ORIGINAL ARTICLE

PLASMA ATHEROGENIC INDEX AND TRIGLYCERIDE-GLUCOSE INDEX FOR IDENTIFYING THE CARDIOVASCULAR RISK IN WOMEN WITH NORMAL BIOCHEMICAL AND ANTHROPOMETRIC PARAMETERS

Tatiane Dräger Dal Ponte Pinheiro[1]; Brenda da Silva[2]; Mariana Spanamberg Mayer[3]
Rodrigo Fernando dos Santos Salazar[4], Mariana Migliorini Parisi[5]
Gabriela Bonfanti Azzolin[6]

Highlights: 1. Cardiometabolic indices predict cardiovascular events. 2. AIP may be indicative of lipid imbalance and subclinical cardiovascular events. 3. TyG index is an alternative for the evaluation of insulin resistance.

PRE-PROOF

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[1] Universidade de Cruz Alta. Programa de Pós-Graduação em Atenção Integral à Saúde. Cruz Alta/RS, Brasil.
https://orcid.org/0000-0002-5993-1884
[2] Universidade de Cruz Alta. Programa de Pós-Graduação em Atenção Integral à Saúde. Cruz Alta/RS, Brasil.
Universidade do Noroeste do Estado do Rio Grande do Sul. Ijuí/RS, Brasil.
https://orcid.org/0000-0002-8879-3353
[3] Universidade de Cruz Alta. Programa de Pós-Graduação em Atenção Integral à Saúde. Cruz Alta/RS, Brasil.
https://orcid.org/0000-0002-2514-3783
[4] Universidade de São Paulo. São Paulo/SP, Brasil.
http://orcid.org/0000-0001-5808-4321
[5] Universidade de Cruz Alta. Programa de Pós-Graduação em Atenção Integral à Saúde. Cruz Alta/RS, Brasil.
https://orcid.org/0000-0002-2298-7809
[6] Universidade de Cruz Alta. Programa de Pós-Graduação em Atenção Integral à Saúde. Cruz Alta/RS, Brasil.
https://orcid.org/0000-0003-2602-6092

ABSTRACT

Women have a specific hormonal risk associated with contraception, pregnancy and menopause, in addition to more risk factors for the development of cardiovascular diseases (CVD); and rapid, non-invasive, low-cost cardiovascular risk prediction tools can streamline the identification and prevention of CVD. Objective of the study to evaluate the risk of developing CVD in adult women using cardiometabolic indices such as plasma atherogenic index (AIP) and triglyceride-glucose (TyG) index for insulin resistance. This is an observational, cross-sectional and retrospective study. Data on the metabolic, clinical and anthropometric profile of adult women were analyzed and used for risk stratification of developing CVD through the use of TyG and AIP indices. Of the participating women (n = 60, 28.55 ± 8.30 years), 50% women had an increased risk according to AIP despite having normolipidemia, normoglycemia, and normal BMI. Also, they had higher TyG index values. Further, the correlations of TyG and AIP with biometric and lipid parameters were associated with metabolic syndrome. AIP and TyG index can identify the risk of developing CVD, even in the presence of normal anthropometric and biochemical parameters.

Keywords**:** Cardiovascular Diseases, Atherosclerosis, Insulin resistance, female, biomarkers.

Índice aterogênico plasmático e índice De triglicérides-glicose para identificação do risco cardiovascular em mulheres com parâmetros bioquímicos e antropométricos normais

RESUMO

As mulheres apresentam risco hormonal específico associado à contracepção, gravidez e menopausa, além de mais fatores de risco para o desenvolvimento de doenças cardiovasculares (DCV); e ferramentas de previsão de risco cardiovascular rápidas, não invasivas e de baixo custo podem agilizar a identificação e prevenção de DCV. Objetivo do estudo foi avaliar o risco de desenvolver DCV em mulheres adultas utilizando índices cardiometabólicos como índice aterogênico plasmático (AIP) e índice triglicerídeo-glicose (TyG) para resistência à insulina. Trata-se de um estudo observacional, transversal e retrospectivo. Dados do perfil metabólico, clínico e antropométrico de mulheres adultas foram analisados e utilizados para estratificação de risco de desenvolver DCV por meio dos índices TyG e AIP. Das mulheres participantes (n = 60, 28,55 ± 8,30 anos), 50% das mulheres apresentaram risco aumentado de acordo com a AIP apesar de apresentarem normolipidemia, normoglicemia e IMC normal. Além disso, eles apresentaram valores de índice TyG mais altos. Além disso, as correlações de TyG e AIP com parâmetros biométricos e lipídicos foram associadas à síndrome metabólica. AIP e índice TyG podem identificar o risco de desenvolver DCV, mesmo na presença de parâmetros antropométricos e bioquímicos normais.

Palavras-chave: Doenças Cardiovasculares, Aterosclerose, Resistência à insulina, feminino, biomarcadores.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in Brazil and worldwide, and cardiovascular risk is specific and often underestimated in women.[1] In general, women are more likely to contract chronic or incapacitating diseases than men, with probabilities of 81.2% and 73.1% in women and men, respectively. In addition, elderly women have a high prevalence of chronic morbidities, especially CVD.[2]

Hence, women have a greater number of cardiovascular risk factors than men of the same age, such as hypertension, diabetes mellitus, and obesity.[3] In addition, women have specific hormonal risks associated with contraception, pregnancy, and menopause.[1] The high prevalence of risk factors for CVD in the female population may be associated with the involvement of women in the labor market, which exposes them to stress, sedentary lifestyles, alcoholism, smoking, and inadequate eating habits. Furthermore, women have additional responsibilities related to work, family care, and domestic activities.[4]

It has long been recognized that prevention of CVD is the best method to combat CVD, and noninvasive, low-cost, fast, and specific prediction tools are necessary to identify individuals at a high cardiovascular risk.[5,6] Therefore, a series of cardiometabolic indices have been proposed and used for the cardiovascular risk stratification of different populations, such as plasma atherogenic index (AIP), the triglyceride-glucose (TyG) index, and hypertriglyceridemic-waist phenotype (HTW).[6,7,8]

AIP is associated with lipid imbalance, especially high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels, and cardiovascular risk. Thus, AIP cautions the risk of developing atherosclerosis, an important risk factor for acute myocardial infarction, stroke, and other heart and vascular diseases.[9] TyG index is a mathematical model that predicts the degree of insulin resistance from the TG and fasting glucose levels; it is a more accessible risk marker of insulin resistance because the other existing tests are expensive and not routinely performed.[7] In addition, the detection of phenotypic characteristics such as HTW is possibly associated with cardiovascular risk. HTW involves simple, low-cost, and easily applicable measures, such as waist circumference and TG levels, which must be simultaneously high.[8]

Thus, considering the incidence of cardiovascular risk factors in the female population and the importance of the early detection of these factors, we aimed to evaluate the risk of developing CVD in adult women with normal biochemical and anthropometric parameters using cardiometabolic indices such as TyG index, AIP, and HTW.

MATERIALS AND METHODS

This observational, cross-sectional, and retrospective study included women who participated in an Occupational Health Program conducted by a private company in the state of Rio Grande do Sul, Brazil. Data on metabolic profiles and anthropometric and clinical characteristics were provided by the company. These data were analyzed considering the objectives of the present study. This study was approved by the Research Ethics Committee of University of Cruz Alta (CAAE: 86904618.1.0000.5322; protocol number 2.630.865).

In total, 61 women aged 20–60 years who underwent periodic examinations according to the Occupational Health Program conducted by the participating company in 2018 were included in the study.

The metabolic profiles were analyzed by evaluating clinical (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), anthropometric (weight, height, body mass index [BMI], and waist circumference [WC]) and laboratory data (fasting glucose [GLI], total cholesterol [TC], very low-density lipoprotein cholesterol [VLDL-C], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglyceride [TG] levels).

For the stratification of the risk of developing CVD, the following cardiometabolic indices were used: (1) HTW, calculated based on WC and TG levels, both of which should be simultaneously high based on the criteria defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III, with WC levels >88 cm and TG levels >150 mg/dL[8-10]; (2) AIP, calculated as log[TG/HDL-C] and classified as follows: <0.11, low risk;

0.11–0.21, intermediate risk; and >0.21, high atherogenic risk[(9)]; and (3) TyG index, an indicator of insulin resistance, calculated as Ln[TG × GLI]/2.[7]

Categorical data were expressed as absolute frequency (n) and relative frequency (%). Non-categorical data were expressed as median and interquartile range. The data were evaluated for normality using the Kolmogorov–Smirnov test. Considering that the data were not normally distributed, the Kruskal–Wallis nonparametric test was used for the analysis. Analyzes with $p<0.05$ were considered significant.

Principal Component Analysis (PCA) was used as a multivariate analysis technique to analyze interrelationships between a large number of variables. Based on the input variables, we sought to explain the input variables in terms of their inherent dimensions (components). The main components were extracted using the Pearson correlation matrix. For outlier detection, it was calculating the distance between a point and distribution by considering how many standard deviations away the two points are. This stage of multivariate data treatment was processed using Origin® software and an Excel® spreadsheet. The confidence level adopted was 95% ($p<0.05$). From the correlation matrix obtained, we sought to present the interactions of the factors to preserve the relationships between each parameter, direct interaction (positive components) or inverse (negative components), as well as applying a scale (green, yellow, red) to demonstrate whether the synergisms were strong, moderate or weak.

RESULTS

The general data of the participants are presented in Table 1. Based on the average patient age, the population comprised young adult women. The mean SBP and DBP were within the normal ranges specified by the Update of the Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology, which considers SBP ≤120 mmHg and DBP ≤80 mmHg as normal.[11] Although the mean WC of the participants was within the normal limit proposed by the NCEP, the mean BMI indicated the prevalence of overweight among the study participants.[8,10] BMI is the most commonly used index for body adiposity assessment, and conventionally, a BMI of 25–29.9 kg/m² and ≥30 kg/m² is considered to indicate overweight and obesity, respectively.[12]

The average GLI level was <99 mg/dL, in agreement with the values for normoglycemia accepted and adopted by the American Diabetes Association.[13] Similarly, the mean levels of plasma lipids were within the reference limits set by the Updated Cardiovascular Prevention

Guideline of the Brazilian Society of Cardiology - 2019, which recommends TC level <190mg/dL; HDL-C >40 mg/dL; TG <150 mg/dL and LDL-C <130 , demonstrating a prevalence of normolipidemia among the study participants.[14]

Table 1**.** Clinical, anthropometric, and laboratory profile of women who participated in an Occupational Health Program

Parameter	**General data***	**Data according to cut-offs#**
Age (years)	27 (22 – 34)	-
SBP (mmHg)	115 (110 – 120)	n = 7 (11,34%)
DBP (mmHg)	70 (70 – 80)	n = 5 (8,34%)
Weight (kg)	66,3 (57,33 – 78,25)	-
Height (m)	1,63 (1,58 – 1,69)	-
BMI (kg/m^2)	24,5 (22,25 – 29)	n = 14 (23,34%)
WC (cm)	83 (72 - 92)	n = 17 (28,34%)
GLI (mg/dL)	81 (76 – 85,75)	n = 1 (1,67%)
TC (mg/dL)	175 (158,3 – 195,3)	n = 17 (28,34%)
VLDL-C (mg/dL)	18,4 (13,7 – 27,1)	-
LDL-C (mg/dL)	100,6 (86,2 – 116,6)	n = 9 (15%)
HDL-C (mg/dL)	53,5 (47 – 61)	n = 8 (13,34%)
TG (mg/dL)	92 (68,5 – 135,5)	n = 8 (13,34%)
TyG	8,21 (7,93 – 8,61)	-
AIP	0,21 (0,075 – 0,415)	-
HTW	n = 3 (5%)	-

Source: Data from this study. *Refers to all individuals involved in the study. #Refers to individuals with altered parameters according to the cutoffs defined in the study. Categorical data expressed as absolute frequency (n) and relative frequency (%); non-categorical data expressed as median and interquartile range. SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC: waist circumference; GLI: fasting glucose; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol, TG: triglyceride; TyG: TyG index; AIP: plasma atherogenic index. HTW: hypertriglyceridemic-waist phenotype. (mg/dL) milligrams per deciliter; (kg/m^2) kilogram per squared meter; (mmHg) millimeters of mercury.

The mean AIP indicated that the participating women had an intermediate risk of developing CVD. Furthermore, only three (5%) women tested positive for HTW.

While performing risk stratification according to AIP, the participants were classified into three groups—low risk (n = 18, 30%), intermediate risk (n = 12, 20%), and high risk (n = 30, 50%). The characteristics of these groups are presented in Table 2. Compared to the low- and intermediate risk groups, the high-risk group had a higher body weight, WC level, VLDL-C level, and TG, level and a lower HDL-C level. Moreover, this group had a higher TyG value, despite having GLI levels similar to those of the low- and intermediate-risk groups. In addition, there were no differences in age, blood pressure, BMI, and TC and LDL-C levels among the groups.

Table 2: Stratification of cardiovascular risk by plasma atherogenic index of women involved in the study.

	AIP <0.11 Low risk (n=18)	**AIP 0.11 – 0.21 Intermediate risk (n=12)**	**AIP > 0.21 High risk (n=30)**
Age (years)	27,5 (24 – 35)	21,5 (19,25 – 26,5)	27,5 (22,75 – 35)
SBP (mmHg)	110 (110 – 120)	115 (102,5 – 120)	120 (110 – 120)
DBP (mmHg)	70 (67,5 – 80)	70 (70 – 80)	70 (67,5 – 80)
Weight (kg)	62,55 (55,93 – 66,85)*	62,85 (57,33 – 87,48)	73,35 (63,15 – 86,6)
Height (m)	1,64 (1,58 – 1,70)	1,63 (1,56 – 1,68)	1,63 (1,59 – 1,69)
BMI (kg/m^2)	22,50 (21 – 24,25)	24 (20,75 – 30,75)	26 (24 – 31,75)
WC (cm)	76 (70 – 84)**	71,5 (69,25 – 93,50)*	86 (80,5 – 98,5)
GLI (mg/dL)	82,5 (75,5 – 85,25)	77,50 (76 – 81,75)	81 (76,75 – 86)
TC (mg/dL)	205,3 (174 – 242)	167,5 (160 – 175,3)	177 (160,8 – 201-8)
VLDL-C (mg/dL)	13 (10,6 – 14) ****	15,70 (14,15 – 19,25)**	27 (21,4 – 30,25)
LDL-C (mg/dL)	94,3 (82,2 – 136)	97,70 (93,25 – 107)	102,3 (87,7 – 126)
HDL-C (mg/dL)	61 (55,75 – 67,25)****	53,5 (49 – 64,75)	48 (41,25 – 54,25)
TG (mg/dL)	65 (53 – 70)****	78,5 (70,75 – 96,25)**	135 (107 – 151,3)
TyG	7,84 (7,70 – 7,98)****	8,05 (7,9 – 8,17)**	8,60 (8,34 – 8,75)
IAP	0,025 (-0,06 – 0,055)****	0,16 (0,15 – 0,18)**	0,41 (0,3 – 0,52)

Source: Data from this study. (*p<0.05), (**p<0.01), (***p<0.001) and (****p<0.0001), indicate difference in the high-risk group, assessed by the Kruskal-Wallis test. Data expressed as median and interquartile range. PAS: SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC: waist circumference; GLI: fasting glucose; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol, TG: triglyceride; TyG: TyG index; AIP: plasma atherogenic index. (mg/dL) milligrams per deciliter; (kg/m^2) kilogram per squared meter; (mmHg) millimeters of mercury.

To evaluate the relationship between the individual risk biomarkers and the cardiometabolic indices, the possible correlations were investigated (Table 3). TyG index and AIP were positively correlated with body weight, WC, CA levels, VLDL-C levels and TG levels. Additionally, the TyG index was positively correlated with TC levels and AIP index was positively correlated with BMI and negatively correlated with HDL-C levels. Furthermore, TyG and AIP correlated strongly and positively each other.

Table 3. Correlations between cardiometabolic indicators and clinical parameters

	Age	**SBP**	**DBP**	**Weight**	**Height**	**BMI**	**WC**	**GLI**	**TC**	**VLDL-C**	**LDL-C**	**HDL-C**	**TG**	**TyG**	**IAP**
Age	1,00000	0,03360	0,17472	0,23125	-0,13236	0,27655	0,32193	0,21879	0,00383	0,04170	-0,04334	0,06369	0,04170	0,03713	-0,02803
SBP	0,03360	1,00000	0,64017	0,49152	0,14874	0,41332	0,39555	0,22139	0,03491	0,06859	0,16118	-0,27973	0,06859	0,12315	0,19539
DBP	0,17472	0,64017	1,00000	0,39243	0,10677	0,33277	0,40254	0,18659	0,02801	0,07917	0,08142	-0,14857	0,07917	0,10358	0,12749
Weight	0,23125	0,49152	0,39243	1,00000	0,17491	0,87352	0,90879	0,38755	0,09542	0,36910	0,13804	-0,30484	0,36910	0,41483	0,42268
Height	-0,13236	0,14874	0,10677	0,17491	1,00000	-0,17300	-0,06067	0,10875	0,29879	0,22295	0,20674	0,09694	0,22295	0,22726	0,12418
BMI	0,27655	0,41332	0,33277	0,87352	-0,17300	1,00000	0,87514	0,31967	-0,03319	0,21072	0,04928	-0,30559	0,21072	0,25730	0,30293
WC	0,32193	0,39555	0,40254	0,90879	-0,06067	0,87514	1,00000	0,42758	0,04634	0,35665	0,13438	-0,38815	0,35665	0,42013	0,46185
GLI	0,21879	0,22139	0,18659	0,38755	0,10875	0,31967	0,42758	1,00000	-0,08713	0,09325	-0,05419	-0,14495	0,09325	0,24524	0,11946
TC	0,00383	0,03491	0,02801	0,09542	0,29879	-0,03319	0,04634	-0,08713	1,00000	0,34617	0,86468	0,25844	0,34617	0,31807	0,15904
VLDL-C	0,04170	0,06859	0,07917	0,36910	0,22295	0,21072	0,35665	0,09325	0,34617	1,00000	0,14899	-0,20610	1,00000	0,95787	0,87398
LDL-C	-0,04334	0,16118	0,08142	0,13804	0,20674	0,04928	0,13438	-0,05419	0,86468	0,14899	1,00000	-0,16080	0,14899	0,14739	0,19423
HDL-C	0,06369	-0,27973	-0,14857	-0,30484	0,09694	-0,30559	-0,38815	-0,14495	0,25844	-0,20610	-0,16080	1,00000	-0,20610	-0,23542	-0,61102
TG	0,04170	0,06859	0,07917	0,36910	0,22295	0,21072	0,35665	0,09325	0,34617	1,00000	0,14899	-0,20610	1,00000	0,95787	0,87398
TyG	0,03713	0,12315	0,10358	0,41483	0,22726	0,25730	0,42013	0,24524	0,31807	0,95787	0,14739	-0,23542	0,95787	1,00000	0,89783
AIP	-0,02803	0,19539	0,12749	0,42268	0,12418	0,30293	0,46185	0,11946	0,15904	0,87398	0,19423	-0,61102	0,87398	0,89783	1,00000

Source: Data from this study. (r > 0,3, weak correlation); (0,3 ≤ r < 0,7, moderate correlation); (r ≥ 0,7, strong correlation) assessed by multivariate analysis (PCA). SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; WC: waist circumference; GLI: fasting glucose; TC: total cholesterol; VLDL-C: very low-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol, TG: triglyceride; TyG: TyG index; AIP: plasma atherogenic index.

DISCUSSION

In this study, although several anthropometric and laboratory parameters of the studied population were within the normal ranges, conditions associated with risk of developing CVD were identified using cardiometabolic indices. This observation reiterates the findings of previous studies that cardiometabolic indices such as AIP and TyG index may be better predictors of cardiovascular events than individual risk factors such as lipid profile.[6]

Furthermore, it should be noted that the study population comprised young women of reproductive age. Considering that a large proportion of the female population in this age group uses oral contraceptives and that this class of medications has been previously associated with changes in metabolism and a more atherogenic lipid profile,[15] the use of oral contraceptives can be considered an exclusive risk factor for women in this age group, reiterating the importance of identifying women with significant cardiovascular risks.

In our study, 70% women presented intermediate or high risks of developing CVD according to AIP. This index may be indicative of lipid imbalance and subclinical cardiovascular events. Although high TG levels are strongly associated with the incidence of CVD, its contribution to cardiovascular risk is often underestimated.[16] In this sense, AIP evaluates the relationship between TG and HDL-C levels and presents the strong predicting power of acute myocardial infarction and atherosclerosis since high TG levels are related to increased levels of small LDL-C particles that have high atherosclerotic power.[17]

In a cross-sectional study including 340 healthy women, AIP was strongly associated with serum concentrations of dimethylarginine, adipocytes, and fatty acid-binding protein; Framingham scores; and Castelli index, showing that AIP can be a potential biomarker for the early diagnosis of CVD events.[6] In addition, IAP has been considered a good predictor of CVD risk in postmenopausal women.[17]

Furthermore, we found that the high-risk group had higher TyG values compared to the low- and intermediate-risk groups, indicating higher insulin resistance, although the GLI levels did not differ between the risk groups. Statistically, there was a strong and significant correlation between these indices, suggesting that AIP may also be related to changes in glucose metabolism.

Insulin resistance (IR) is the reduction in the ability of insulin to stimulate glucose utilization. As a compensatory mechanism, beta-pancreatic cells increase insulin production and secretion;

however, this does not affect glucose tolerance. IR has been a prominent public health problem, affecting several age groups, especially women aged >40 years.[18] This risk factor needs to be controlled for the prevention of CVD in this population. However, the assessment of IR is not included in routine medical tests, and IR-related laboratory tests are not available in most health services.

Thus, TyG index is an alternative to other tests for the evaluation of IR due to its lower cost and greater ease of application in health services. In a study involving 5,576 women and 3,988 men without diabetes, three cardiometabolic indices were applied, including TyG index. In the stratified analyses of obesity, BMI, and HDL-C levels, TyG index was significantly associated with type II diabetes, regardless of obesity.[19]

Furthermore, in our study, the high-risk group had a higher WC and body weight. Moreover, TyG index and AIP were positively correlated with the anthropometric parameters of weight, WC levels, and BMI, reiterating the association between body composition and the development of IR and increased cardiovascular risk. WC provide important data for the nutritional aid of patients due to its relationship with predisposition to diseases that affect all systems of the body due to the action of viscerally stored TG that affects important organs such as the liver, lung, and heart.[20]

Overweight is a recognized worldwide and national epidemic and is a cardiovascular risk factor of the century. Additionally, among the cardiovascular risk factors described and identified, there is a lack of data on the primary preventive actions and coping measures of overweight.[21]

The high-risk group in our study had higher VLDL-C and TG levels and lower HDL-C levels than the low- and intermediate-risk groups. In addition to being isolated a risk factor, dyslipidemia associated with other altered metabolic levels can lead to the development of metabolic syndrome (MS). MS is a group of diseases including hypertension and obesity, and MS-associated changes in lipid and carbohydrate metabolism which increase the risks of developing cardiovascular disorders.[22] Studies conducted in Brazil show that the prevalence of MS was higher in women than in men,[23] reiterating the importance of controlling and preventing these risk factors among women.

In particular, the relative risk of cardiovascular events is higher in women with low HDL-C levels than in men; the target goal is higher in women than in men by 10 mg/dL. Evidence suggests that a 1% increase in the HDL-C levels reduces the risk of some cardiovascular complications by 2%–4%.[24] In this study, this relationship between low HDL levels and increased cardiometabolic risk can be perceived by the negative correlation between HDL-C levels and AIP index.

In addition, as a proposed indicator of cardiovascular risk, HTW involves simple, low-cost, and easily applicable measures to evaluate clinical and public health. However, in our study, HTW was less sensitive than AIP to identify cardiovascular risk; HTW identified fewer individuals at cardiovascular risk as compared to AIP. This is observed, because even in the high-risk group indicated by the AIP index, where we found higher TG and TC values, these values were below proposed limits proposed for the characterization of the HTW phenotype.

This study has some limitations. This is a cross-sectional study that evaluated only laboratory tests and some clinical characteristics. Genetic predispositions, factors such as physical activity and history of cardiovascular diseases, as well as medication use, were not assessed. Therefore, a prospective study to monitor participants and verify the incidence of future cardiovascular events could be carried out.

In conclusion, we confirmed that the cardiometabolic indices AIP and TyG index are useful in identifying women at risk of developing CVD, even in the presence of normal anthropometric and biochemical parameters, thereby representing preclinical outcomes and leading to the prevention of complications. Thus, AIP and TyG index appear can be used as low-cost, fast, effective, and noninvasive markers for the identification of risk factors and prevention of CVD, which are the best measures to combat CVD.

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Tatiane Dräger Dal Ponte Pinheiro: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Brenda da Silva: Data curation, Formal analysis, Writing – original draft; Writing – review & editing.

Mariana Spanamberg Mayer: Data curation, Formal analysis; Writing – original draft, Writing – review & editing.

Rodrigo Fernando dos Santos Salazar: Formal analysis, Writing – review & editing.

Mariana Migliorini Parisi: Conceptualization, Supervision, Writing – review & editing.

Gabriela Bonfanti Azzolin: Conceptualization, Formal analysis, Project administration, Writing – review & editing.

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Corresponding Author

Gabriela Bonfanti Azzolin

Universidade de Cruz Alta. Programa de Pós-Graduação em Atenção Integral à Saúde.

Rodovia Municipal Jacob Della Mea, s/n km 5,6 - Parada Benito

Cruz Alta/RS, Brasil. CEP 98020-290

E-mail: gbonfantiazzolin@gmail.com

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