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Obesity phenotypes in urban middle-class cohorts; the PRIT-Lindavista merging evidence in Mexico: the OPUS PRIME study

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Abstract

Background and aims: even though overweight and obesity (O/O) are stated diseases, there is still a claim for a so-called “healthy obese” phenotype. Only few reports have explored the presence of different metabolic phenotypes along the body mass index (BMI) range and their corresponding associations to cardiovascular risks.

Methods: as of BMI, and according to the presence of metabolic syndrome (MS) features (waist circumference, blood pressure, fasting glycemia, and lipid profile), phenotypes were determined. Cardiovascular risk was estimated with atherogenic quotients: total cholesterol/HDL-c, LDL-c/HDL-c and the triglycerides (TG)/HDL-c index.

Results: in 8,405 mexican adults, 36% lean, 43% overweight and 21% obese, nine phenotypes were identified: for each weight category there were subjects with normal metabolism (none MS factors), intermediate (≤ 2) and dysmetabolic (≥ 3). Only 10.8% of O/O had normal metabolism, and 5.8% of the lean persons were dysmetabolic. Atherogenic risk was higher in dysmetabolic obese persons, but the risk was high among all dysmetabolic people, independently of the weight status. TG/HDL-c showed the same trend.

Conclusions: elevated cardiometabolic risk derives from the high prevalence of O/O. A great proportion of non-obese people have intermediate dysmetabolism. A genetic predisposition to obesity, insulin resistance, diabetes and dyslipidemia in Mexican population is blended with a sedentary lifestyle and high-calorie diet.

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to an unhealthy lifestyle, yielding to a catastrophic epidemic of diabetes, and cardiovascular diseases.

Background

Mexico faces an evolving epidemic of overweight and obesity (O/O)\(^1,2\) resulting from changes in population habits, leading to a hypercaloric diet alongside a sedentary lifestyle, added to a genetic predisposition to fat accumulation and development of diabetes\(^1\).

Recently, evidence showing that O/O are neither homogenous conditions nor impose similar cardiometabolic risk to all individuals has emerged. Four well-defined phenotypes have been so far identified: lean healthy (LH), obese unhealthy (OU), the metabolically healthy obese (MHO), and the metabolically obese but with normal weight (MONW)\(^3,5\). The pathogenic phenotypes impose different therapeutic and/or preventive approach. Patients with MHO and MONW individuals are in a higher risk for cardiovascular outcomes or diabetes.

Although a clear-cut picture of the epidemiology of O/O in Mexico has been established a short time ago\(^2,6\), no study has been addressed to identifying the prevalence of the above described phenotypes. The PRIT and the Lindavista studies\(^7,8\), whose partial or early results have been already published, are independent observations focused towards the prevalence of essential vascular risk factors in middle-class samples of Mexico City inhabitants. The main purpose of the OPUS PRIME (Obesity Phenotypes in Urban Middle-Class Cohorts. The PRIT-Lindavista Merging Evidence in MExico) study was to estimate the frequency of the different metabolic phenotypes in a combined cohort of the contemporary population of Mexico City, and the cardiometabolic risk inherent to each phenotype.

Methods

Study population. The basic methodology of the two base studies has been published previously\(^7,8\). Briefly, the PRIT (Prevalence of Cardiovascular Risk Factors in Hospital General de México Workers) study assembled a sample of more than 5,000 workers of a Mexican hospital (physicians, nurses, administrative employees, janitors and maintenance employees), who were assessed in order to establish the frequency of cardiovascular and metabolic risk factors: diabetes, overweight or obesity, hypertension smoking habits, and dyslipemias. For its side, the Lindavista study was originally an intervention trial on cardiovascular risk factors, using also a cohort of urban middle-class Mexico City inhabitants (a cohort of 2602 subjects ≥35 years, free of clinical cardiovascular or life-threatening chronic diseases), with two parallel arms: one in which therapeutic interventions were done intensively by cardiologists at the Hospital Regional “Primero de Octubre”, and a control group where standard preventive interventions were conducted by primary care physicians. In the present combined analysis, baseline data from both studies were merged.

Ethics. Both studies were approved by their Ethics and Research Institutional Committees and conducted according with the Declaration of Helsinki, Good Clinical Practices and Mexican Federal Regulations; informed consent was approved by each institutional review committee and was signed before any measurements were taken.

Anthropometric and cardiometabolic assessment. Body weight was measured in kg; height was obtained in meters with a wall-stadiometer and body mass index (BMI; kg/m\(^2\)) was calculated. Abdominal circumference was measured in cm. Blood pressure was determined by means of mercurial sphygmomanometers. Fasting serum glucose, total cholesterol (TC; mg/dL); cholesterol of the high-density lipoproteins (HDL-c; mg/dL) and triglycerides (TG; mg/dL) were determined using colorimetric assay kits, following the manufacturer’s instructions. Low-density lipoprotein cholesterol (LDL-c; mg/dL) was calculated using the Friedewald formula.\(^9\) Cut-off points of all variables were established according with the current national and international guidelines on hypertension\(^10\) (systolic and diastolic blood pressures ≥130/85 mmHg for the diagnosis of the MS); dyslipidemia\(^11\) (hypertriglycerideremia ≥150 mg/dL and hypoalphalipoproteinemia if LDL-c <40 mg/dL in men and <50 mg/dL in women) and dysglycemia\(^12\) (normal if fasting glycemia was <100 mg/dL, impaired fasting glycemia when fasting blood glucose was between 100 and 125 mg/dL, and downright diabetes mellitus if glycemia was ≥126 mg/dL). According with the World Health Organization\(^13\), the subjects were divided in three weight categories: normal weight (BMI <25), overweight (25-29.99) and obesity (≥30). A waist circumference ≥90 cm in men and ≥80 cm in women\(^14\) was considered as indicator of abdominal adiposity.

MS was diagnosed with at least three of five traits\(^15\): abdominal obesity, hypertriglycerideremia, hypoalphalipoproteinemia, dysglycemia, and systolic and diastolic blood pressures ≥130/85 mmHg.
Estimation of risks. In order to characterize the metabolic and cardiovascular risk of the studied subjects we ruled out both, the Framingham\textsuperscript{16} and the newer Pool Cohort Equations\textsuperscript{17} algorithms because neither of them account BMI and TG as a risk criteria, and because smoking (not considered in this analysis focused on O/O) adds considerable risk predominantly in young people, independently of their metabolic status. Instead, we used the atherogenic indexes TC/HDL\textsuperscript{18} and LDL/HDL\textsuperscript{19}, quotients displaying the balance among the atherogenic lipid fractions and the “good” cholesterol tissue removing fraction (HDL-c). These indexes have been extensively used to predict cardiovascular disease due to the imbalance between pro-atherogenic and protective lipoproteins, leading to—as their name states- atherosclerosis and further contributing to the development of coronary artery disease (CAD). In addition, the TG/HDL\textsuperscript{20} was also assessed as it has been associated with the risk for developing insulin resistance and it has also been proposed as the most powerful independent predictor of CAD when it is $>4$.

Statistical analysis. Phenotype frequencies (i.e., proportions) were calculated and then divided according to BMI and gender. Afterwards, the relative frequencies of MS abnormalities (e.g., dysglycemia, hypertension, etc.) and of the atherogenic indexes thus cardiovascular risk, were calculated in relation to each phenotype. Finally, we calculated the relative risks. Finally, after applying a chi-squared test that showed significantly association among variables, we calculated the relative risk of obese and overweighted individuals with higher cardiovascular risk (according with elevated TG/HDL ratio) in comparison with participants with normal BMI. GraphPad Prism v.5 was used to performed statistical analysis; $p<0.05$ value was considered as significant in all tests.

Results

The databases combined 8,405 subjects, 68.1\% of them women. Table I shows the proportion of individuals according to BMI. In both genders, the frequency of weight categories was similar, but women had a slightly greater proportion of obesity and, in correspondence, a lesser number of overweighted individuals.

Table II shows the relative frequency of the metabolic phenotypes encompassed in the three weight categories.
ries (normal, overweight and obesity); each having three different metabolic statuses according with the number of MS traits: normometabolic (none), intermediate (one or two) or dysmetabolic (three or more). Data show that many lean individuals were not entirely normometabolic, but had one or two features of the MS, mainly hypoalphalipoproteinemia and/or hypertriglyceridemia. In the same manner, many overweight or obese subjects were not entirely dysmetabolic, but had just one or two MS abnormalities, or even, none. The proportion of the “healthy obese” phenotype was rather low in our sample.

Figure 1 gathers the data regarding the relationship among O/O status and the frequency of the MS traits in men (A) and women (B). There are differences among genders: the proportion of low HDL and hypertriglyceridemia was greater in women than in men in lean, but showed no differences in the other weight categories. Notwithstanding, although subjects with dysmetabolic obesity had the greater proportion of MS factors, there were not statistical differences among these persons and those with dysmetabolic overweight. Subjects pertaining to the intermediate normal weight group had the lesser proportions of hypertension and dysglycaemia. Although there was a statistical difference among intermediate and full-blown dysmetabolic phenotypes in each weigh category, no difference was found among groups. It was detected a tight (r=0.99) correlation between blood pressure ≥130/85 mmHg and weight category in the intermediate and dysmetabolic phenotypes. Concerning glycaemia, the high correlation was seen only in the intermediate phenotypes and no in the dysmetabolic, because almost 70% of the individuals pertaining to the latter category had abnormal fasting glycaemia (graphs not shown). The proportion of subjects with hypoalphalipoproteinemia and hypertriglyceridemia in both genders was remarkable. Dysmetabolic women had greater proportion of both dyslipidemias than men of the same categories. Men and women with normal weight had a sizable proportion of low HDL, indicating that these abnormalities are not exclusively related to overweight or obesity.

Table III shows the distribution of atherogenic indexes LDL/HDL and TC/HDL. Obese dysmetabolic subjects exhibited the highest values of both indexes, denoting the most elevated atherogenic risk. Nevertheless, dysmetabolic phenotypes of the three weight categories, had also relatively high risk values, pointing out that lean but dysmetabolic individuals have also a substantially elevated atherogenic risk. The TC/HDL

![Figure 1](https://example.com/figure1.png)

**Fig. 1.**—Percentage of subjects with no metabolic syndrome (MS) factors (normometabolic); ≥2 MS factors (Intermediate) and ≥3 MS factors (Dysmetabolic) in lean, overweight and obese Body Mass Index categories in a sample of 8,405 Mexican adults. A) Men; B) Women. C) Triglyceride/HDL ratio levels in subjects with no metabolic syndrome (MS) factors (normometabolic); ≥2 MS factors (Intermediate) and ≥3 MS factors (Dysmetabolic) in lean, overweight and obese Body Mass Index categories in a sample of 8,405 Mexican adults. D) Triglyceride/HDL ratio levels grouped as Ideal+ Normal (<2) and High + to High (≥4) in Lean, Overweight and Obese subjects.

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**Mexican cardiometabolic phenotypes**

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Regarding the TG/HDL ratio, which establishes metabolic and cardiovascular risk, the normal-weight but dysmetabolic subjects had a similar risk profile to those with dysmetabolic O/O. In general, as seen in Figure 1C, the risk according to the TG/HDL ratio increased as BMI did and moreover, after grouping low-risk (i.e., normal+ideal) and high-risk (i.e., high+too high) categories, as shown in Figure 1D, it became more evident that the overall cardiometabolic risk increased within weight categories as the number of MS features did. We statistically evaluated such phenomenon by calculating relative risks (RR). Table IV shows that there is a significant increase in the relative risk of being at high cardiometabolic risk (i.e., high+too high TG/HDL risk category) as BMI increases despite that the metabolic phenotype is the same (e.g., a dysmetabolic subject has a higher probability (156%) of being at high cardiometabolic risk if he/she is obese than if he/she has a normal body weight).

### Discussion

Results found in this work delineate the metabolic status affecting a sample of the contemporary urban population of Mexico. Indirectly, the data give account of the high prevalence of not only obesity and diabetes, but also of a wider metabolic disarrangement, including hypoalphalipoproteinemia and hypertriglyceridemia.

The simplest approach to O/O, making these adiposity abnormalities a synonym of the so-called “metabolic syndrome” has a lot of shortcomings and deceitful conclusions. In order to clarify this tangled question it can be say that, in the majority of the cases of abdominal obesity, insulin resistance is a measurable phenomenon, and the secondary hyperinsulinism is a pathogenic factor responsible of comorbidities accompanying the O/O condition. Nevertheless, recent observations have disclosed that not in all the obese or overweight subjects are dysmetabolic yielding a “healthy obese” phenotype. However, a recent meta-analysis proved that, in comparison with metabolically healthy normal-weight individuals, obese or overweight persons have a greater risk for outcomes and complications. In the other hand, there are normal-weight persons with some or all the comorbidities of the MS, except weight excess. Again, some terms that have been used to designate these phenotypes are not, in our judgment, very convenient. The phrase “metabolically obese but with normal weight (MONW)” seems inappropriate because is too long and rather confusing.

### Table III

<table>
<thead>
<tr>
<th>Category and phenotypes</th>
<th>LDL/HDL values</th>
<th>Lean (%)</th>
<th>Intermediate (%)</th>
<th>Dysmetabolic (%)</th>
</tr>
</thead>
<tbody>
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<td>&lt;2.5</td>
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<td>≥3.5</td>
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<tr>
<td>Normometabolic (%)</td>
<td>64.5</td>
<td>26.7</td>
<td>8.8</td>
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<tr>
<td>Intermediate (%)</td>
<td>49.3</td>
<td>27.4</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>Dysmetabolic (%)</td>
<td>33.6</td>
<td>27.2</td>
<td>38.6</td>
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<tr>
<td>Overweight</td>
<td>59.2</td>
<td>26.5</td>
<td>14</td>
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<tr>
<td>Normometabolic (%)</td>
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<td>31.5</td>
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<tr>
<td>Intermediate (%)</td>
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<td>55.9</td>
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<tr>
<td>Obesity</td>
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<td>38.8</td>
<td>30.5</td>
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</tr>
<tr>
<td>Normometabolic (%)</td>
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<td>27.7</td>
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<tr>
<td>Intermediate (%)</td>
<td>19.8</td>
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### Table IV

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<th>Category and phenotypes</th>
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<th>Lean (%)</th>
<th>Intermediate (%)</th>
<th>Dysmetabolic (%)</th>
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</thead>
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<tr>
<td>Normometabolic (%)</td>
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<td>Intermediate (%)</td>
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<tr>
<td>Dysmetabolic (%)</td>
<td>14.4</td>
<td>42</td>
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</tr>
<tr>
<td>Obesity</td>
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<tr>
<td>Intermediate (%)</td>
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<td>48.8</td>
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</tr>
<tr>
<td>Dysmetabolic (%)</td>
<td>14.4</td>
<td>42</td>
<td>43.5</td>
<td></td>
</tr>
</tbody>
</table>

Relative risk and their corresponding p-value are shown of TG/HDL ratios grouping normal+ideal ranges and high+very high categories. Only metabolically altered subjects (i.e., intermediate and dysmetabolic) were included and analysis was performed within BMI categories.

HDL risk category as BMI increases despite that the metabolic phenotype is the same (e.g., a dysmetabolic subject has a higher probability (156%) of being at high cardiometabolic risk if he/she is obese than if he/she has a normal body weight).
We instead propose the three classical weight categories: normal weight, overweight and obesity, adding the sub-phenotype characteristic: normometabolic, intermediate or dysmetabolic. Our data show a broad continuum in the expression of the binomial weight-metabolism, in which in one pole there is the weight excess, mainly abdominal adiposity, while in the other extreme lays an abnormal metabolism, due presumably to insulin resistance and reactive hyperinsulinism.

It is apparent that in contemporary Mexicans, both factors play important roles in the genesis of O/O. One third of the population of the combined cohorts had normal weight, and three fifths, overweight or obesity. Our study also shows that for each weight category the more sizable proportion corresponded to intermediate phenotypes, i.e., persons with one or two traits of MS: more than two thirds of the normal-weight subjects, and more that the half of those with overweight or obesity. Only 1353 participants (16% of the entire population, 27% of the normal-weight subjects and 9.8% of the O/O population) were metabolically healthy people, with a normal glucose and lipid metabolism, and absence of blood pressure ≥130/85 mm Hg.

More relevant is the fact showing that the abnormal dysmetabolic phenotypes bring up a higher metabolic and cardiovascular risk. Measuring these risks in the way we did (through lipid quotients), it is clear that both, excess weight and a dysmetabolic state, impose a threatening risk to the bearers of these anthropometric or metabolic derangements. The TG/HDL quotient has been used frequently to predict diabetes or cardiovascular outcomes26. For example, in the WISE27 study this index was a strong predictor of all-cause mortality and cardiovascular events in women with suspected ischemic heart disease. The recent study of Murguía-Romero28 in 2244 apparently healthy college students, demonstrated that the TG/HDL ratio cutoff points used in middle-aged Caucasian of both genders can be used in our population to identify insulin resistant individuals with elevated cardiometabolic risk.

**Limitations of the study.** There are several limitations in this study. Firstly, both merging cohorts’ samples were not probabilistic, and so there are more women than men. Secondly, samples were assembled with persons living in Mexico City, so, this fact impedes to extend the conclusions of the study to the rest of the country that has a lot of regional different peculiarities. Third, we assume that TG/HDL quotient reflects insulin resistance, but we do not measure it directly. It is known that the index does not reflect insulin resistance at least in obese women of African descent29, although indeed indicate that metabolic state in Mexicans30.

**Conclusions**

Mexican population, a truly genetic “melting pot” but with a dominant Amerindian ancestry, has a genomic composition prone to obesity, diabetes, hypertriglyceridemia and hypoalphalipoproteinemia. In addition, a cluster of nutritional and lifestyle modifications has yielded to a very fast epidemiological transition, with a skyrocketing increase of cardiometabolic diseases, to the point that nowadays, diabetes, ischemic heart disease and stroke are the leading causes of general mortality in our population.

Our data show that the majority of normal-weight subjects had already a subtle metabolic abnormality, just waiting for the bursting of the full-blown hemodynamic and metabolic shamble of the overweight or obese dysmetabolism. The usefulness and low-cost of the TG/HDL quotient allows singling out those individuals with insulin resistance and upraised cardiometabolic risk, in order to implement the therapeutic and preventive measures.

A sustained and well-funded nation-wide campaign with the decisive support of the medical community and the entire society, against malnourishment and obesity is now mandatory in order to reduce drastically, in a relatively short period of time, the magnitude of the O/O epidemic and all its catastrophic consequences.

**Conflict of interest statement**

All authors declare no actual or potential conflict of interest.

**Acknowledgements**

GFS, GGS, EM, and GC conceived the general study, performed statistical analysis and wrote, revised and approved the submitted version. VS, AM, LSR, UN, LA, and IOC participated in the collection, data gathering, construction of data bases, analysis and writing of the base-studies herein merged (i.e., Prit & Lindavista).

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**References**


