

Natural Course of Metabolically Healthy Phenotype and Risk of Developing Cardiometabolic Diseases: a three years follow-up study

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Abstract

Background:

Whether the metabolically healthy obese (MHO) phenotype is a single, stable or a transitional, fluctuating state is currently unknown. The Mexican-Mestizo population has a genetic predisposition for the development of type 2 diabetes and other cardiometabolic complications. Little is known about the natural history of metabolic health in this population. The aim of this study was to analyze the transitions over time among individuals with different degrees of metabolic health and body mass index, and evaluate the incidence of cardiometabolic outcomes according to phenotype.

Methods:

The study population consisted of a metabolic syndrome cohort with at least three years of follow up. Participants were apparently-healthy urban Mexican adults ≥ 20 years with a BMI ≥ 20 kg/m². Metabolically healthy phenotype was defined using the criteria of the NECP ATP III metabolic syndrome criteria and the subjects were stratified into 4 groups according to their BMI and metabolic health. For cardiometabolic outcomes we estimated the incidence of cardiometabolic outcomes and standardized them per 1, 000 person-years of follow-up. Finally, to evaluate the risk for transition and development of cardiometabolic outcomes, we fitted Cox Proportional Hazard regression models.

Results:

Amongst the 5,541 subjects, 54.2% were classified as metabolically healthy and 45.8% as unhealthy. The MHO prevalence was 39.3%. Up to a third of the population changed from their initial category to another and the higher transition rate was observed in MHO (42.9%). We also found several novel factors associated to transition to metabolically unhealthy phenotype; socioeconomic status, number of pregnancies, a high carbohydrate intake, history of obesity and consumption of sweetened beverages. Similarly, visceral adipose tissue (VAT) was a main predictor of transition; loss of VAT $\geq 5\%$ was associated with reversion from metabolically unhealthy to metabolically healthy phenotype (HR 1.545, 95%CI 1.266–1.886). Finally, we observed higher incidence rates and risk of incident T2D and hypertension in the MUHO and MUHL phenotypes compared to MHO.

Conclusions

Metabolic health is a dynamic and continuous process, at high risk of transition to metabolically unhealthy phenotypes over time. It is imperative to establish effective processes in primary care to prevent such transitions.

Background

Obesity is a chronic and multifactorial disease associated with an increased risk for type 2 diabetes (T2D), arterial hypertension, atherogenic dislipidemia, nonalcoholic fatty liver disease, cardiovascular disease (CVD) and cancer (1–4). Interestingly, a subgroup of overweight/obese patients remain free of cardiometabolic co-morbidities. This condition is known as the metabolically healthy obesity (MHO) phenotype. Currently, there is no universally accepted definition for these patients; up to 30 different criteria have been published (5–7). As a consequence, the prevalence of the MHO phenotype varies enormously depending on the definition applied (8–10). Several cohort studies have

reported that the MHO phenotype is not exempt for the development of incident T2D and cardiovascular disease (10–12). However, the risk appears to be much lower than that reported for obese individuals with the metabolic syndrome (this phenotype is known as metabolically unhealthy obesity (MUHO)). Furthermore, different cohort studies with differing years of follow-up, have reported that between 30–50% of MHO people develop metabolic complications over time (13–14).

Some authors have proposed that MHO individuals are a unique group of obese patients resistant to the development of cardiometabolic complications. Thus, additional studies are needed to confirm if MHO is a transition state or a stable phenotype (5). In the Mexican population, little is known about the natural history of MHO. In addition, the percentage of cases that transition between metabolically healthy (MH) phenotypes to unhealthy phenotypes (MUH) has not been reported for in Mexican mestizos. This is a population with a genetic predisposition for the development of T2D and other cardiometabolic complications. The aim of this study is to analyze the transitions over time among individuals with different degrees of metabolic health (MH and MUH) and body mass index (BMI), and evaluate the incidence of cardiometabolic outcomes according to phenotype.

Methods

Study population and procedures.

The study population was obtained from the Metabolic Syndrome (MS) cohort. This was a three-year study that evaluated MS components in people who developed incident type 2 diabetes, arterial hypertension and cardiovascular mortality in an urban population living in central Mexico (nine cities). The characteristics of the MS cohort have been described elsewhere (15). Briefly, the study sample was composed of apparently-healthy adults ≥ 20 years with a BMI ≥ 20 kg/m². At baseline, individuals with previously diagnosed T2D or fasting plasma glucose ≥ 126 mg/dL, coronary artery disease (CAD), cerebrovascular disease, alcoholism, taking corticosteroids, liver disease, chronic kidney disease or life-threatening diseases that would prevent the three-year follow-up, were excluded. All assessments were performed in the morning. The evaluation consisted of a clinical examination using standardized questionnaires (supplementary material), anthropometric measurements and a blood draw (a blood sample was obtained after a 9–12 hour fast for the measurement of serum glucose, insulin, total and HDL cholesterol, triglycerides, apolipoprotein B, and C-reactive protein levels). Weight was measured in kilograms and height in meters: the body mass index was calculated by dividing the weight by the height in meters squared. Waist to height ratio (WHtR) was calculated dividing the waist circumference (in centimeters) by the height (in centimeters). Participants were interviewed to obtain a medical history (including personal and family history of the most common chronic diseases), sociodemographic data, dietary information (24-h diet recall, 7-day food frequency questionnaire, the three-factor eating questionnaire) and physical activity habits (evaluated by short version of the International physical activity questionnaire IPAQ and defined as active or inactive) (16). Two blood pressure measurements were obtained 10 minutes apart while participants were seated, and the average of the two measurements was used in the analysis. Some of the variables were analyzed as continuous and/or categorical in the univariate analyses: glucose (<90 or ≥ 90 mg/dL), age (<50 or ≥ 50 years), apoB (>90 th percentile for sex, <99 or ≥ 99 mg/dL for women and <108 or ≥ 108 mg/dL for men) and HDL-C (<40 or ≥ 40 mg/dL for men and <50 or ≥ 50 mg/dL for women). Consumption of sweetened beverages was defined as intake <4 or ≥ 4 times a week, history of childhood obesity was defined as the diagnosis of obesity before the age of 18 and socio-economic status was defined as low, medium or high, as referred to by the subjects.

Subjects were contacted after a three-year period (± 6 months) and invited to repeat the evaluations using the same tools and methods. The response rate was 80.7%. The study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición and all participants signed an informed consent form.

Biochemical evaluations

All serum samples were kept frozen until processed in a central laboratory certified by the External Comparative Evaluation of Laboratories Program of the College of American Pathologists (Departamento de Endocrinología y Metabolismo, Instituto Nacional de Ciencias Médicas y Nutrición, México City). Plasma glucose concentration was measured by an automated glucose analyzer (Yellow Springs Instruments Co.), serum insulin concentration was measured by using a chemiluminescent immunoassay (Beckman Coulter Access 2). Lipid concentrations (total cholesterol, triglycerides, and HDL cholesterol), apo A, apo B, uric acid, creatinine and hepatic enzymes were measured using colorimetric assays (Unicel DxC 600 Synchron Clinical System Beckman Coulter). HOMA2-IR and HOMA2-S were calculated using fasting glucose and insulin using the HOMA2 calculator released by the Diabetes Trials Unit, University of Oxford: HOMA Calculator. Visceral adipose tissue (VAT) was calculated using Metabolic Score for Visceral Fat (METS-VF) Eq. (17), described previously by our group. This novel surrogate index estimates intra-abdominal adipose tissue incorporating a non-insulin-based IR index (METS-IR) (18), anthropometric measures of body-fat distribution (WtHr), genre, and age. METS-VF has better correlation and performance with VAT-DXA compared to other surrogate VAT indexes.

BMI/Metabolic Health phenotypes and outcomes definitions.

Metabolic health was defined using the criteria of the NECP ATP III metabolic syndrome criteria revised by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) scientific statement (19): systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; fasting plasma glucose concentration ≥ 100 mg/dL; HDL-C concentration < 40 mg/dL in men and < 50 mg/dL in women; fasting plasma TG concentration ≥ 150 mg/dL; or treatment with antihypertensive, lipid lowering, or glucose-lowering medications. Subjects had to meet ≤ 1 of the criteria (waist was excluded) to be metabolically healthy. To define metabolically unhealthy participants, at least ≥ 2 criteria had to be met. In addition, BMI was categorized as lean (BMI < 25 Kg/m²) or as overweight-obese (BMI ≥ 25 Kg/m²). In this way, we obtained 4 groups of patients: 1) metabolically healthy lean (MHL), 2) metabolically unhealthy lean (MUHL), 3) metabolically healthy overweight/obese (MHO) and 4) metabolically unhealthy overweight/obese (MUHO), respectively. At follow-up, incident T2D was defined as a previous diagnosis of type 2 diabetes, taking hypoglycemic medication and/or fasting glucose levels ≥ 7.0 mmol/dL (≥ 126 mg/dL) according to American Diabetes Association guidelines. Incident arterial hypertension was defined as previous medical diagnosis, taking antihypertensive medication and/or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. 7636 participants were recruited at baseline, of whom a total of 6144 participants agreed to continue with a follow-up visit. In total, 5541 had complete information to permit group classification (Fig. 1).

Statistical analysis

Data are presented as media \pm SD or as median and interquartile range, categorical variables are expressed as frequencies and percentages. Proportions and medians are compared using chi-square test and Mann-Whitney-U test. To evaluate the proportions of subjects who transitioned between phenotypes, we used McNemar's test. We also fitted Cox Proportional Hazard regression models to evaluate factors associated to transitions between phenotypes.

For cardiometabolic outcomes we estimated the incidence of cardiometabolic outcomes by dividing the number of new cases and standardized them per 1,000 person-years of follow-up. Finally, to evaluate the risk for the development of cardiometabolic outcomes by phenotype, we fitted Cox Proportional Hazard regression models considering incident cardiometabolic outcome or censoring in years, whichever occurred first. Model assumptions were verified using Schöenfeld residuals. A p-value < 0.05 was considered as the statistical significance threshold. All analyses were performed using R software version 3.6.2, Statistical Package for Social Sciences software (SPSS, version 25.0) and GraphPad Prism version 7.0.

Results

Baseline characteristics

Baseline characteristics are shown in (supplementary table 1). Amongst the 5,541 subjects, 3002 participants were classified as metabolically healthy (54.2%) and 2539 participants as metabolically unhealthy (45.8%). In the metabolically healthy phenotypes, subjects were younger, more often women, had a bachelor's degree or higher and lower BMI compared to metabolically unhealthy phenotypes ($p < 0.05$).

According to BMI and metabolic health categories, subjects were classified as metabolically healthy lean (14.9%), metabolically unhealthy lean (5.4%), metabolically healthy overweight/obese (39.3%) and metabolically unhealthy overweight/obese (40.4%). Of note, 79.7% of the entire study population ($n = 4412$) had a BMI ≥ 25 Kg/m². MHO subjects had healthier habits in terms of smoking, alcohol consumption and physical activity compared to MUHO subjects ($p < 0.001$). Moreover, MHL and MHO subjects had significantly higher HOMA2-S, but lower HOMA2-IR and visceral adipose tissue (VAT) evaluated by METS-VF compared to MUHL and MUHO subjects ($p < 0.001$).

Transitions between phenotypes

After 3 years of follow-up (± 6 months), 63.4% of the subjects remained in the same group, while 36.6% of the individuals transitioned to another phenotype.

First, we analyzed the cohort from the perspective of metabolic health, independent of BMI, and we found that 39.2% of the individuals who were metabolically healthy at baseline transitioned to metabolically unhealthy phenotype; and 17.9% who were metabolically unhealthy at baseline reverted to metabolically healthy phenotype. Hence, at follow-up, subjects in the metabolically healthy group decreased in proportion to 41.2% (baseline 54.2%) and those in the metabolically unhealthy group increased in proportion to 58.8% (baseline 45.8%) (Fig. 2).

Then, we analyzed the 4 phenotypes stratified by BMI and metabolic health. We found that 53.6% ($n = 443$) of the metabolically healthy lean subjects remained in the same phenotype. However, 18.5% ($n = 153$) progressed to metabolically unhealthy lean, 18.4% ($n = 152$) to metabolically healthy obesity and 9.5% ($n = 78$) to metabolically unhealthy obesity (Fig. 2).

In the metabolically unhealthy lean group, 48.8% ($n = 148$) remained in the same phenotype, 5.2% ($n = 16$) transitioned to metabolically healthy obesity and 24.8% ($n = 75$) to metabolically unhealthy obesity phenotypes, while 21.1% ($n = 64$) reverted to the metabolically healthy lean phenotype.

In the MHO phenotype, 51.9% ($n = 1130$) remained in the same phenotype. Interestingly, only 5.1% ($n = 112$) and 2.3% ($n = 50$) of individuals in this group reverted to metabolically healthy and unhealthy lean groups respectively, while the majority (40.6%, $n = 884$) progressed to metabolically unhealthy obesity phenotype.

Finally, in the MUHO group, 80.2% (n = 1793) remained in the same phenotype, while 1.2% (n = 27), 3% (n = 66) and 15.7% (n = 350) transitioned to metabolically healthy lean, metabolically unhealthy lean and metabolically healthy obese phenotypes, respectively.

Thus, at the time of follow-up the proportion of subjects in the 4 different phenotypes were as follow: 11.7% metabolically healthy lean (21.5% reduction), 7.5% metabolically unhealthy lean (37% increase), 29.7% metabolically healthy overweight/obese (24.25% reduction) and 51.1% metabolically unhealthy overweight/obese (26.5% increase) (Fig. 2).

Factors associated with transitions between phenotypes

We analyzed parameters that allow us to identify which participants will progress to another phenotype. First, we compared basal characteristics from participants who transitioned with those who remained in the same group, according to metabolic health.

We found that subjects who progressed from metabolically healthy to metabolically unhealthy phenotype were older, more often men, had higher BMI, C-reactive protein, insulin and ApoB levels, ($p < 0.001$). Also, they had higher values of HOMA-IR, WHtR and METS-VF, $p < 0.001$ (**Supplementary Table 2**). The opposite was observed in those subjects who reverted from the metabolically unhealthy to the metabolically healthy profile. We fitted Cox-proportional hazard models to evaluate factors associated with the transitions. In the univariate analysis, progression from metabolically healthy to metabolically unhealthy phenotypes showed a positive association with age, gender (male), higher BMI, WHtR, METS-VF, HOMA2-IR, glucose and Apo B concentrations, a diet high in carbohydrates (>60%) and C-reactive protein levels. (**supplementary Table 3**). Furthermore, subjects who remained maintained or gained weight had higher risk of progression to an unhealthy phenotype compared with subjects who lost weight. In contrast, the variables associated with an increased probability of reverting from a metabolically unhealthy phenotype to a metabolically healthy were greater HOMA-S and HDL-C levels and weight loss $\geq 5\%$.

Next, we evaluated the transition from metabolically healthy to metabolically unhealthy by BMI categories. The main predictors associated with a transition from metabolically healthy lean to metabolically unhealthy lean were gender (male), age, HOMA2-IR, METS-VF, WHtR, glucose, ApoB and number of pregnancies, whilst HDL-cholesterol and socioeconomic status were factors associated with a decreased risk of progression. For the MHO subjects, in addition to the aforementioned factors, BMI, history of childhood obesity, and a diet with > 60% carbohydrates intake were associated with higher risk of progression to metabolically unhealthy obesity; weight loss > 5%, physical activity, HDL-C, vegetables consumption (> 2 days per week) and HOMA2-S > 80% were associated with a lower risk of progression (**Supplementary Table 3**).

Factors associated with lower probability of reversion from the metabolically unhealthy lean category to metabolically healthy lean were gender (male), age, METS-VF and glucose. In contrast, HDL-cholesterol, weight loss $\geq 5\%$ and HOMA2-S $\geq 80\%$ were associated with a higher risk of reversion from metabolically unhealthy obesity to metabolically healthy obesity, whilst sugar sweetened beverage consumption and number of pregnancies were associated with a lower risk of regression. (Supplementary table 4).

Visceral adipose tissue as predictive factor to transitions between phenotypes.

METS-VF (a VAT estimator) was associated with transitions between phenotypes. First, we evaluated the effect of VAT in the transitions between phenotypes according to BMI categories. We observed that metabolically healthy lean subjects with VAT ≥ 600 gr had a higher risk of progression to a metabolically unhealthy lean phenotype, whilst MHO

subjects with VAT ≥ 800 gr had a higher risk of progression to a metabolically unhealthy obesity; [$\beta = 0.441$, HR 1.555, 95%CI 1.139–2.121, $p = 0.005$] and [$\beta = 0.279$, HR 1.322, 95%CI 1.103–1.584, $p = 0.002$] respectively.

Subsequently, we analyzed the changes in VAT, and observed that loss of VAT $\geq 5\%$ was associated with a 54.5% probability of reversion from metabolically unhealthy to metabolically healthy phenotype [$\beta = 0.435$, HR 1.545, 95%CI 1.266–1.886].

Finally, we evaluated the changes (%) in VAT according to changes in weight and we found that an increase in VAT in patients who lost weight ($\geq 5\%$) or remained with stable weight were associated to lower risk of reversion from MUH to MH phenotype; [$\beta = -0.014$, HR 0.9857, 95%CI 0.996–1.000, $p = 0.087$] and [$\beta = -0.016$, HR 0.983, 95%CI 0.974–0.992, $p < 0.001$] respectively. However, the changes in VAT were not associated to progression from MH to MUH. All models were adjusted by age and BMI and stratified by sex.

Metabolically healthy phenotype and cardiometabolic outcomes

We evaluated the cardiometabolic complications that developed in the cohort during follow-up. The groups were analyzed according to their metabolic health. In the metabolically healthy group, after 7215.41 person-years we identified 79 cases of incident T2D (IR 10.94 per 1,000 person-years, 95%CI 8.53–13.36), and 370 cases of incident hypertension (IR 51.28 per 1,000 person-years, 95%CI 46.05–56.50). In contrast, after 6195.83 person-years, in the metabolically unhealthy subjects, there were 214 cases of incident T2D (IR 34.55 per 1,000 person-years, 95%CI 29.92–39.18) and 447 cases of incident hypertension (IR 72.17 per 1,000 person-years, 95%CI 65.48–78.86). It appears that the metabolically healthy phenotype is a protective factor for the development of incident T2D (HR 0.397, 95%CI 0.303–0.520) and hypertension (HR 0.807, 95%CI 0.698–0.933), (Fig. 3). These models were adjusted for sex, BMI, age, smoking, physical activity and family history of T2D and hypertension.

Next, we evaluated the incidence rates according to BMI and metabolic health; here there was a lower incidence rate for any cardiometabolic outcome for the metabolically healthy lean phenotype (IR 9.62 CI 5.29–13.95 for diabetes and IR 36.98 CI 28.49–45.47 for hypertension) and the higher incidence for metabolically unhealthy obese phenotype (Table 1). The metabolically healthy obese and metabolically unhealthy lean phenotypes had relatively similar incidence rates for hypertension; although for incident diabetes, there was a lower rate for MHO subjects compared to MUHL.

Table 1
Cardiometabolic outcomes incidence rates (cases/1000 persons per year) in the study sample stratified by metabolic phenotype.

Cardiometabolic outcome	Phenotype	Number of cases (%)	IR	95%CI
Type 2 Diabetes	MHL	19 (2.3)	9.62	5.29–13.95
	MUHL	12 (4.0)	16.99	7.37–26.60
	MHO	60 (2.8)	11.44	8.55–14.34
	MUHO	202 (9.0)	36.81	31.73–41.49
Hypertension	MHL	73 (8.8)	36.98	28.49–45.47
	MUHL	39 (12.9)	55.22	37.88–72.55
	MHO	297 (13.6)	56.66	50.22–63.11
	MUHO	408 (18.2)	74.35	67.14–81.57

Finally, we fitted Cox-proportional hazard models to evaluate the risk for the development of cardiometabolic outcomes by phenotype. We considered the metabolically healthy lean phenotype as a reference group (Fig. 3 and Table 2). The metabolically unhealthy obese phenotype had the highest risk for incident T2D and hypertension (HR 2.21 95% CI 1.319–3.716, $p = 0.003$ and HR 2.355 95% CI 1.844–3.007 $p = <0.001$ respectively); metabolically unhealthy lean showed increased risk for incident hypertension (HR 2.615 95% CI 1.319–3.716, $p = 0.003$) but not T2D. MHO subjects were not at risk for diabetes and hypertension in these models.

Table 2
Cardiometabolic complications developed by subjects during the following (divided by BMI and metabolic health). Models were adjusted by sex, BMI, age, smoking, physical activity and family history of T2D and hypertension.

Cardiometabolic outcome	Phenotype	Beta	Wald	HR	95CI%	p
Type 2 Diabetes	MHL	-	-	-	-	-
	MUHL	0.539	2.086	1.715	0.825–3.564	0.149
	MHO	-0.188	0.459	0.829	0.481–1.427	0.498
	MUHO	0.795	9.044	2.214	1.319–3.716	0.003
Hypertension	MHL	-	-	-	-	-
	MUHL	0.961	40.583	2.615	1.946–3.515	<0.001
	MHO	0.192	2.277	1.211	0.944–1.554	0.131
	MUHO	0.857	47.127	2.355	1.844–3.007	<0.001

Discussion

This observational study describes the metabolic health transitions that occur over a 3-year time period in an unbiased set of Mexican adults. Despite being an apparently healthy population at baseline, only a fraction of the participants were metabolically healthy lean (14.9%) using the ATPIII criteria. In addition, almost 80% of the cohort had a BMI ≥ 25 Kg/m², which coincides with the high prevalence of overweight/obesity in our country (20). Different

MHO prevalences have been reported. In our population, the MHO prevalence was 39.3%. In Europe, the prevalence of MHO was 26%, Southeast Asia 37% and North America 43%, whilst higher prevalences have been reported in South America and African populations, 71% and 86% respectively. In contrast, the lowest prevalence have been identified in the Middle East (23%) (21–23).

Our data suggest that metabolic health is a dynamic and continuous process. Up to a third of the population changed from their initial category to another. Most of the transitions occurred in the direction of the unhealthy phenotype. Several studies have reported such changes, however there are dramatic differences among studies, as the findings depend on the criteria used to define metabolic health, the BMI cut-off to define normal weight/obesity, the follow-up time, as well as the predominance of certain characteristics such as gender, age and race/ethnicity (24–34). However, all the cohorts coincided with metabolic deterioration over time. In these cohorts, 33–52% of individuals metabolically healthy transitioned to a metabolically unhealthy phenotype. The Nurses' Health Study (30), one of the studies with the longest follow-up (30 years), reported that healthy women transitioned to a metabolically unhealthy status over time in all BMI categories, although the risk was higher in those with a greater degree of adiposity compared to those at normal weight (84% vs 68%). Even though the follow-up of our cohort was relatively short, we documented that the higher transition rate was observed in metabolically healthy obese compared to metabolically healthy lean (42.9% vs 27.9% respectively). This evidence provides strong support for considering the MHO condition as a transition stage rather a unique stable condition.

Several studies have examined the transitions between phenotypes (28–34). Factors that have previously been described as predictors of transition to a metabolically unhealthy phenotype have also been documented in this study; in particular sociodemographic factors, adiposity and insulin resistance (age, gender, BMI, lipids, glucose, HOMA-IR, HOMA-S, VAT, WHtR, among others). However, this analysis shows that other factors may increase the risk of progressing to a metabolically unhealthy phenotype in our population, especially in subjects with a BMI ≥ 25 Kg/m². These include socioeconomic status, number of pregnancies, a high carbohydrate diet, a low intake of vegetables, a low level of physical activity, history of obesity before the age of 18, and consumption of sweetened beverages (the latter was not statistically significant but showed a trend, with a $p = 0.063$). Conversely, factors that prevent the reversion from a metabolically unhealthy phenotype to a metabolically healthy profile, in those with BMI ≥ 25 Kg/m² included smoking, alcohol consumption and consumption of sweetened beverages. Many of these lifestyle factors are prevalent in our population. According to data from the National Health and Nutrition Survey 2016, more than 80% of children and 35% of adolescents in Mexico do not meet the physical activity recommendations (35). The prevalence of physical inactivity in adults was 29% in 2018 (20). The percentage of adults who eat vegetables is less than 50% (44.7%) and among children and adolescents it is 22% and 24.9% respectively (20). Our country has a high prevalence of overweight/obesity in children and adolescents (35.6% and 38.5% respectively). Alcohol consumption and smoking are found in 63.8% and 11.4% of adults respectively. Finally, the consumption of sweetened beverages is high, estimated at 85.9% in adults and similarly high in those under 18 years of age (20). The prevalence of overweight and obese persons continues to grow, and the metabolic syndrome is frequent (between 36.8 and 49.8%, depending on the criteria used) (36).

Increased body fat is associated with the development of long-term cardiometabolic complications. However, fat distribution is a determining factor in the development of these complications, especially ectopic deposits such as visceral fat mass. Our results show that a higher amount of visceral fat is associated with progression towards a metabolically unhealthy phenotype, while those who have loss of visceral fat are more likely to revert to a metabolically healthy phenotype, even regardless of the BMI. Interestingly, we found that the increase of VAT even in subjects who lose weight is associated to higher risk of progression to unhealthy phenotype. Different studies have

reported that the higher visceral fat mass contributes to the pathophysiology of cardiometabolic diseases through different mechanisms such as inflammation, greater release of free fatty acids in the circulation and alterations in the secretion of adipokines (37).

The incidence and risk of cardiometabolic diseases attributable to metabolic health have been analyzed in several studies (29–34, 38–40). In the Framingham study (31), there was a higher risk for incident T2D and arterial hypertension in the metabolically healthy obese subjects compared to the metabolically healthy lean subjects, but a lower risk compared to the metabolically unhealthy obese phenotype. In the Multi-Ethnic Study of Atherosclerosis (MESA) (32–33), similar results were reported, but on analysis of the impact of ethnicity, interestingly the Hispanic group had a higher risk of transition to a metabolically unhealthy phenotype and for development of cardiometabolic outcomes than Caucasians and African-Americans. Our findings confirm a higher incidence of cardiometabolic outcomes in metabolically unhealthy phenotypes. The metabolically unhealthy lean subjects had a higher risk of developing cardiometabolic complications during follow-up, even higher than MHO phenotype. Similar findings have been reported in other studies (41–43). Prospective studies show that the risk of incident diabetes and CV disease is higher among MUHL than in MHO persons (43). The metabolically unhealthy lean phenotype is often not included in prevention programs.

Our study has strengths and limitations. First, we analyzed transitions between metabolic health categories stratified by BMI and evaluated the incidence and risk for the development cardiometabolic outcomes in a population with high genetic and environmental predisposition. This is the first study that analyzes the behavior among persons with differing degrees of metabolic health in Mexico. A potential limitation is the relatively short follow-up time compared to other studies, this may influence the robustness of the findings.

Conclusion:

Metabolic health is an unstable phenotype at high risk of transition to metabolically unhealthy phenotypes over time. The greatest risk for transition was observed in the MHO subjects. It is imperative that we establish effective processes in primary care to contain such transitions. (44). Such strategies should be prioritized in people with obesity, regardless of their metabolic health, but also among those who are at normal weight but have evidence of impaired metabolic health.

Abbreviations

MHO (metabolically healthy obese), MHL (metabolically healthy lean), MUHL (metabolically unhealthy lean), MUHO (metabolically unhealthy obese), T2D (type 2 diabetes), MS (metabolic syndrome), CVD (cardiovascular disease), MH (metabolically healthy), MUH (metabolically unhealthy), MESA (Multi-Ethnic Study of Atherosclerosis), HOMA-IR (homeostatic model assessment-insulin resistance), HOMA-S (homeostatic model assessment-sensitivity), VAT (visceral adipose tissue), WHtR (waist-to-height ratio), BMI (body mass index), METS-VF (Metabolic Score for Visceral Fat).

Declarations

-Ethics approval and consent to participate: The study was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición and all participants signed an informed consent form.

-Consent for publication: Not applicable.

-Availability of data and materials: Data is available from the corresponding author upon reasonable request.

-Competing interests: The authors declare that they have no competing interests

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-Authors' contribution: Research idea and study design: **DEL, AVV**; data acquisition: **CAAS**; data analysis/interpretation: **DEL, AVV, CAAS**; statistical analysis: **AVV**; manuscript drafting: **DEL, AVV, RM, ICB, CAAS**; supervision or mentorship: **CAAS**. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Supplementary Tables

Supplementary Table 1: Baseline characteristics of groups according to BMI and metabolic health. Abbreviations; T2D: Type 2 diabetes: CVD; Cardiovascular disease: BMI; Body mass index.

Supplementary table 2: Predictors to identify participants who progress/revert to a metabolically healthy/metabolically unhealthy phenotype. Abbreviations; T2D: Type 2 diabetes: CVD; Cardiovascular disease: BMI; Body mass index.

Supplementary table 3: Univariate analysis to evaluate factors associated with the transitions according to metabolic health. Abbreviations: BMI; Body mass index: WHtR; Waist-height ratio.

Supplementary table 4: Factors associated with progression according to metabolic health and BMI. Abbreviations: BMI; Body mass index: WHtR; Waist-height ratio.

Supplementary table 5: Factors associated with reversion according to metabolic health and BMI. Abbreviations: BMI; Body mass index: WHtR; Waist-height ratio.

Tables

Table 1: Cardiometabolic outcomes incidence rates (cases/1000 persons per year) in the study sample stratified by metabolic phenotype.

Cardiometabolic outcome	Phenotype	Number of cases (%)	IR	95%CI
Type 2 Diabetes	MHL	19 (2.3)	9.62	5.29-13.95
	MUHL	12 (4.0)	16.99	7.37-26.60
	MHO	60 (2.8)	11.44	8.55-14.34
	MUHO	202 (9.0)	36.81	31.73-41.49
Hypertension	MHL	73 (8.8)	36.98	28.49-45.47
	MUHL	39 (12.9)	55.22	37.88-72.55
	MHO	297 (13.6)	56.66	50.22-63.11
	MUHO	408 (18.2)	74.35	67.14-81.57

Table 2: Cardiometabolic complications developed by subjects during the following (divided by BMI and metabolic health). Models were adjusted by sex, BMI, age, smoking, physical activity and family history of T2D and hypertension.

Cardiometabolic outcome	Phenotype	Beta	Wald	HR	95CI%	p
Type 2 Diabetes	MHL	-	-	-	-	-
	MUHL	0.539	2.086	1.715	0.825-3.564	0.149
	MHO	-0.188	0.459	0.829	0.481-1.427	0.498
	MUHO	0.795	9.044	2.214	1.319-3.716	0.003
Hypertension	MHL	-	-	-	-	-
	MUHL	0.961	40.583	2.615	1.946-3.515	<0.001
	MHO	0.192	2.277	1.211	0.944-1.554	0.131
	MUHO	0.857	47.127	2.355	1.844-3.007	<0.001

Figures

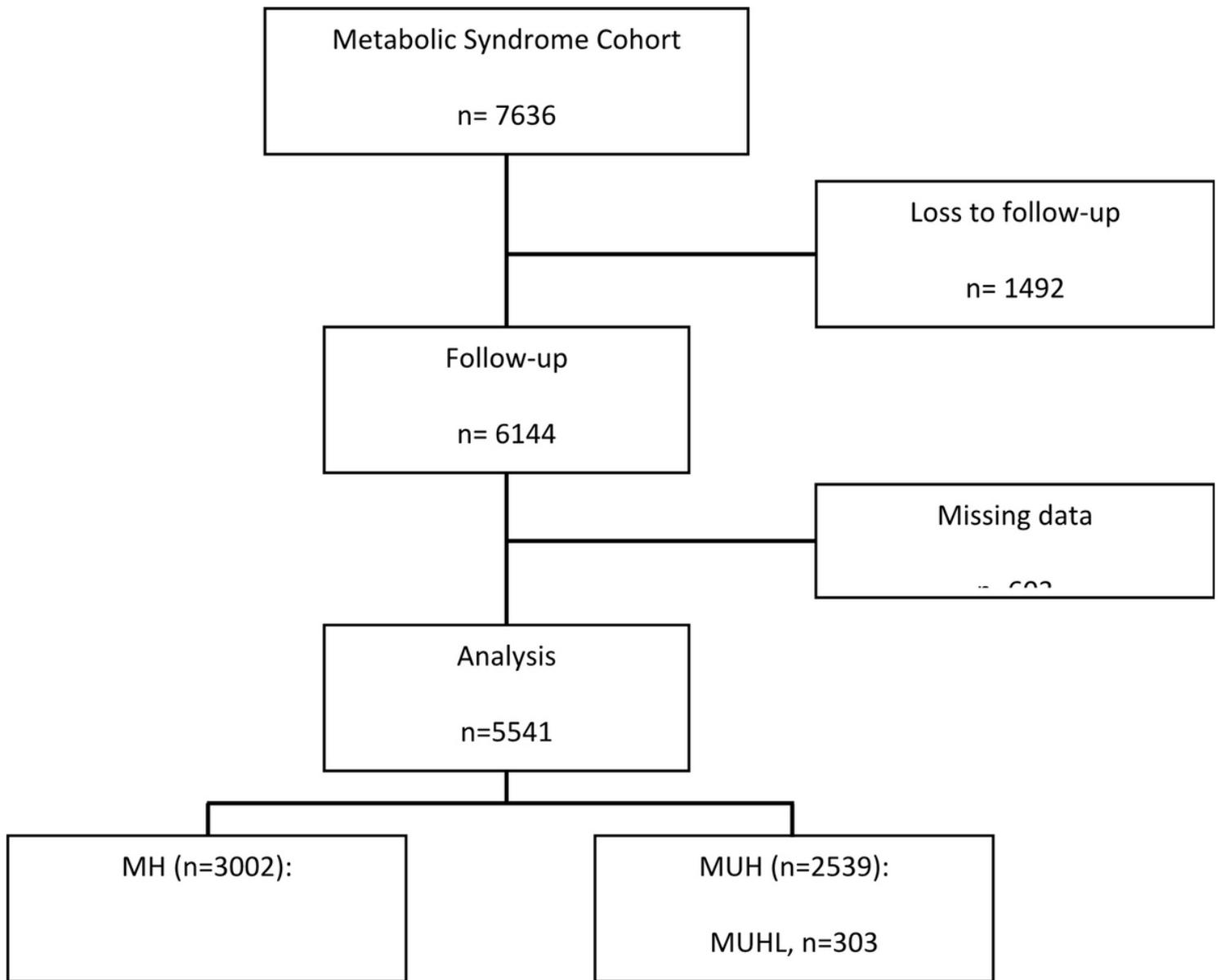


Figure 1

Flowchart of study participants at baseline and follow-up, outlining reasons for exclusion.

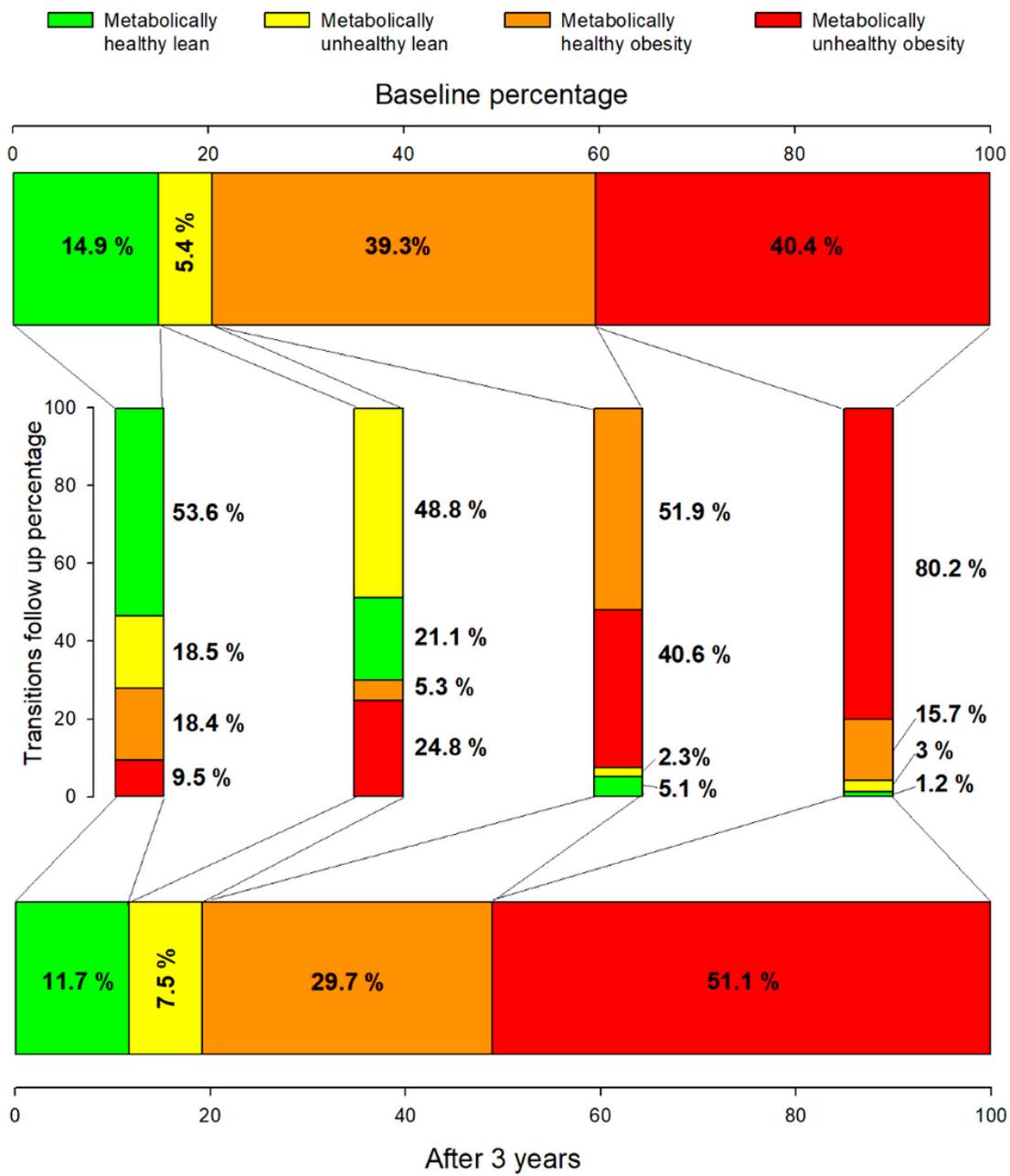


Figure 2

Permanence and transitions (progressions and reversals) of the 4 groups in the study.

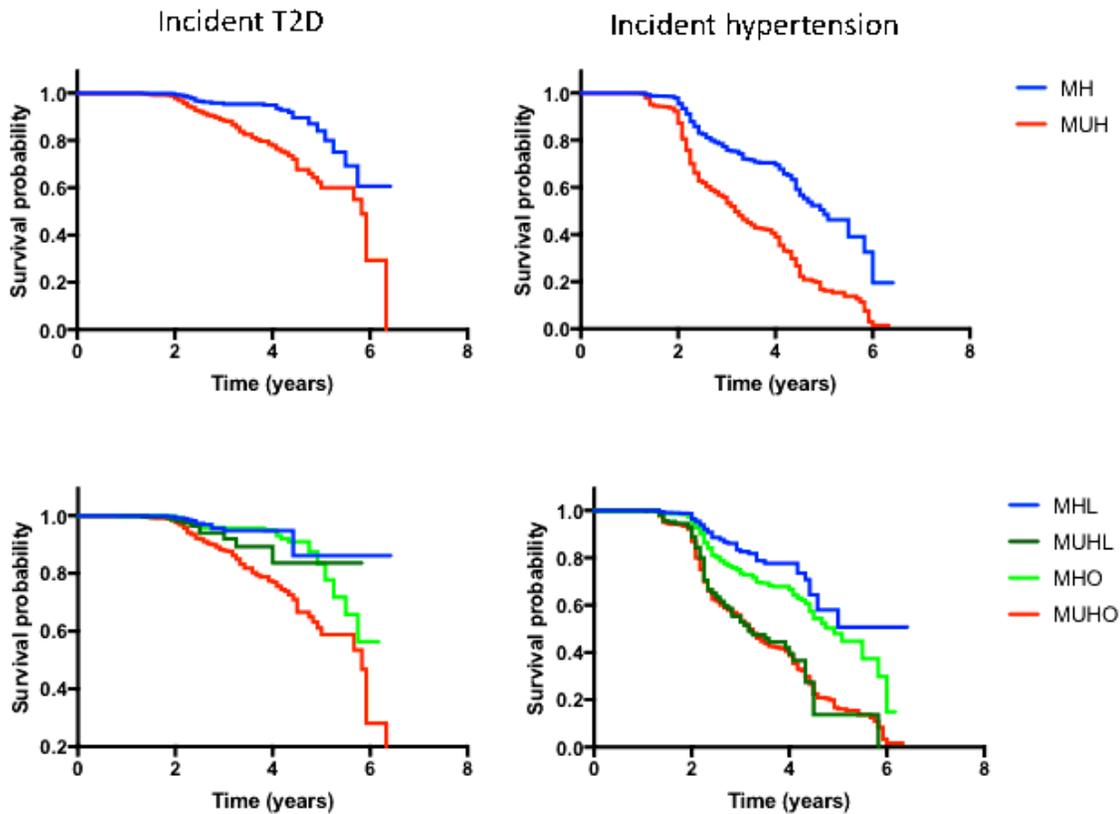


Figure 3

Kaplan-Meier survival curves for incident cardiometabolic outcomes according to stratified phenotype.

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