

Metabolically Healthy but Obese, a Matter of Time? Findings From the Prospective Pizarra Study

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Background: Prospective longitudinal studies evaluating the relevance of “Metabolically Healthy but Obese” (MHO) phenotype at risk for type 2 diabetes mellitus (T2D) and cardiovascular diseases are few and results are contradictory.

Methods: As a representative of the general population, 1051 individuals were evaluated in 1997–1998 and re-evaluated after 6 years and 11 years. Subjects without known T2D were given an oral glucose tolerance test. Anthropometric and biochemical variables were measured. Four sets of criteria were considered to define MHO subjects besides body mass index ≥ 30 kg/m²: A: Homeostatic Model of Assessment-Insulin Resistance Index (HOMA-IR) <90th percentile; B: HOMA-IR <90th percentile, high-density lipoprotein cholesterol >40 mg/dL in men and high-density lipoprotein cholesterol >50 mg/dL in women, triglycerides <150 mg/dL, fasting glucose <110 mg/dL, and blood pressure $\leq 140/90$ mm Hg; C: HOMA-IR <90th percentile, triglycerides <150 mg/dL, fasting glucose <110 mg/dL, and blood pressure $\leq 140/90$ mm Hg; D: HOMA-IR <90th percentile, triglycerides <150 mg/dL, and fasting glucose <110 mg/dL. Subjects with T2D at baseline were excluded from the calculations of incidence of T2D.

Results: The baseline prevalence of MHO phenotype varied between 3.0% and 16.9%, depending on the set of criteria chosen. Metabolically nonhealthy obese subjects were at highest risk for becoming diabetic after 11 years of follow-up (odds ratio = 8.20; 95% confidence interval = 2.72–24.72; $P < .0001$). In MHO subjects the risk for becoming diabetic was lower than in metabolically nonhealthy obese subjects, but this risk remained significant (odds ratio = 3.13; 95% confidence interval = 1.07–9.17; $P = .02$). In subjects who lost weight during the study, the association between MHO phenotype and T2D incidence disappeared, even after adjusting for HOMA-IR.

Conclusions: The results suggest that MHO is a dynamic concept that should be taken into account over time. As a clinical entity, it may be questionable. (*J Clin Endocrinol Metab* 98: 2318–2325, 2013)

The prevalence of obesity is constantly increasing, and it now represents one of the major health care and social problems of our time. In Spain, the prevalence of obesity is 28.5%, and 51% of adult persons are overweight (1).

Obesity is a risk factor for several clinical and metabolic problems. However, there is huge individual variability in the risk for metabolic and clinical morbidity associated with obesity (2, 3). This has led to the description in the medical literature of a group of obese subjects who, despite having a high body mass index (BMI), are relatively resistant to the development of clinical and metabolic abnormalities associated with obesity. These subjects have been referred to as “Metabolically Healthy but Obese” (MHO) (4). A systematic review of 14 recently published studies (5) found that the prevalence of the MHO phenotype ranged from 18% to 44%, although prevalence rates as low as 6% of obese subjects have also been reported (6). However, the criteria used to identify MHO subjects are far from being systematized. In some studies the most important criterion was the absence of type 2 diabetes mellitus (T2D) or certain fasting serum glucose levels (7, 8). Most studies have considered insulin resistance, measured by the Homeostatic Model of Assessment-Insulin Resistance index (HOMA-IR) (9–12), the hyperinsulinemic-euglycemic clamp (4, 13–15), oral glucose tolerance test (OGTT) (16), fasting serum insulin (17), or by an insulin suppression test (18). Sometimes, the only criterion of metabolic normality has been insulin sensitivity (4, 10, 12, 15–17, 19), whereas in other studies the criteria required favorable levels of high-density lipoprotein cholesterol (HDL-c), triglycerides, blood pressure (BP), serum uric acid, C-reactive protein, plasma fibrinogen, white blood cell count, among other factors (5), and in yet others the criterion chosen was the metabolic syndrome (20, 21). The cutoff values have differed greatly between the studies. Some studies have selected values above the highest quartile of the HOMA-IR (9, 13, 16, 22); others have used tertiles (11) or the 90th percentile of the HOMA-IR (9), and others have chosen different cutoff values (8, 13, 23). Most of these studies were cross-sectional and found that MHO subjects have a favorable body fat distribution, hormonal and lipid profile, and proinflammatory cytokine and adipokine levels (5, 20).

However, longitudinal prospective studies evaluating the risk over time of the MHO phenotype for T2D and cardiovascular diseases are few and the results are contradictory. At least 2 studies have found that MHO subjects have a lower risk for developing T2D and cardiovascular diseases (22, 24), although other recent studies have found no difference between MHO and the rest of the obese population (6, 19, 25, 26).

Only a few observational studies include a prospective linkage to mortality records, with contradictory results. Kuk et al found that obesity, even in the absence of overt metabolic aberrations, is associated with an increased risk for all-cause mortality (6), whereas Hamer et al concluded that MHO persons were not at increased risk of cardiovascular disease and all-cause mortality compared with MHNO persons (27).

The aim of this study, therefore, was to evaluate the persistence of MHO over the years and to check the hypothesis of a lower risk for T2D in MHO subjects in a cohort from the south of Spain with a follow-up of 11 years.

Materials and Methods

Baseline study

In 1997–1998 a study was undertaken in Pizarra, a town in the province of Malaga (Andalusia, Spain). The characteristics of the study have been reported previously (28, 29). A total of 1051 individuals completed the baseline study, giving a final participation of 70.3%. Individuals were selected randomly from the municipal census. The inclusion age was 18–65 years, and individuals were excluded from the study if they were institutionalized for any reason, were pregnant, or had a severe clinical or psychological disorder. The final sample distribution, by age and sex, was not significantly different from the population distribution. All the participants were informed about the nature of the study and gave their written consent. The study was approved by the Ethics and Clinical Research Committee of Carlos Haya Hospital.

6-year follow-up study

The cohort was re-evaluated in 2003–2004. All those who had completed the baseline study ($n = 1051$) were invited by letter or by phone to attend for another clinical and anthropometric examination and another OGTT. In total, 820 individuals completed this 6-year follow-up study (78.4%). Of the 231 who did not complete the study, 21 had died, 91 could not be traced, and 119 no longer wished to collaborate in the study. The 141 individuals who had T2D at baseline were excluded from all the calculations of the incidence.

11-year follow-up study

In 2009–2010 the cohort was re-evaluated, and the 141 individuals who had T2D at baseline and at 6-year follow-up study were again excluded from all the calculations of the incidence in the 11-year follow-up study. In total, 547 individuals from the baseline study and 554 from the 6-year follow-up completed the 11-year follow-up study.

Procedures

The same methodology was used for both the prevalence and the incidence studies. All the participants were interviewed and given a standardized clinical examination. Measurements were made of weight and height, and the BMI was calculated ($\text{weight}/\text{height}^2$). The blood glucose level was measured at the 3 study

points using the glucose oxidase method (Accu-Chek; Roche Diagnostics, Barcelona, Spain) at fasting and 120 minutes after an OGTT with 75 g of glucose. The fasting serum insulin level was measured at baseline and at 6-year follow-up by RIA (Coat a Count RIA kit; DPC, Los Angeles, California, USA).

Insulin resistance was estimated with the HOMA equation, as follows (30): $\text{HOMA-IR} = (\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)})/22.5$. Triglycerides and HDL-c were measured using enzymatic methods at the 3 study points. Glycosylated hemoglobin (HbA_{1c}) was measured by HPLC using the analyzer VARIANT II TURBO (Bio-Rad Laboratories, Inc, Hercules, California, USA) and was only available for the 11-year follow-up study.

At all 3 study points, blood pressure (BP) was measured twice with a sphygmomanometer with an interval of 5 minutes between measurements and the average of the 2 measurements used in the analyses.

Classification criteria

The World Health Organization 1998 criteria were used to classify the participants with T2D, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) (31). Participants were considered to be obese if their BMI was $\geq 30 \text{ kg/m}^2$ (32). They were considered to have hypertension if their BP was $\geq 140/90 \text{ mm Hg}$ or they were receiving antihypertensive treatment (33).

The following variables were used to classify MHO:

1. Not having known T2D or unknown T2D discovered during the OGTT.
2. Fasting serum glucose $< 110 \text{ mg/dL}$.
3. $\text{BMI} \geq 30 \text{ kg/m}^2$.
4. Triglycerides $< 150 \text{ mg/dL}$.
5. $\text{HDL-c} > 40 \text{ mg/dL}$ in men and $\text{HDL-c} > 50 \text{ mg/dL}$ in women.
6. $\text{HOMA-IR} < 90\text{th}$ percentile of the frequency distribution of baseline and 6-year follow-up studies, excluding known T2D and unknown T2D subjects.
7. Blood pressure $< 140/90 \text{ mm Hg}$ or not receiving antihypertensive treatment.

Using these variables, we defined 4 different sets of criteria to assess the MHO phenotype based on previously published studies (5):

- A: $\text{BMI} \geq 30 \text{ kg/m}^2$ and $\text{HOMA-IR} < 90\text{th}$ percentile.
- B: $\text{BMI} \geq 30 \text{ kg/m}^2$, $\text{HOMA-IR} < 90\text{th}$ percentile, $\text{HDL-c} > 40 \text{ mg/dL}$ in men and $\text{HDL-c} > 50 \text{ mg/dL}$ in women, triglycerides $< 150 \text{ mg/dL}$, fasting glucose $< 110 \text{ mg/dL}$, and $\text{BP} < 140/90 \text{ mm Hg}$.
- C: $\text{BMI} \geq 30 \text{ kg/m}^2$, $\text{HOMA-IR} < 90\text{th}$ percentile, triglycerides $< 150 \text{ mg/dL}$, fasting glucose $< 110 \text{ mg/dL}$, and $\text{BP} < 140/90 \text{ mm Hg}$.
- D: $\text{BMI} \geq 30 \text{ kg/m}^2$, $\text{HOMA-IR} < 90\text{th}$ percentile, triglycerides $< 150 \text{ mg/dL}$, and fasting glucose $< 110 \text{ mg/dL}$.

Using these different sets of criteria, the subjects were classified into one of the following categories:

1. Metabolically healthy nonobese (MHNO)
2. Metabolically nonhealthy nonobese (MNHNO)
3. Metabolically healthy obese (MHO)
4. Metabolically nonhealthy obese (MNHNO)

Statistical analysis

Data are presented as means \pm SD or proportions. Differences between the baseline study and the 6-year and 11-year follow-up studies were determined by the *t* test for paired samples or the Wilcoxon test. The level of rejection of a null hypothesis was ≤ 0.01 . The hypothesis testing for qualitative variables was done using the χ^2 test. Multivariate analysis was performed using stepwise logistic regression. For incidence rates, 95% confidence intervals (CI) were computed. The odds ratio (OR) and 95% CI were calculated using the β coefficient from the different logistic regression models.

Results

Table 1 summarizes the general characteristics of the Pizarra study at the three points of the study (baseline, 6-year follow-up and 11-year follow-up). The prevalence of obesity increased significantly during the study.

Table 1. General Characteristics of the Population in the 3 Moments of the Study (Baseline, 6-year Follow-up, and 11-year Follow-up)

	Baseline Characteristics			6-y Follow-up Characteristics		11-y Follow-up Characteristics	
	Full Sample	Final Sample ^a (6-y Follow-up)	Final Sample ^b (11-y Follow-up)	Final Sample ^c (11-y Follow-up)	Final Sample (6-y Follow-up)	Final Sample (Compared with Baseline)	Final Sample (Compared with 6-y Follow-up)
N	1051	820	547	554	820	547	554
Age, y	40.0 \pm 13.8	40.10 \pm 13.55	41.16 \pm 13.25	47.79 \pm 13.56	46.13 \pm 13.92	51.68 \pm 13.48	52.23 \pm 13.36
Sex, M/F	396/655	311/508	208/339	204/394	304/516	200/347	202/352
BMI, kg/m^2	27.5 \pm 5.2	27.48 \pm 4.97	27.60 \pm 4.81	28.78 \pm 5.12	28.52 \pm 5.15	29.19 \pm 5.85	29.15 \pm 5.38
HOMA-IR	2.85 \pm 2.81	2.78 \pm 2.42	2.87 \pm 2.65	2.47 \pm 2.38	2.50 \pm 2.58	—	—
Obesity, %	28.8	27.5	28.5	36.9	35.0	38.8	38.6
HOMA-IR $> 90\text{th}$ percentile, %	22.7	21.5	21.3	24.5	23.6	—	—
Triglycerides $> 150 \text{ mg/dL}$, %	17.4	18.2	17.8	21.3	21.3	21.9	22.9

Data are means \pm SD or proportion (%). —, data not available.

^a People at risk in the final sample who could be classified according to their diabetes status at the 6-y follow-up study.

^b People at risk in the final sample who could be classified according to their diabetes status at the 11-y follow-up study.

^c People at risk in the final sample in the 6-y follow-up who could be classified according to their diabetes status at the 11-y follow-up.

Table 2. Prevalence According to BMI and Metabolic Profile at Baseline and the 6-y Follow-up Study

Baseline	6-y Follow-up				Total Baseline
	MHNO	MNHNO	MHO	MNHO	
MHNO	279 (74.0)	60 (15.9)	22 (5.8)	16 (4.2)	377 (52.7)
MNHNO	36 (29.8)	54 (44.6)	5 (4.1)	26 (21.5)	121 (16.9)
MHO	11 (10.5)	5 (4.8)	50 (47.6)	39 (37.1)	105 (14.7)
MNHO	6 (5.4)	6 (5.4)	20 (17.9)	80 (71.4)	112 (15.7)
Total 6-y follow-up	332 (46.4)	125 (17.5)	97 (13.6)	161 (22.5)	715

Data are number of subjects (prevalence).

MHO phenotype prevalence at baseline and at the 6-year follow-up study

The prevalence of the MHO phenotype using criterion A was 16.9% at baseline and 18.7% at the 6-year follow-up. Of the 123 MHO subjects at baseline, 37 (30.1%) became MNHO by the 6-year follow-up ($P < .0001$).

Using criterion B, the prevalence of the MHO phenotype was 3% at baseline and 3.7% at the 6-year follow-up. Of the 23 MHO subjects at baseline, 11 (47.8%) became MNHO by the 6-year follow-up ($P < .0001$).

Using criterion C, the prevalence of the MHO phenotype was 4.9% at baseline and 4.6% at the 6-year follow-up. Of the 32 MHO subjects at baseline, 15 (46.9%) became MNHO by the 6-year follow-up ($P < .0001$).

Using criterion D, the prevalence of the MHO phenotype was 14.7% at baseline and 13.6% at the 6-year follow-up. Of the 105 MHO subjects at baseline, 39 (37.1%)

became MNHO by the 6-year follow-up ($P < .0001$) (Table 2).

In all 4 sets of criteria a significant reassignment in the classification has occurred over the years ($P < .0001$).

As an example, we chose criterion D to show the combined prevalence of MHO subjects. We chose this criterion because of its similar concordance with criterion A (where HOMA-IR is the main variable) and the prevalence is higher than with the others. Also, all the criterion D variables contributed significantly to the explanation of the incidence of T2D, more than they did so separately (Figure 1). In addition, with this criterion the MHO prevalence was similar to that already published. Table 2 shows the combined prevalence of MHO subjects according to criterion D. Despite a similar prevalence of MHO at baseline and the 6-year follow-up (14.2% vs 13.6%), 37.1% were reclassified as MNHO and 41.9% became metabolically nonhealthy (obese and nonobese) at the 6-year follow-up. On the other hand, 76.8% of MNHO subjects and 66.1% of MNHNO subjects at baseline were still metabolically nonhealthy at the 6-year follow-up, whereas 20.1% of MHNO subjects became metabolically nonhealthy at the 6-year follow-up study.

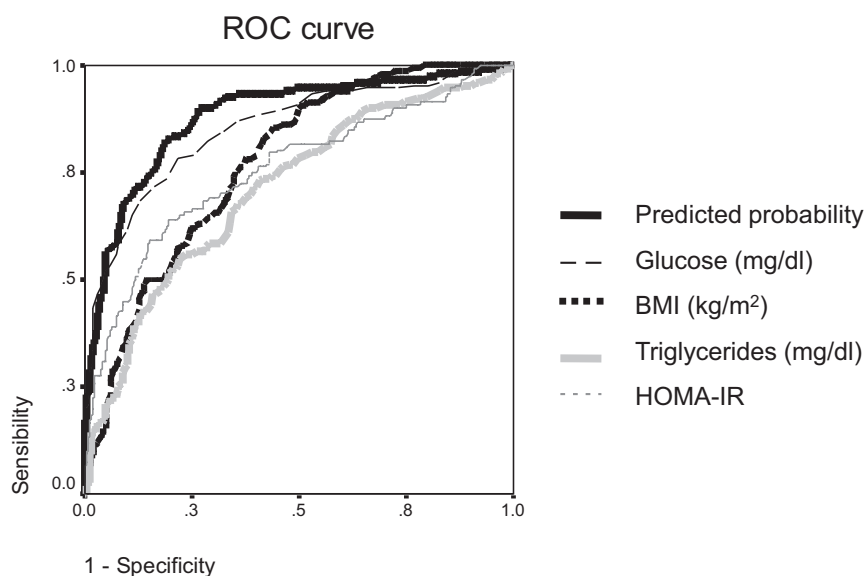


Figure 1. The receiver operating characteristic (ROC) curve for HOMA-IR, BMI, triglycerides, and fasting serum glucose to predict T2D at the 6-year follow-up. The predicted probabilities were calculated using a logistic regression model (dependent variable: T2D incidence in the 6-year follow-up; independent variables: HOMA-IR, BMI, triglycerides, and fasting serum glucose). The area under the ROC curve to predict T2D at the 6-year follow-up was 0.82, a higher value than that corresponding to each variable considered separately.

T2D risk prediction in MHO

To calculate the incidence of T2D according to the BMI and the metabolic profile, we used criterion D.

In persons without T2D at baseline, the OR of becoming diabetic by the 6-year or 11-year follow-up points was higher in those subjects who were MNHO (Table 3), although the OR of becoming diabetic was significant in both the MHO and the MNHNO. In all cases, the strength of the association remained after adjusting the logistic regression models for age, sex, weight change, and abnormal glucose regulation (Table 3).

Table 3. Incidence of T2D at the 6-y and the 11-y Follow-up According to a Metabolic Profile Associated With Obesity

	Incidence of T2D (new cases) (%) and OR of having T2D at the 6-y follow-up			Incidence of T2D (new cases) (%) and OR of having T2D at the 11-y follow-up		
	(N)(n)(%)	OR (95% CI)	OR (95% CI) ^a	(N)(n)(%)	OR (95% CI)	OR (95% CI) ^a
MHNO	(337)(23)(6.8)			(244)(8)(3.3)		
MNHNO	(71)(16)(22.5)	3.97 (1.97–7.99) ^b	2.74 (1.28–5.86) ^d	(49)(7)(14.3)	4.91 (1.69–14.27) ^c	4.44 (1.88–10.49) ^e
MHO	(81)(17)(21.0)	3.62 (1.83–7.17) ^b	2.16 (1.07–4.36) ^d	(59)(11)(18.6)	6.76 (2.58–17.69) ^b	4.12 (1.82–9.34) ^f
MNHO	(50)(21)(42.0)	9.88 (4.89–19.97) ^b	4.57 (2.21–9.46) ^b	(35)(12)(34.3)	5.70 (5.70–41.49) ^b	9.83 (4.41–21.89) ^b

N, total number of subjects; n, number of new cases with T2D; %, n100/N.

^a Adjusted for age, sex, weight change, and abnormal glucose regulation (IFG, IGT).

^b $P < .0001$; ^c $P = .002$; ^d $P = .001$; ^e $P = .031$; ^f $P = .009$.

HbA_{1c} levels at the 11-year follow-up study

At the 11-year follow-up HbA_{1c} levels were measured. As expected, those subjects who had become diabetic by the 11-year follow-up had higher HbA_{1c} levels than the nondiabetic persons ($5.66 \pm 0.34\%$ vs $6.68 \pm 0.81\%$; $P < .001$).

The HbA_{1c} levels were higher in MHO and MNHO subjects than in nonobese subjects (MHNO and MNHNO). These higher levels occurred in both the newly diagnosed diabetic subjects and those who remained nondiabetic (Figure 2) ($P = .005$).

Contribution of insulin resistance to the incidence of diabetes

In subjects without T2D at baseline, insulin resistance measured by the HOMA-IR at baseline contributed significantly to the explanation of the T2D risk at the 6-year follow-up (OR = 1.24; 95% CI = 1.10–1.40; $P < .0001$) (Supplemental Table 4, model 1, published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). At the 6-year follow-up study, 9.8% of the nonobese subjects at baseline had become obese and 2.9% of the obese subjects had lost weight and decreased their BMI below 30.

The incidence of T2D at 6-year follow-up was significantly associated with the development of obesity in nonobese subjects (OR = 4.87, 95% CI = 2.4–9.91; $P < .0001$) and with the presence of obesity at baseline and at 6-year follow-up (OR = 3.79; 95% CI = 2.08–6.91; $P < .0001$) (Supplemental Table 4, model 2). However, obese subjects at baseline who were no longer obese at 6-year follow-up did not experience an increase in their T2D risk (OR = 0.71; 95% CI = 0.08–5.76; $P = \text{NS}$) (Supplemental Table 4, model 2).

The addition of the HOMA-IR to the model did not result in a significant increase in the degree of contribution of the model to the explanation of new T2D cases at the 6-year follow-up (Supplemental Table 4, model 3).

Discussion

The first conclusion from this study is that a substantial fraction of individuals who are MHO at baseline are no longer metabolically healthy at 6-year follow-up and the second conclusion is that MHO subjects are also at substantially increased risk for development of T2D, with a similar risk to that of MNHO subjects.

Obesity-related metabolic complications are well known. However, the huge individual variability in the risk of metabolic and clinical morbidity associated with obesity (2, 3), apart from the empiric observation of the existence of obese subjects without metabolic complications, has led to the description of an obese phenotype that has received different names; in this study, as in others recently published (4, 17), it has been called “Metabolically Healthy but Obese” (MHO). However, the results of this study call into question that MHO phenotype is a highly stable diagnosis over time.

Insulin resistance is one of the most important mediating mechanisms in the explanation of many obesity-related metabolic problems. Thus, it is not surprising that insulin resistance is included in almost all the criteria used to define MHO subjects (5). The problem, however, derives from the definition of insulin resistance. In our study, we, like others (9), used the 90th percentile of the frequency distribution of the values of HOMA-IR of those subjects without any abnormal glucose regulation detected from an OGTT, including unknown T2D. This is important because HOMA-IR values are known to be abnormally high in subjects with IFG, IGT, or unknown T2D (34). Most population studies, including the Pizarra study (28), have included T2D subjects who were unaware of their diabetic status (unknown T2D). In addition, the IGT phenotype is only detected after an OGTT. Thus, the criterion of normality is usually established based on a metabolically healthy population. If we had chosen only subjects without known T2D, then the HOMA-IR cutoff at

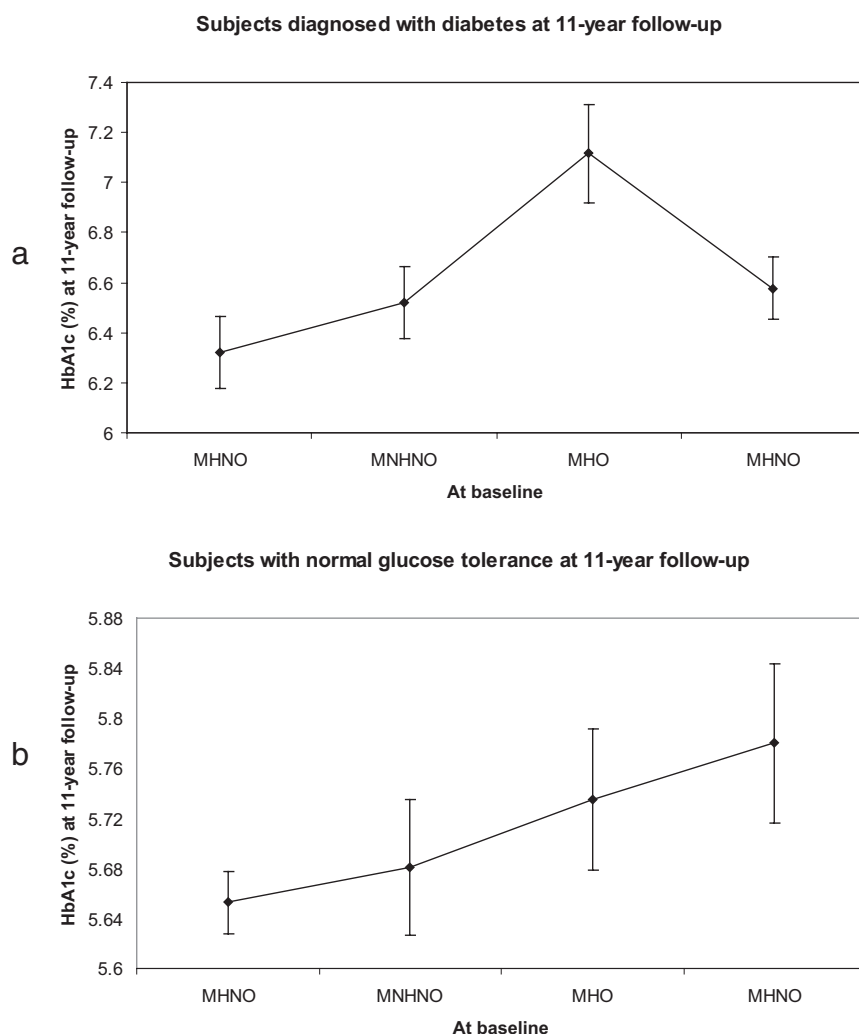


Figure 2. Data are mean \pm SD. HbA_{1c} at 11-year follow-up according to obesity phenotype at baseline ($P = .005$) and T2D incidence by the 11-year follow-up point ($P < .0001$). Obesity phenotype was associated with HbA_{1c} levels at 11-year follow-up point, in both new cases of T2D (A) and those who did not become diabetic (B).

baseline would have been 4.80 instead of 3.3, and 3.92 instead of 3.01 at the 6-year follow-up, which would have modified the prevalence of MHO subjects.

This strict definition could be one explanation for the lower prevalence of MHO subjects found in our study as compared with most other studies (5). At baseline and at the 6-year follow-up, the HOMA-IR correlated significantly with the BMI ($P < .0001$), but the degree of contribution of the HOMA-IR to the variance was modest at both time points, 14% at baseline and 17% at the 6-year follow-up. In both cases, the inclusion of the abnormal glucose regulation phenotype (IFG, IGR, and unknown T2D) in the regression model increased the contribution to the explanation of the variance to 25% and 31%, respectively. The high prevalence of abnormal glucose regulation phenotypes in the general population (1) requires the consideration of these aspects to allow the interpretation of

the insulin resistance patterns and to establish the associations between obesity and insulin resistance (34).

On the other hand, a BMI ≥ 30 kg/m² is one of the criteria required for a MHO phenotype; if the number of obese subjects increases, the MHO prevalence will probably change. This was the case in our study, in which the prevalence of obesity was high (28%) at baseline and even higher (36% and 38%) at the 6-year and 11-year follow-up points. This baseline prevalence, though, is similar to that recently reported for the Spanish population (1).

Another important question concerns the association of other metabolic abnormalities with insulin resistance. In our study, the association between HOMA-IR <90th percentile and normal levels of triglycerides, HDL-c, BP, and fasting glucose levels reduced the prevalence of the MHO phenotype to 3% at baseline and 3.7% at the 6-year follow-up. The requirement of normality for other markers, such as C-reactive protein or white blood cell count, would reduce the prevalence of the MHO phenotype even further.

Obesity is one of the most important risk factors for T2D. However, whatever the criteria chosen, the consideration of the MHO phenotype

should be associated with a lower risk for T2D than found in MNHNO subjects. It makes little sense to consider individuals at substantially increased risk for T2D as metabolically healthy. In our study, although the MNHNO subjects had a higher risk of T2D at both the 6-year and the 11-year follow-up points, the MHO subjects had a similar risk to the MNHNO subjects. This is not surprising if we notice that the phenotype of 1 of every 3 subjects changed over the years, especially if they were MHO. This change of phenotype occurred despite the relative stability of the HOMA-IR over the study period, a fact also noted by Ferrannini et al, who found that levels barely changed over the years (35). This is probably one of the reasons in the risk prediction models BMI had, independently, more explanatory power in the risk for T2D than insulin resistance itself. On the other hand, the T2D risk related to MHO phenotype has been somewhat independent of the weight

change throughout the study. The highest T2D risk was associated with the incidence of obesity whatever the pattern insulin resistance.

Several recent studies have evaluated the risk of the association between BMI and different metabolic abnormalities. Most of these evaluated cardiovascular diseases over long periods of time. All the studies agree that the association between obesity and metabolic abnormalities increases the cardiovascular risk (6, 22, 24, 25, 36) but the results dissent concerning the risk for MHO subjects. Meigs et al (22) studied 2092 subjects followed up for 11 years and found that the cardiovascular risk was lower in subjects with a BMI ≥ 30 kg/m² without the metabolic syndrome (National Cholesterol Education Program's Adult Treatment Panel) or a HOMA-IR <75th percentile. St-Pierre et al (24) studied 1824 nondiabetic men followed up for 13 years and concluded that although obesity is an important risk factor for ischemic heart disease, variations in BMI alone reflect poorly the risk of ischemic heart disease associated with features of the insulin resistance syndrome. However, other recent longitudinal studies found that obesity, even in the absence of overt metabolic aberrations, is associated with an increased risk for all-cause mortality (6, 36) and higher incidences of metabolic abnormalities compared with nonobese subjects (26).

The cutoff values used in these studies to define insulin resistance may have been too high, thus excluding many subjects who could have a risk pattern of insulin resistance and that would have contributed to the rise in the risk for T2D. However, if lower cutoff values are used to ensure that almost all MHO subjects are really noninsulin resistant (as used in our study), the prevalence of the MHO phenotype is 0.2%–0.3% when the HOMA-IR 10th percentile is used as a criterion or 0.3%–4.5% when the HOMA-IR 25th percentile is used. In this latter case, the mean HOMA-IR values of MHO subjects are still significantly higher than the MHNO subjects (2.93 ± 5.08 vs 0.69 ± 0.42). To be sure that subjects are really metabolically healthy, we should choose obese subjects who have similar HOMA-IR values to the nonobese subjects, but this would reduce the prevalence of the MHO phenotype considerably.

One of the limitations of our study is that the prevalence of the MHO phenotype was lower than expected, which decreased the statistical power of the prediction of the T2D risk at the 11-year follow-up. On the other hand, this study has the strength that the phenotyping for metabolic abnormalities was done by OGTT, unlike most previous studies that used a clinical criterion together with fasting glucose. Indeed, our study is longitudinal and designed mainly to determine the prevalence and incidence of T2D

in a population from southern Spain (29) followed up for 11 years.

The results of our study, taken as a whole, suggest that the MHO phenotype is just an expression of the biological diversity of all the continuous variables such as BMI, insulin resistance, or plasma lipids. A gradation of the risk, though, does not mean that the risk does not exist, as could be the case when talking about the MHO phenotype. Thus, it may be that MHO as a clinical entity should be called into question. The results of this study suggest that MHO is a dynamic concept that should be considered over time. This is especially true in the context of the increasing prevalence and incidence of obesity, accompanied by several metabolic complications, although not all these metabolic complications are associated with insulin resistance and obesity.

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