.1 $\pm$ 0.4*	1.8 $\pm$ 0.7
Total cholesterol (mmol/l)	$\geq 5.2$	4.3 $\pm$ 0.5*	5.4 $\pm$ 0.9
LDL cholesterol (mmol/l)	$\geq 2.6$	2.6 $\pm$ 0.4*	3.4 $\pm$ 0.8
HDL cholesterol (mmol/l)	$\leq 1.3$	1.5 $\pm$ 0.2*	1.3 $\pm$ 0.3

Values are means  $\pm$  SD. \*Significantly different from at risk group ( $P < 0.05$ ). When 4 out of 5 criteria are met, a diagnosis of the MHO individual could be made.

ever, since the “clamp” technique is time consuming for the measurement of insulin sensitivity and a method reserved for research purposes, we deemed it useful to develop and propose more practical clinical markers in order to identify MHO patients by combining the evaluation of insulin sensitivity from fasting values of HOMA [4] and a lipid profile [8].

In this volunteer patient population, 19 postmenopausal women were identified as a MHO individual out of 154 subjects (12.3%). By design, these MHO individuals showed significantly lower levels of HOMA, triglycerides, total-cholesterol and LDL-cholesterol as well as significantly higher values for HDL-cholesterol than at risk individuals. Thus, one could suggest that these individuals are “metabolically healthy”, based on these parameters. Although, we noted that ~12% of our cohort met the MHO criteria, the true prevalence of MHO individuals in the population is unknown.

The proposed choice for MHO clinical markers is partially based on the National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III) [8] for the lipid profiles, and from the study of Brochu *et al.* [4] for HOMA. Pooling criteria from these studies adds scientific rigor and clinical relevance in our attempt to establish suggested criteria for the identification of MHO individuals. Although somewhat arbitrary, we would suggest that when 4 out of 5 of the listed clinical markers are satisfied, a diagnosis of the MHO individual could be made. This type of approach is somewhat analogous to the characterization of the metabolic syndrome used by the ATP III in which 3 out of 5 criteria must be met to meet the diagnosis of the metabolic syndrome [8]. However, we chose for 4 out of 5 criteria because we seek to apply more strict criteria because the

goal is to define a true MHO population which is different from a non-metabolic syndrome population. It should be noted that the list of criteria could be modified and that the cut-points should be refined in future studies in particular for blood pressure, waist circumference, fasting glucose and eventually post-load glycemia. Nonetheless, we feel this represents a first attempt to provide valid criteria to identify MHO individuals based on a reasonably large sample size. We understand that the presentation of a new set of criteria is open to criticism. For example, even the metabolic syndrome criteria proposed more than 20 years ago are still being widely debated.

Patients meeting this profile theoretically could have a lower risk for cardiovascular disease. Interestingly, a recent prospective study suggested that the metabolic syndrome and not obesity *per se* predicts future cardiovascular risk in women [9]. Thus, it is possible that obesity treatment should be directed at the metabolic syndrome, *per se*, and not at the high levels of body fat. It should be noted that it is not our intention to convey the notion that MHO individuals have a global healthy profile. A more prudent statement would be that MHO individuals are potentially metabolically healthy. These individuals, however, may still be at risk for other obesity related complications such as sleep apnea, cancer and musculoskeletal problems. Furthermore, it is unknown whether MHO individuals remain metabolically healthy during the span of their lifetime.

We acknowledge that inclusion criteria in this study could introduce a selection bias that may artificially augment the number of MHO individuals in our cohort. The inclusion of both total and LDL-cholesterol should be re-evaluated since these two parameters are highly correlated and that LDL-cholesterol abnormalities in obesity are more qualitative than quantitative [10]. Moreover, the measurement of plasma insulin levels for the determination of HOMA may also need to be re-evaluated. The absence of standardisation for insulin assay does not allow proposing a strict definition for the HOMA cut-point which validity is limited to the specific radioimmunoassay used in this study [11]. It should be noted that HOMA values in the MHO group (2.30  $\pm$  1.2) were higher than the proposed defining level ( $\Omega$ 1.95). This is explained by the fact that we opted to chose 4 out of 5 criteria for the diagnosis of the MHO individual. Therefore, several MHO subjects met all the lipid profile criteria but not the HOMA criteria. Finally, these criteria may eventually need to be broadened to include surrogates markers of cardiovascular risk such as intima-media thickness and inflammatory markers.

We believe our results may be useful for clinical and research purposes. It is important to educate health care professionals and physicians regarding the different needs of subsets of obese individuals. The identification of the MHO individual in both clinical and scientific settings could have important implications for therapeutic medical decision making. The tendency to treat obese individuals

with a “one size fits all” may be counterproductive with the MHO individual. Furthermore, these clinical markers may be of use in subject characterization in research protocols for future studies. If MHO and at risk obese individuals are statistically analyzed within the same cohort, the mixing of “apples and oranges” may obscure data interpretation. Finally, these types of criteria will need to be evaluated in a randomly selected population that is more diverse in nature.

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