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BRIEF COMMUNICATION

Homeostasis model assessment of insulin resistance (HOMA-IR) and metabolic syndrome at baseline of a multicentric Brazilian cohort: ELSA-Brasil study

Modelo de avaliação da homeostase de resistência à insulina (HOMA-IR) e síndrome metabólica na linha de base de uma coorte brasileira multicêntrica: estudo ELSA-Brasil

Modelo homeostático para evaluar la resistencia a la insulina (HOMA-IR) y síndrome metabólico en la línea de base de una cohorte brasileña multicéntrica: estudio ELSA-Brasil

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Abstract

Homeostasis model assessment of insulin resistance (HOMA-IR) is a method to measure insulin resistance. HOMA-IR cut-offs for identifying metabolic syndrome might vary across populations and body mass index (BMI) levels. We aimed to investigate HOMA-insulin resistance cut-offs that best discriminate individuals with insulin resistance and with metabolic syndrome for each BMI category in a large sample of adults without diabetes in the baseline of the Brazilian Longitudinal Study of Adult Health *(ELSA-Brasil). Among the 12,313 participants with mean age of 51.2 (SD 8.9) years, the prevalence of metabolic syndrome was 34.6%, and 60.1% had overweight or obesity. The prevalence of metabolic syndrome among normal weight, overweight and obesity categories were, respectively, 13%, 43.2% and 60.7%. The point of maximum combined sensitivity and specificity of HOMA-IR to discriminate the metabolic syndrome was 2.35 in the whole sample, with increasing values at higher BMI categories. This investigation contributes to better understanding HOMA-IR values associated with insulin resistance and metabolic syndrome in a large Brazilian adult sample, and that use of cut-off points according to ROC curve may be the better strategy. It also suggests that different values might be appropriate across BMI categories.*

Metabolic Syndrome; Insulin Resistance; Cohort Studies

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Introduction

Insulin resistance is one of the pathogenic mechanisms of the metabolic syndrome and is a common condition that allows identification of the risk of diabetes and metabolic syndrome [1]. The gold standard method to assess insulin resistance is the hyperinsulinemic-euglycemic clamp, which is not useful for clinical and epidemiological investigations. The homeostasis model assessment of insulin resistance (HOMA-IR) is a method based on fasting glucose and insulin plasmatic levels, which was validated by Matthews et al. [2] and has been used for defining insulin resistance for clinical and research purposes in several populations. In Brazil, the *Brazilian Metabolic Syndrome Study* (BRAMS), with a population from 18 to 78 years old, used the 90th percentile to establish 2.7 as a cut-off to define insulin resistance in healthy people (n = 297) with body mass index (BMI) < 30kg/m², and 2.3 as the value that best discriminates the presence of metabolic syndrome [3]. However, HOMA-IR cut-offs might differ across populations and BMI levels and establishing HOMA-IR values that correlate with insulin resistance and with metabolic syndrome is still necessary [4].

The *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil) is a large multicentric cohort conducted in six Brazilian capitals, which analyzed data of 15,105 civil servants from three different geographical regions [5]. We aimed to investigate HOMA-IR cut-offs that best discriminate insulin resistance and metabolic syndrome for each BMI category among individuals without diabetes mellitus in this large sample.

Methods

This is a cross-sectional analysis of the ELSA-Brasil study, described previously [5]. Participants were enrolled between August 2008 and December 2010. All participants were volunteers, between 35 and 74 years old, and provided an informed consent form. All Institutional Review Boards approved this study.

For this analysis, we excluded 7 participants with missing data of fasting glucose, 12 of insulin, 52 of metabolic syndrome, 141 with underweight (BMI < 18.5kg/m²), and 2,580 with diabetes mellitus, which led to a final sample of 12,313 participants.

Height (in cm) was measured using a fixed stadiometer (accuracy of 0.1cm), and weight (kg) was measured with an electronic digital scale (Toledo, Brazil, to the nearest 100g). Waist (mid-point between lowest rib and iliac crest) circumference was measured by inelastic tapes (cm). The average of two measures was used for analyses. BMI [weight (kg)/height (m)²] was calculated. According to BMI, participants were stratified into categories: normal weight ≥ 18.5 to 24.9kg/m², overweight 25-29.9kg/m², obesity ≥ 30kg/m². Blood pressure was defined by the average of two measures, after five minutes of rest in the sitting position [5].

Race/skin color, physical activity, alcohol and tobacco use were self-reported [5]. Blood samples were collected after an overnight fast for fasting glucose, total cholesterol, triglycerides, *high-density* lipoprotein cholesterol (HDL-c), insulin. fasting glucose was determined by the hexokinase method (enzymatic colorimetric); total cholesterol by cholesterol oxidase method (enzymatic colorimetric), triglycerides by glycerol-phosphate peroxidase; HDL-c by homogeneous colorimetric without precipitation, insulin by immunoenzymatic assay, all of them with an ADVIA 1200 Siemens system (Deerfield, United States) [6]. HOMA-IR was calculated from fasting glucose and insulin as [fasting glucose (mg/dL) X 0.0555 X fasting serum insulin (mUI/L)/22.5]².

The quality and control of all data collected and stored were ensured according to the study protocol [5].

Since there is no consensus about whether the 75th and the 90th percentile of HOMA-IR should be used as cut-off points for identifying individuals with insulin resistance, we calculated both for the overall population and for each BMI category [4,7]. We defined metabolic syndrome by the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity criteria for Latin American populations [1].

Data are described as means and standard deviation, median with interquartile range (IQR) and frequencies. Pairwise group comparisons were performed using the Mann-Whitney U test or the chi-square test. Receiving operator characteristic (ROC) analyses were conducted and the area under the curve (AUC) with 95% confidence intervals (95%CI) for the whole population and for each BMI category was estimated to investigate HOMA-IR accuracy at identifying metabolic syndrome. The point of the ROC with maximum sensitivity and specificity was determined by the Youden index [8].

We performed a sub-analysis with the exclusion of participants with BMI ≥ 30kg/m² (n = 2,399). All analyses were performed using the statistical software Stata 14 (https://www.stata.com).

Results and discussion

Among the 12,313 participants studied, 34.6% (n = 4,262) had metabolic syndrome and 60.1% (n = 7,399) had overweight or obesity. The prevalence of metabolic syndrome among normal weight, overweight and obesity categories were, respectively, 13%, 43.2% and 60.7%. Table 1 presents the population characteristics. After exclusion of participants with obesity, 2,805 (28.3%) had metabolic syndrome.

For the population without metabolic syndrome, HOMA-IR 75th and 90th percentiles were 2.75 and 3.73, respectively. Regarding the participants without obesity and metabolic syndrome (n = 7,109), HOMA-IR 75th and 90th percentiles were, respectively, 2.55 and 3.43. The 90th percentile of the population without obesity and metabolic syndrome at ELSA-Brasil baseline was higher than that of the healthy population in the BRAMS study (2.7). This difference might be related to the inclusion of younger participants compared to ELSA-Brasil (≥ 18 years vs. ≥ 35 years, respectively) [9], and perhaps because ELSA-Brasil included participants from six capitals of different parts of the country: South, Southeast and Northeast.

Table 1

Characteristics of the population studied according to the metabolic syndrome *, at baseline of the *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil), 2008-2010.

Characteristics	Total [N = 12,313]	With metabolic syndrome [n = 4,262; 34.6%]	Without metabolic syndrome [n = 8,051; 65.4%]	p-value
Age in years [mean ± SD]	51.2 ± 8.9	53.4 ± 8.9	50.0 ± 8.7	< 0.01
Female [n (%)]	6,902 (56.1)	2,011 (47.2)	4,891 (60.8)	< 0.01
Race/Skin color [n (%)]				0.05
White	6,577 (54.0)	2,202 (52.3)	4,375 (54.8)	
Black	1,782 (14.7)	647 (15.4)	1,135 (14.3)	
Mixed (*Pardo*)	2,411 (28.0)	1,213 (28.8)	2,198 (27.6)	
Mixed (Asian/Indian)	404 (3.3)	145 (3.5)	259 (3.3)	
Physical activity [n (%)]				
Low	9,254 (76.3)	3,368 (80.3)	5,886 (74.1)	< 0.01
Moderate	1,944 (16.0)	603 (14.4)	1,341 (16.9)	
High	927 (7.7)	222 (5.3)	705 (9.0)	
Alcohol use [n (%)]				> 0.05
No	1,255 (10.2)	425 (10.0)	830 (10.3)	
Former	2,335 (19.0)	835 (19.6)	1,500 (18.7)	
Current	8,709 (70.8)	2,997 (70.4)	5,712 (71.0)	
Smoking [n (%)]				< 0.01
Never	7,226 (58.7)	2,217 (52.0)	5,009 (62.2)	
Former	3,517 (28.6)	1,459 (34.2)	2,058 (25.6)	
Current	1,570 (12.7)	586 (13.8)	984 (12.2)	

(continues)

Table 1 (continued)

Characteristics	Total [N = 12,313]	With metabolic syndrome [n = 4,262; 34.6%]	Without metabolic syndrome [n = 8,051; 65.4%]	p-value
DBP (mmHg) [mean ± SD]	75.6 ± 10.5	80.7 ± 10.6	72.9 ± 9.4	< 0.01
SBP (mmHg) [mean ± SD]	119.6 ± 16.4	127.6 ± 16.9	115.4 ± 14.4	< 0.01
BMI (kg/m^2) [mean ± SD]	26.6 ± 4.5	29.0 ± 4.4	25.4 ± 3.9	< 0.01
BMI category [n (%)]				< 0.01
Normal weight	4,909 (39.9)	639 (15.0)	4,270 (53.1)	
Overweight	5,000 (40.6)	2,164 (50.8)	2,836 (35.2)	
Obesity	2,399 (19.5)	1,457 (34.2)	942 (11.7)	
Waist circumference (cm) [mean ± SD]				
Women	86.5 ± 11.8	94.5 ± 10.9	83.2 ± 10.5	< 0.01
Men	94.2 ± 11.0	100.5 ± 9.6	89.6 ± 9.6	< 0.00
HDL-c (mg/dL) [median (IQR)]				
Women	60 (52-71)	51 (46-61)	64 (56-74)	< 0.01
Men	49 (43-57)	45 (40-53)	52 (42-60)	< 0.01
Triglycerides (mg/dL) [median (IQR)]	110 (79-157)	165 (115-216)	95 (71-124)	< 0.01
Fasting glycemia (mg/dL) [mean ± SD]	99.2 ± 8.6	104.8 ± 7.7	96.3 ± 7.5	< 0.01
HOMA-IR [median (IQR)]	2.32 (1.56-3.47)	3.39 (2.39-4.62)	1.90 (1.34-2.74)	< 0.01

BMI: body mass index; DBP: diastolic blood pressure; HDL-c: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation.

Note: participants who were underweight (n = 141) were excluded.

* Metabolic syndrome according to joint interim statement for Latin American populations 1 – necessary 3 out of 5 criteria: – waist circumference ≥ 90cm men or ≥ 80cm women; triglycerides ≥ 150mg/dL or drug treatment for high triglycerides; HDL-c < 40mg/dL men or < 50mg/dL women or drug treatment for low HDL-c; SBP ≥ 130mmHg and/or DBP ≥ 85mmHg or drug treatment for arterial hypertension; fasting glycemia ≥ 100mg/dL or drug treatment for elevated glucose.

The value with the maximum combined sensitivity and specificity to discriminate metabolic syndrome was 2.35 both for the whole population and among participants without obesity. Area under the curve ROC (95%CI) for total sample was 0.78 (0.77-0.79). There was a clear gradient of HOMA-IR values that best discriminate the metabolic syndrome across BMI categories with the highest values within the obese subgroup (Table 2). This suggests that it may be appropriate to apply different HOMA-IR values to define insulin resistance, according to the BMI category.

The large sample that included participants from diverse Brazilian states, the methodological rigor in data collection, centralized analysis of the laboratory tests, and the rigorous quality control procedures are strengths of this study. However, we acknowledge that the inclusion of participants with a minimum age of 35 years limits generalizing these results to younger Brazilian populations. Also, ELSA-Brasil is not a population-based study, and generalization to the entire Brazilian population should be done with caution.

The point of maximum combined sensitivity and specificity of HOMA-IR to discriminate the metabolic syndrome was 2.35 in the whole sample, with increasing values at higher BMI categories. In a Spanish population the threshold value of HOMA-IR, considering, metabolic syndrome components was 2.05 [9]. Different values were found in the literature according to the HOMA-IR percentile used as criteria to define insulin resistance, mean of age and BMI of studied population [4,9]. Our investigation contributes to better understanding HOMA-IR values associated with insulin resistance and metabolic syndrome in a large Brazilian adult sample, and that use of cut-off points according to ROC curve may be the better strategy. Our findings also suggest that different values might be appropriate and should be adopted across the different BMI categories.

Table 2

Homeostasis model assessment of insulin resistance (HOMA-IR) values for the overall population and according to the body mass index (BMI) at baseline of the *Brazilian Longitudinal Study of Adult Health* (ELSA-Brasil), 2008-2010.

HOMA-IR values	Overall population [N = 12,313]	BMI		
		Normal weight [n = 4,909]	Overweight [n = 5,000]	Obesity [n = 2,399]
75th percentile	3.47	2.39	3.57	5.04
90th percentile	4.82	3.29	4.69	6.61
VMCSS *	2.35	1.73	3.01	3.67
	Sensitivy: 76.3% (75.3-77.3)	Sensitivy: 79.4% (74.7-84.1)	Sensitivy: 55.8% (54.4-57.2)	Sensitivy: 62.6% (61.0-64.2)
	Specificity: 65.2% (64.5-65.9)	Specificity: 57.2% (55.6-58.8)	Specificity: 76.3% (75,1-77.5)	Specificity: 66.5% (65.2-67.8)

* The point of maximum combined sensitivity and specificity to discriminate the metabolic syndrome was determined by the Youden index [9].

Contributors

M. F. H. S. Diniz and A. M. R. Beleigoli planned the study, analyzed the data and wrote the manuscript. M. I. Schmidt, B. B. Duncan, A. L. P. Ribeiro, P. G. Vidigal, I. M. Benseñor, P. A. Lotufo, I. S. Santos, and R. H. Griep critically reviewed and edited the manuscript for important intellectual content. S. M. Barreto helped with the statistical analysis of the data and critically reviewed and edited the manuscript for important intellectual content.

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Resumo

O modelo de avaliação da homeostase da resistência à insulina (HOMA-IR) é um método para medir a resistência à insulina. Os pontos de corte do HOMA-IR para identificar a síndrome metabólica podem variar entre as populações e os níveis de índice de massa corporal (IMC). Nosso objetivo foi investigar os pontos de corte do HOMA-IR que melhor discriminam indivíduos com resistência à insulina e com síndrome metabólica para cada categoria de IMC em uma grande amostra de adultos sem diabetes na linha de base do Estudo Longitudinal de Saúde do Adulto *(ELSA-Brasil). Entre os 12.313 participantes com média de idade de 51,2 (DP 8,9) anos, a prevalência de síndrome metabólica foi de 34,6%, e 60,1% apresentavam sobrepeso ou obesidade. As prevalências de síndrome metabólica nas categorias de peso normal, sobrepeso e obesidade foram, respectivamente, 13%, 43,2% e 60,7%. O ponto de máxima sensibilidade e especificidade combinadas do HOMA-IR para discriminar a síndrome metabólica foi de 2,35 em toda a amostra, com valores crescentes nas categorias de IMC mais elevadas. Esta investigação contribui para o melhor entendimento dos valores de HOMA-IR associados à resistência à insulina e síndrome metabólica em uma grande amostra de adultos brasileiros, e que o uso de pontos de corte de acordo com a curva ROC pode ser a melhor estratégia. Também sugere que valores diferentes podem ser apropriados nas categorias de IMC.*

Síndrome Metabólica; Resistência à Insulina; Estudos de Coortes

Resumen

El modelo homeostático para evaluar la resistencia a la insulina (HOMA-IR) es un método para medir la resistencia a la insulina. Los cortes HOMA-IR para identificar el síndrome metabólico pueden variar entre las poblaciones y los niveles del índice de masa corporal (IMC). El objetivo fue investigar los cortes de HOMA-IR que mejor discriminaban individuos con resistencia a la insulina y con síndrome metabólico para cada categoría de IMC, en una extensa muestra de adultos sin diabetes en la base de referencia del Estudio Longitudinal de Salud del Adulto *(ELSA-Brasil). Entre los 12.313 participantes con una media de edad de 51,2 años (DE 8,9), la prevalencia de síndrome metabólico fue 34,6%, y un 60,1% sufría sobrepeso u obesidad. La prevalencia de síndrome metabólico entre las categorías: peso normal, sobrepeso y obesidad fueron respectivamente, 13%, 43,2% y 60,7%. El punto de máxima sensibilidad combinada y especificidad de HOMA-IR para discriminar el síndrome metabólico fue 2,35 en toda la muestra, con valores crecientes en las categorías de IMC más altas. Esta investigación contribuye a entender mejor los valores HOMA-IR, asociados con resistencia a la insulina y síndrome metabólico en una gran muestra de adultos brasileños, además del planteamiento de que el uso de puntos de corte según la curva ROC es quizás la mejor estrategia a seguir. También sugiere que valores diferentes pueden ser apropiados a través de las categorías de IMC.*

Síndrome Metabólico; Resistencia a la Insulina; Estudios de Cohortes

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