



# Associations of Irisin and visceral adiposity index with cardiometabolic risk and their predictive value in Jordanian adults: A cross-sectional study

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## ABSTRACT

**Introduction:** Irisin affects obesity and cardiometabolic syndrome (CMS) risk factors, but its precise mechanism and relationship with visceral adiposity index (VAI) remain unclear. The aim of this research is to explore the associations between circulating irisin, VAI, obesity indices, and cardiometabolic risk, and to test their predictive values.

**Methods:** This cross-sectional study included a systematic random sample of 300 Jordanian adults, aged 19-65 years, comprising 100 obese individuals with Type 2 diabetes mellitus (T2D) (G1), 100 obese individuals without T2D (G2), and 100 normal-weight non-diabetics (G3), with a 1:1 sex ratio. Standard protocols were followed to measure waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHpR), waist-to-height ratio (WHtR), and body mass index (BMI), along with circulating irisin, fasting blood glucose (FBG), lipid profile, and VAI. Multivariate analysis, receiver operating characteristic curves, and area under the curve (AUC) were used for comparing the CMS risk predictive value.

**Results:** Irrespective of sex, irisin (ng/mL) was significantly lower ( $p < 0.01$ ) in G1 (136.62) compared to G2 (234.40) and G3 (299.27). VAI was highest ( $p < 0.01$ ) in G1 (7.54) compared to G2 (6.15) and G3 (6.15). BMI, WC, WHpR, and WHtR negatively correlated ( $p < 0.01$ ) with irisin. BMI and irisin did not correlate with VAI, which positively correlated ( $p < 0.05$ ) with WC, WHtR, WHpR, FBG, and triglycerides. WC had the highest AUC (0.781), followed by BMI (0.775), irisin (0.770), WHtR (0.748), WHpR (0.717), and VAI, having the lowest (0.679). FBG and BMI increased CMS odds; irisin was inversely related to CMS.

**Conclusion:** Irisin may serve as a promising biomarker for predicting CMS risk, whereas VAI appears to be the weakest predictor among obesity indices.

**Keywords:** Irisin; cardiometabolic risk; diabetes; visceral adiposity index; obesity indices

## INTRODUCTION

Cardiometabolic syndrome (CMS) encompasses a cluster of metabolic risk factors, such as insulin resistance, visceral obesity, hypertension, and dyslipidemia, which increase cardiovascular morbidity and mortality risk (1,2). Its global prevalence varies due to differing diagnostic definitions (1). While both genetic and environmental factors contribute to its etiology, body mass index (BMI) is insufficient on its own for assessing visceral fat. Therefore, waist circumference (WC), waist-to-hip ratio (WHpR), and waist-to-height ratio (WHtR) are necessary measurements (3). WC and WHpR are limited in distinguishing between visceral and subcutaneous fat (4). The visceral adiposity index (VAI),

which combines high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), BMI, and WC, shows promise as a marker for visceral obesity and CMS risk (5,6), correlating with cardiovascular events and CMS components; however, consensus on its use is still lacking (7).

Irisin, a myokine from FNDC5 produced during exercise, impacts obesity and CMS by promoting adipocyte browning and insulin secretion (8,9). While it shows promise as a treatment for obesity and Type 2 diabetes (10), its relationship with CMS and BMI is still debated (11,12). The connection between irisin and VAI, along with their predictive value for CMS, has not been studied. This research aims to explore the link between VAI and circulating irisin levels and their potential as predictors of CMS and related risk factors in Jordanians.

## METHODS

This cross-sectional study involved a systematic random sample of 300 Jordanian adults, aged 19-65 years, divided

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into three groups: 100 obese individuals with type 2 diabetes mellitus (T2D) (G1), 100 obese individuals without T2D (G2), and 100 normal-weight individuals without T2D (G3), with a 1:1 sex ratio. Following a systematic random sampling technique, every fifth eligible patient or companion was recruited from the endocrinology clinics at King Abdullah II Hospital in Irbid, Jordan. Obese participants with T2D had a BMI of 30 kg/m<sup>2</sup> or higher and were diagnosed by an endocrinologist, while obese participants without T2D had a BMI of 30 kg/m<sup>2</sup> or more and fasting blood glucose (FBG) of <110 mg/dL. Normal-weight participants had a BMI of 25 kg/m<sup>2</sup> or less. Exclusion criteria included age under 19 or over 65, pregnancy or lactation, Type 1 diabetes, and major illnesses. The sample size (n = 300 participants) was determined based on the assumption that 50% of the population has the factor of interest, allowing for a 5% absolute precision and a 95% confidence level.

All participants provided written informed consent after they were informed about the study's objectives and nature. The study received approval from the Institutional Scientific Committee at the University of Jordan and the Institutional Review Board of the King Abdullah II University Hospital (KAUH 1/145/2021, December 2, 2021). Structured interviews collected demographic, lifestyle, and medical data for eligibility confirmation. Anthropometric measurements: height, weight, WC, and hip circumference (HC) circumferences were taken in duplicate, and blood pressure was measured using a calibrated sphygmomanometer after 15 min of rest (13). Indices of BMI, WHpR, and WHtR were calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>), WC/HC, and WC/height, respectively (13).

All participants were face-to-face interviewed to obtain information on their physical activity levels. Physical activity was classified into low activity (<90 min/week), moderate activity (90-240 min/week), and high activity (>240 min/week) according to self-reported information (13). Smoking status was classified as either current smoker or non-smoker, and marital status as married or unmarried. Menopausal status in women was considered as cessation of menstruation over a period of 12 months, and medical history, including family history of T2D, dyslipidemia, hypertension, and heart disease (including ischemic heart disease, stroke, or congestive heart failure), was also obtained. In addition, participants with obesity, whether or not they had T2D, were asked about any medications they used to treat hyperglycemia and dyslipidemia.

Venous blood samples (5 mL) were processed within 30 min after a 10-12-h overnight fast. Serum levels (mg/dL) of FBG, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and HDL-C were analyzed in duplicates and in a single batch using conventional enzymatic techniques with commercial kits.

Serum irisin concentrations (ng/mL) were quantified using a sensitivity- and specificity-validated commercially available MyBioSource Human Irisin enzyme-linked immunosorbent assay (ELISA) kit (Cat No. MBS 2600406, ISO 9001:2015 Certified Laboratory, Spain), following the manufacturer's instructions. This sandwich-type ELISA uses a pre-coated monoclonal antibody on the plate, along with biotin-labeled polyclonal antibodies and

avidin-peroxidase conjugates to ensure high specificity and accuracy. All samples were processed in duplicate and in a single batch to minimize inter-test variability (coefficient of variation <5%). Standardized protocols were used, and samples were handled carefully and immediately frozen at -80°C to maintain sample integrity and analytical quality.

The VAI was calculated using sex-specific equations that incorporate BMI, WC, TG, and HDL-C. The formulas are as follows (14):

- For males:  $VAI = WC/39.68 + (1.88 \times BMI) \times (TG/1.03) \times (1.31/HDL-C)$
- For females:  $VAI = WC/36.58 + (1.89 \times BMI) \times (TG/0.81) \times (1.52/HDL-C)$

The diagnosis of CMS followed the International Diabetes Federation criteria (15). Participants were considered at risk if their WC was ≥94 cm for men and ≥80 cm for women, along with any two of the following: TG ≥150 mg/dL or treatment for TG, HDL-C <40 mg/dL for men or <50 mg/dL for women or treatment for HDL-C, blood pressure ≥130/85 mmHg or treatment for hypertension, or FBG ≥100 mg/dL or previously diagnosed with T2D.

Data analysis was conducted using the Statistical Package for the Social Sciences version 19.0, with continuous variables expressed as mean ± standard error. Between-group comparisons were performed using one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test where appropriate, while sex differences within groups were also evaluated. Chi-square tests were used for categorical variables, and Pearson correlation assessed relationships between variables. Receiver operating characteristic (ROC) and area under the curve (AUC) analyses evaluated the diagnostic performance of irisin, VAI, and anthropometric indices for predicting CMS, with a significance level set at  $p < 0.05$ . Risk analysis for the development of CMS was also performed and reported as odds ratios (OR) with their corresponding  $p$ -value and 95% confidence interval (CI).

## RESULTS

In this sample of Jordanian adults, 71.0% of participants met the criteria for CMS, with a higher prevalence in men (74.7%) compared with women (67.3%) (Figure 1).

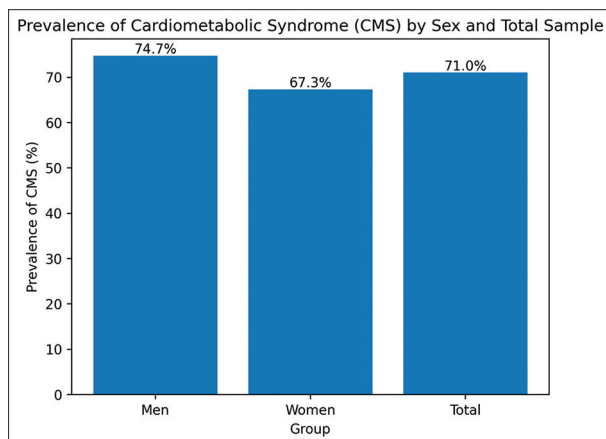
There were no appreciable age differences (ANOVA  $p > 0.05$ ) between the groups or between the sexes, as Table 1 demonstrates. Group differences were substantial ( $p < 0.001$ ) for most anthropometric parameters, including height, weight, BMI, WC, HC, WHpR, and WHtR. Compared to the G3: Normal-weight controls, the G2: Obese without T2D (both with and without T2D) had substantially higher BMIs and WCs ( $p < 0.001$ ). Compared to obese women without T2D ( $108.21 \pm 1.77$  cm), normal-weight women had the lowest WC ( $92.56 \pm 1.63$  cm,  $p < 0.001$ ), while obese women with the disease had the highest WC ( $118.55 \pm 1.99$  cm).

Table 2 shows the demographic and health characteristics of the study groups. The vast majority of participants reported low physical activity across all groups (100% of obese and obese with diabetes vs. 74% of normal-weight men and 88% of normal-weight women). No significant differences ( $p > 0.05$ ) were observed in marital status and smoking status between the three study groups, or in

**TABLE 1.** Age and anthropometric measures of the study participants

| Indicator                | Obese with type-2 diabetes mellitus | <i>p</i> ‡ | Obese                      | <i>p</i> ‡ | Normal                     | <i>p</i> ‡ | <i>p</i> (ANOVA) |
|--------------------------|-------------------------------------|------------|----------------------------|------------|----------------------------|------------|------------------|
| Age (years)              |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 49.36±1.090 <sup>a</sup>            | 0.932      | 48.68±1.196 <sup>a</sup>   | 0.814      | 49.06±1.395 <sup>a</sup>   | 0.29       | 0.812            |
| Women (n=50)             | 49.24±0.984 <sup>a</sup>            |            | 48.28±1.207 <sup>a</sup>   |            | 46.72±1.701 <sup>a</sup>   |            |                  |
| Weight (kg)              |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 102.168±2.267 <sup>a</sup>          | 0.000      | 101.584±2.028 <sup>a</sup> | 0.000      | 73.312±1.204 <sup>b</sup>  | 0.000      | <0.001           |
| Women (n=50)             | 90.590±1.452 <sup>a</sup>           |            | 85.692±1.698 <sup>b</sup>  |            | 61.572±0.832 <sup>c</sup>  |            |                  |
| Height (cm)              |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 172.800±1.221 <sup>a</sup>          | 0.000      | 174.340±1.128 <sup>a</sup> | 0.000      | 176.200±1.184 <sup>a</sup> | 0.000      | <0.001           |
| Women (n=50)             | 159.980±0.867 <sup>ab</sup>         |            | 158.000±0.729 <sup>a</sup> |            | 162.340±0.796 <sup>b</sup> |            |                  |
| BMI (kg/M <sup>2</sup> ) |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 34.130±0.573 <sup>a</sup>           | 0.113      | 33.447±0.531 <sup>a</sup>  | 0.295      | 23.539±0.193 <sup>b</sup>  | 0.451      | <0.001           |
| Women (n=50)             | 35.468±0.607 <sup>a</sup>           |            | 34.331±0.650 <sup>a</sup>  |            | 23.328±0.201 <sup>b</sup>  |            |                  |
| WC (cm)                  |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 117.746±2.068 <sup>a</sup>          | 0.780      | 115.742±1.621 <sup>a</sup> | 0.002      | 98.327±1.146 <sup>b</sup>  | 0.005      | <0.001           |
| Women (n=50)             | 118.550±1.999 <sup>a</sup>          |            | 108.212±1.766 <sup>b</sup> |            | 92.562±1.628 <sup>c</sup>  |            |                  |
| HC (cm)                  |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 115.736±1.734 <sup>a</sup>          | 0.041      | 117.700±1.461 <sup>a</sup> | 0.370      | 102.862±1.273 <sup>b</sup> | 0.796      | <0.001           |
| Women (n=50)             | 120.894±1.784 <sup>a</sup>          |            | 119.680±1.642 <sup>a</sup> |            | 103.326±1.259 <sup>b</sup> |            |                  |
| WHpR                     |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 1.018±0.011 <sup>a</sup>            | 0.021      | 0.984±0.009 <sup>b</sup>   | 0.000      | 0.987±0.008 <sup>b</sup>   | 0.000      | <0.001           |
| Women (n=50)             | 0.982±0.011 <sup>a</sup>            |            | 0.905±0.010 <sup>b</sup>   |            | 0.895±0.010 <sup>b</sup>   |            |                  |
| WHtR                     |                                     |            |                            |            |                            |            |                  |
| Men (n=50)               | 0.682±0.012 <sup>a</sup>            | 0.001      | 0.664±0.009 <sup>a</sup>   | 0.149      | 0.559±0.007 <sup>b</sup>   | 0.362      | <0.001           |
| Women (n=50)             | 0.742±0.013 <sup>a</sup>            |            | 0.686±0.012 <sup>b</sup>   |            | 0.570±0.010 <sup>c</sup>   |            |                  |

T2D: Type 2 diabetes; BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHpR: Waist to hip ratio; WHtR: Waist to height ratio. Means in the same row with different superscripts are statistically significant ( $p < 0.05$ ), using One-Way ANOVA and *post hoc* Tukey Test. ‡ The *P*-value represents the difference between males and females within the same column group for each indicator, using the One-Way ANOVA test. ANOVA: Analysis of variance

**FIGURE 1.** Prevalence of cardiometabolic syndrome among the study sample according to International Diabetes Federation criteria.

menopausal status among women, as determined by Chi-square analysis. Obese men and women with and without T2D reported ( $p < 0.05$ ) the presence of hypertension, but not normal men and women. All participants reported ( $p < 0.05$ ) the presence of a family history of hypertension, T2D, dyslipidemia, but not heart disease.

The FBG of the G1: Obese with T2D was significantly higher than that of the normal and obese non-diabetic groups in both men and women (Table 3) ( $p < 0.001$ ). Participants with diabetes or obesity had significantly lower HDL-C than the other groups ( $p < 0.01$ ), with the differences being more noticeable in men. The TG, TC, LDL-C, systolic blood pressure (SBP), and diastolic blood pressure

(DBP) all showed a significant group effect. The G3: Normal-weight controls had the lowest values ( $p < 0.05$  for DBP;  $p < 0.001$  for SBP), while G1: Obese with T2D had the highest SBP ( $132.84 \pm 1.76$  mmHg) and DBP ( $84.08 \pm 0.87$  mmHg). G1: Obese with T2D had the lowest levels of irisin ( $136.62 \pm 9.77$  ng/mL), the G2: Obese without T2D had levels in the middle ( $234.40 \pm 10.50$  ng/mL), and G3: Normal-weight controls had the highest levels ( $299.27 \pm 7.88$  ng/mL). There were significant differences between all groups ( $p < 0.001$ ). The VAI, on the other hand, was much higher in the T2D group ( $7.54 \pm 0.41$ ) than in either the obese non-diabetic ( $6.15 \pm 0.25$ ) or normal groups ( $6.15 \pm 0.35$ ),  $p < 0.01$ .

Pearson correlation analyses based on Tables 4 and 5 showed that BMI, WC, WHpR, and WHtR were all positively and significantly correlated with FBG, SBP, DBP, and TG ( $p < 0.01$ ), and negatively correlated with irisin ( $p < 0.01$ ). There was a notable, significant negative relationship between WHpR and HDL-C ( $r = -0.152$ ,  $p < 0.01$ ). There was a negative relationship between irisin levels and weight ( $r = -0.324$ ), BMI ( $r = -0.342$ ), WC ( $r = -0.305$ ), HC ( $r = -0.193$ ), WHpR ( $r = -0.251$ ), and WHtR ( $r = -0.389$ ) ( $p < 0.01$ ). On the other hand, VAI had a weaker inverse relationship with HDL-C ( $r = -0.462$ ,  $p < 0.001$ ) but a positive correlation with FBG ( $r = 0.271$ ,  $p < 0.01$ ), TG ( $r = 0.825$ ,  $p < 0.001$ ), and WHpR ( $r = 0.143$ ,  $p < 0.01$ ). Particularly for WHtR and BMI in connection to SBP and FBG, these correlations were stronger in women than in men (Tables 4 and 5).

Based on Table 6 and Figure 2A, ROC analysis for the overall participants showed that WC had the highest AUC

**TABLE 2.** Demographic and health characteristics of the study participants

| Variables                     | Obese with T2D      |                       | Obese               |                       | Normal              |                       | p-value |
|-------------------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------|
|                               | Men (n=50)<br>n (%) | Women (n=50)<br>n (%) | Men (n=50)<br>n (%) | Women (n=50)<br>n (%) | Men (n=50)<br>n (%) | Women (n=50)<br>n (%) |         |
| Marital status                |                     |                       |                     |                       |                     |                       |         |
| Single                        | 1 (2)               | 5 (10)                | 3 (6)               | 9 (18)                | 9 (18)              | 17 (34)               | 0.705   |
| Married                       | 49 (98)             | 45 (90)               | 47 (94)             | 41 (82)               | 41 (82)             | 33 (66)               |         |
| Menopause                     |                     |                       |                     |                       |                     |                       |         |
| Yes                           | ---                 | 18 (36)               | ---                 | 20 (40)               | ---                 | 19 (38)               | 0.919   |
| No                            | ---                 | 32 (64)               | ---                 | 30 (60)               | --                  | 31 (62)               |         |
| Smoking                       |                     |                       |                     |                       |                     |                       |         |
| Smoker                        | 26 (52)             | 10 (20)               | 28 (56)             | 6 (12)                | 22 (44)             | 6 (12)                | 0.455   |
| Non-smoker                    | 24 (48)             | 40 (80)               | 22 (44)             | 44 (88)               | 28 (56)             | 44 (88)               |         |
| Physical activity             |                     |                       |                     |                       |                     |                       |         |
| Low                           | 50 (100)            | 50 (100)              | 50 (100)            | 50 (100)              | 37 (44)             | 44 (88)               | 0.080   |
| Active                        | ---                 | ---                   | ---                 | ---                   | 13 (26)             | 6 (12)                |         |
| Highly active                 | ---                 | ---                   | ---                 | ---                   | ---                 | ---                   |         |
| Hypertension                  |                     |                       |                     |                       |                     |                       |         |
| Yes                           | 20 (40)             | 27 (54)               | 10 (20)             | 8 (16)                | 0 (0)               | 0 (0)                 | 0.000   |
| No                            | 30 (60)             | 23 (46)               | 40 (80)             | 42 (84)               | 50 (100)            | 50 (100)              |         |
| T2D family history            |                     |                       |                     |                       |                     |                       |         |
| Yes                           | 39 (78)             | 47 (94)               | 33 (66)             | 34 (68)               | 26 (52)             | 36 (72)               | 0.000   |
| No                            | 11 (22)             | 3 (6)                 | 17 (34)             | 16 (32)               | 24 (48)             | 14 (28)               |         |
| Hypertension- family history  |                     |                       |                     |                       |                     |                       |         |
| Yes                           | 35 (70)             | 45 (90)               | 36 (72)             | 41 (82)               | 31 (62)             | 33 (66)               | 0.024   |
| No                            | 15 (30)             | 5 (10)                | 14 (28)             | 9 (18)                | 19 (38)             | 17 (34)               |         |
| Dyslipidemia- family history  |                     |                       |                     |                       |                     |                       |         |
| Yes                           | 32 (64)             | 28 (56)               | 21 (42)             | 19 (38)               | 22 (44)             | 20 (40)               | 0.008   |
| No                            | 18 (36)             | 22 (44)               | 29 (48)             | 31 (62)               | 28 (56)             | 30 (60)               |         |
| Heart disease- family history |                     |                       |                     |                       |                     |                       |         |
| Yes                           | 22 (44)             | 23 (46)               | 24 (48)             | 21 (42)               | 15 (30)             | 17 (34)               | 0.097   |
| No                            | 28 (56)             | 27 (54)               | 26 (52)             | 29 (48)               | 35 (70)             | 33 (66)               |         |

Data are presented as the number of participants with the percentages given in parentheses, and they are considered statistically significant at  $p < 0.05$ , using the Chi-square test. The  $P$ -value represents the difference in demographic data by groups. T2D: Type 2 diabetes mellitus

for identifying CMS risk (AUC = 0.781), followed by BMI (AUC = 0.775), WHtR (AUC = 0.748), and SBP (AUC = 0.731). The total sample had an irisin AUC of 0.230, while the AUC for HDL-C was 0.437, indicating an inverse relationship with CMS, as lower levels were found in individuals with the syndrome. Under these circumstances, AUCs  $< 0.5$  indicate a reversal of the discriminatory relationship. Therefore, the complementary value (1-AUC) was used for irisin, which is 0.770, representing the adjusted AUC. Therefore, irisin had a particularly good predictive value (AUC = 0.770 after inverse adjustment), better than WHpR (AUC = 0.717) and VAI (AUC = 0.679), which had the lowest predictive value.

In a sex specific analysis, as shown in Figure 2B and C, the AUC values for FBG and SBP were higher in women (FBG = 0.858, SBP = 0.754) than in men (FBG = 0.730, SBP = 0.695).

The multivariate logistic regression analysis identifies independent predictors of CMS as the dependent variable. The model included physical activity, age, sex, HDL, TG, FBG, VAI, irisin, BMI, WC, WHpR, and WHtR. Significant ( $p < 0.01$ ) independent predictors of CMS were FBG (OR = 1.070, 95% CI 1.038-1.103), BMI (OR = 1.148, 95% CI 1.034-1.275), and irisin (OR = 0.995, 95% CI 0.991-0.998). These results indicate that higher FBG and BMI

increase the odds of CMS. However, irisin shows an inverse relationship with CMS after adjusting for the other variables in the model.

## DISCUSSION

This research aimed to identify adult populations at risk for developing CMS using VAI, circulating irisin, and standard anthropometric measurements. Irisin, a myokine produced by exercise, is found at lower serum levels in obese individuals with T2D compared to normal-weight and obese, non-diabetic individuals. These findings align with those of experimental studies in which irisin improves insulin sensitivity and increases glucose tolerance (8,16) and support the hypothesis that irisin has a protective metabolic role (16). While several studies report low irisin levels in obese T2D patients (17,18), Stengel et al. (19) found high levels of irisin, potentially indicating irisin resistance in advanced stages of the disease.

Our results, consistent with another investigation (20), show no significant sex-based differences in irisin levels, contrasting with a previous report of such variations (21). This discrepancy may stem from methodological differences or population heterogeneity. Our prior research also found sex-specific variations and a notable link between circulating irisin, fat-free mass, and performance markers

**TABLE 3.** Biochemical values, calculated indices and blood pressure of the study participants

| Indicator      | Obese with T2D              | <i>p</i> ‡ | Obese                       | <i>p</i> ‡ | Normal                      | <i>p</i> ‡ |
|----------------|-----------------------------|------------|-----------------------------|------------|-----------------------------|------------|
| FBG (mg/dL)    |                             |            |                             |            |                             |            |
| Men (n=50)     | 135.880±8.814 <sup>a</sup>  | 0.105      | 97.42±1.371 <sup>b</sup>    | 0.755      | 97.34±1.414 <sup>b</sup>    | 0.000      |
| Women (n=50)   | 158.940±10.999 <sup>a</sup> |            | 96.76±1.607 <sup>b</sup>    |            | 82.48±1.450 <sup>b</sup>    |            |
| Total (n=100)  | 147.410±7.107 <sup>a</sup>  |            | 97.090±1.051 <sup>b</sup>   |            | 89.910±1.254 <sup>b</sup>   |            |
| HDL-C (mg/dL)  |                             |            |                             |            |                             |            |
| Men (n=50)     | 39.344±1.493 <sup>a</sup>   | 0.000      | 47.088±2.056 <sup>b</sup>   | 0.002      | 43.074±1.550 <sup>ab</sup>  | 0.151      |
| Women (n=50)   | 48.814±1.695 <sup>a</sup>   |            | 55.254±1.590 <sup>b</sup>   |            | 46.62±1.899 <sup>a</sup>    |            |
| Total (n=100)  | 44.079±1.221 <sup>a</sup>   |            | 51.171±1.356 <sup>b</sup>   |            | 44.847±1.232 <sup>a</sup>   |            |
| LDL (mg/dL)    |                             |            |                             |            |                             |            |
| Men (n=50)     | 86.72±3.930 <sup>ab</sup>   | 0.002      | 93.38±3.736 <sup>a</sup>    | 0.000      | 76.700±3.097 <sup>b</sup>   | 0.914      |
| Women (n=50)   | 71.520±2.580 <sup>a</sup>   |            | 75.86±2.720 <sup>a</sup>    |            | 76.220±3.188 <sup>a</sup>   |            |
| Total (n=100)  | 79.120±2.460 <sup>ab</sup>  |            | 84.620±2.462 <sup>a</sup>   |            | 76.460±2.211 <sup>b</sup>   |            |
| TC (mg/dL)     |                             |            |                             |            |                             |            |
| Men (n=50)     | 175.320±6.287 <sup>a</sup>  | 0.097      | 212.120±5.631 <sup>b</sup>  | 0.001      | 195.800±6.925 <sup>ab</sup> | 0.555      |
| Women (n=50)   | 191.56±7.377 <sup>a</sup>   |            | 186.280±4.796 <sup>a</sup>  |            | 190.320±6.137 <sup>a</sup>  |            |
| Total (n=100)  | 183.44±4.890 <sup>a</sup>   |            | 199.200±3.902 <sup>b</sup>  |            | 193.06±4.611 <sup>ab</sup>  |            |
| TG (mg/dL)     |                             |            |                             |            |                             |            |
| Men (n=50)     | 170.780±12.053 <sup>a</sup> | 0.533      | 162.140±8.521 <sup>a</sup>  | 0.307      | 140.080±11.758 <sup>a</sup> | 0.223      |
| Women (n=50)   | 160.380±11.470 <sup>a</sup> |            | 149.240±9.220 <sup>ab</sup> |            | 122.000±8.882 <sup>b</sup>  |            |
| Total (n=100)  | 165.580±8.294 <sup>a</sup>  |            | 155.690±6.280 <sup>a</sup>  |            | 131.304±7.387 <sup>b</sup>  |            |
| SBP (mmHg)     |                             |            |                             |            |                             |            |
| Men (n=50)     | 138.160±2.669 <sup>a</sup>  | 0.002      | 128.100±1.955 <sup>b</sup>  | 0.159      | 124.780±1.740 <sup>b</sup>  | 0.001      |
| Women (n=50)   | 127.520±2.046 <sup>a</sup>  |            | 123.860±2.257 <sup>a</sup>  |            | 117.160±1.413 <sup>b</sup>  |            |
| Total (n=100)  | 132.840±1.756 <sup>a</sup>  |            | 125.980±1.501 <sup>b</sup>  |            | 120.970±1.179 <sup>c</sup>  |            |
| DBP (mmHg)     |                             |            |                             |            |                             |            |
| Men (n=50)     | 84.82±1.128 <sup>a</sup>    | 0.395      | 84.22±1.163 <sup>a</sup>    | 0.751      | 81.06±1.352 <sup>a</sup>    | 0.231      |
| Women (n=50)   | 83.340±1.314 <sup>ab</sup>  |            | 83.600±1.564 <sup>a</sup>   |            | 79.060±0.963 <sup>b</sup>   |            |
| Total (n=100)  | 84.080±0.865 <sup>a</sup>   |            | 83.910±0.970 <sup>a</sup>   |            | 80.060±0.832 <sup>b</sup>   |            |
| Irisin (ng/mL) |                             |            |                             |            |                             |            |
| Men (n=50)     | 125.948±11.923 <sup>a</sup> | 0.277      | 218.524±12.390 <sup>b</sup> | 0.131      | 303.580±12.935 <sup>c</sup> | 0.587      |
| Women (n=50)   | 147.286±15.455 <sup>a</sup> |            | 250.286±16.794 <sup>b</sup> |            | 294.960±9.091 <sup>b</sup>  |            |
| Total (n=100)  | 136.617±9.770 <sup>a</sup>  |            | 234.396±10.504 <sup>b</sup> |            | 299.270±7.877 <sup>c</sup>  |            |
| VAI            |                             |            |                             |            |                             |            |
| Men (n=50)     | 7.217±0.569 <sup>a</sup>    | 0.436      | 5.796±0.270 <sup>ab</sup>   | 0.360      | 5.627±0.421 <sup>b</sup>    | 0.172      |
| Women (n=50)   | 7.856±0.580 <sup>a</sup>    |            | 6.500±0.423 <sup>a</sup>    |            | 6.679±0.552 <sup>a</sup>    |            |
| Total (n=100)  | 7.536±0.406 <sup>a</sup>    |            | 6.148±0.252 <sup>b</sup>    |            | 6.153±0.349 <sup>b</sup>    |            |

T2D: Type 2 diabetes, FBG: Fasting blood glucose, HDL-C: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein, TC: Total cholesterol, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, VAI: Visceral adiposity index. Means in the same row with different superscripts are significantly different, using the One-way ANOVA and *post hoc* Tukey test. ‡The *P*-value represents the difference between males and females within the same column group for each indicator, using the One-way ANOVA test. ANOVA: Analysis of variance

in Jordanian athletes, highlighting the complex relationship between body composition and metabolism (22).

The present study found that the VAI, an indicator of visceral fat dysfunction, was significantly higher in obese participants with T2D, reflecting the clustering of metabolic abnormalities in this population (23). These findings align with previous research, indicating increased VAI values in individuals with CMS (23-25). While no strong association was observed between irisin levels and VAI in general, this is consistent with previous studies conducted in Jordan (25) and suggests that factors such as age, sex, and population characteristics may influence this relationship, as seen in other ethnic groups (26).

In the current sample, 71.0% of Jordanian adults met the criteria for CMS, with a higher prevalence among men (74.7%) than among women (67.3%). Although these results are significantly higher than previous

estimates (27,28), the high prevalence of CMS and its risk indices in Jordanians is confirmed. This increase may be due to the inclusion of higher-risk individuals and rising obesity rates in Jordan (23,27-31). Central obesity, indicated by a larger WC, was the most commonly observed feature, followed by elevated TG, aligning with findings from other regional and international studies (32-35).

Our study found that body measurements relate differently to CMS factors. The WHpR had the strongest connections to TG, HDL-C, and SBP, supporting its role in predicting heart health risks (31,32). Consistently, WC was most associated with DBP, aligning with previous Jordanian research (31). While BMI is commonly used to assess obesity, it showed weaker ties to many CMS factors in our study, echoing findings from other studies (33).

We found a significant correlation between FBG and WHtR, which aligns with research indicating that WHtR is

**TABLE 4.** Correlation coefficients of biochemical indicators, Irisin, cardiometabolic syndrome indices with age, anthropometric measures and blood pressure

| Indicator                     | SBP     | DBP     | FBS      | HDL-C    | LDL     | TC      | TG      | Irisin   | VAI     |
|-------------------------------|---------|---------|----------|----------|---------|---------|---------|----------|---------|
| <b>Age (years)</b>            |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.163** | 0.049   | 0.064    | -0.037   | 0.017   | 0.015   | 0.072   | 0.024    | 0.093   |
| Men (n=150)                   | -0.074  | 0.136   | -0.013   | 0.009    | 0.087   | 0.024   | 0.042   | 0.046    | 0.037   |
| Women (n=150)                 | 0.149   | 0.176*  | 0.119    | -0.053   | -0.096  | -0.001  | 0.094   | 0.010    | 0.148   |
| <b>Weight (kg)</b>            |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.293** | 0.163** | 0.202**  | -0.041   | 0.169** | 0.069   | 0.188** | -0.324** | 0.48    |
| Men (n=150)                   | 0.086   | 0.208*  | 0.116    | 0.001    | 0.191*  | 0.037   | 0.129   | -0.390** | 0.096   |
| Women (n=150)                 | 0.214** | 0.259** | 0.331**  | 0.129    | -0.048  | 0.073   | 0.216** | -0.248** | 0.088   |
| <b>Height (cm)</b>            |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.143*  | 0.036   | -0.108   | -0.255** | 0.153** | 0.072   | 0.063   | 0.012    | -0.052  |
| Men (n=150)                   | -0.023  | 0.019   | -0.248** | -0.024   | -0.043  | 0.041   | -0.023  | 0.070    | 0.020   |
| Women (n=150)                 | -0.026  | -0.128  | -0.018   | -0.196*  | 0.038   | 0.054   | 0.028   | 0.098    | 0.140   |
| <b>BMI (kg/m<sup>2</sup>)</b> |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.226** | 0.164** | 0.291**  | 0.121*   | 0.079   | 0.038   | 0.173** | -0.342** | 0.088   |
| Men (n=150)                   | 0.113   | 0.206*  | 0.258**  | 0.020    | 0.233** | 0.033   | 0.166*  | -0.446** | 0.103   |
| Women (n=150)                 | 0.214** | 0.292** | 0.313**  | 0.190*   | -0.063  | 0.049   | 0.192*  | -0.262** | 0.035   |
| <b>WC (cm)</b>                |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.271** | 0.205** | 0.281**  | -0.017   | 0.127*  | 0.108   | 0.187** | -0.305** | 0.135*  |
| Men (n=150)                   | 0.137   | 0.087   | 0.198*   | -0.051   | 0.267** | 0.077   | 0.180*  | -0.363** | 0.247** |
| Women (n=150)                 | 0.287** | 0.363** | 0.346**  | 0.081    | -0.087  | 0.127   | 0.177*  | -0.247** | 0.191*  |
| <b>HC (cm)</b>                |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.131*  | 0.154** | 0.155**  | 0.095    | 0.066   | 0.084   | 0.093   | -0.193** | 0.061   |
| Men (n=150)                   | 0.058   | 0.109   | 0.086    | -0.043   | 0.236** | 0.082   | 0.091   | -0.242** | 0.141   |
| Women (n=150)                 | 0.207*  | 0.265** | 0.200*   | 0.174*   | -0.076  | 0.097   | 0.116   | -0.165*  | 0.040   |
| <b>WHpR</b>                   |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.280** | 0.137*  | 0.269**  | -0.152** | 0.118*  | 0.071   | 0.191** | -0.251** | 0.143*  |
| Men (n=150)                   | -0.004  | 0.165*  | 0.237**  | -0.024   | 0.119   | 0.012   | 0.182*  | -0.283** | 0.223** |
| Women (n=150)                 | 0.213** | 0.267** | 0.336**  | -0.092   | -0.046  | 0.094   | 0.162*  | -0.214** | 0.281** |
| <b>WHtR</b>                   |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 0.207** | 0.188** | 0.317**  | 0.090    | 0.045   | 0.072   | 0.154** | -0.389** | 0.152** |
| Men (n=150)                   | -0.004  | 0.165*  | 0.292**  | -0.040   | 0.259** | 0.054   | 0.185*  | -0.365** | 0.239** |
| Women (n=150)                 | 0.284** | 0.383** | 0.333**  | 0.122    | -0.095  | 0.107   | 0.162*  | -0.258** | 0.152   |
| <b>SBP (mmHg)</b>             |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 | 1       | 0.530** | 0.154**  | -0.040   | 0.104   | 0.063   | 0.170** | -0.235** | 0.080   |
| Men (n=150)                   | 1       | 0.477** | 0.121    | -0.056   | 0.158   | 0.027   | 0.185*  | -0.194*  | 0.157   |
| Women (n=150)                 | 1       | 0.588** | 0.208*   | 0.118    | -0.106  | 0.080   | 0.113   | -0.264** | 0.077   |
| <b>DBP (mmHg)</b>             |         |         |          |          |         |         |         |          |         |
| Total (n=300)                 |         | 1       | 0.157**  | 0.027    | 0.132*  | 0.149** | 0.151** | 0.041    | 0.072   |
| Men (n=150)                   |         | 1       | 0.057    | 0.017    | 0.161*  | 0.098   | 0.114   | 0.004    | 0.068   |
| Women (n=150)                 |         | 1       | 0.219**  | 0.079    | 0.070   | 0.193*  | 0.178*  | -0.072   | 0.089   |

\*Significant at  $P<0.05$ ; \*\*Significant at  $P<0.01$ ; \*\*\*Significant at  $P<0.001$ . \*BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, WHpR: Waist to hip ratio, WHtR: Waist to height ratio, FBG: Fasting blood glucose, HDL-C: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein, TC: Total cholesterol, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

a better metabolic risk indicator than BMI and WC (34). It effectively identifies individuals with normal BMI but high central adiposity, highlighting its importance in assessing multiple CMS aspects.

The best predictor of CMS, according to ROC analysis, was WC (AUC = 0.781). BMI and irisin (AUC = 0.770) were next in line, while VAI had the poorest diagnostic performance (AUC = 0.679). These findings contrast with some reports that propose VAI as a better predictor than WC

or BMI (36). However, they support the use of irisin as a promising novel biomarker for the CMS risk stratification.

In this study, VAI showed a low predictive performance for CMS, with an AUC of 0.679, indicating a relatively weak indicator. This lower predictive value may result from including participants on lipid-lowering or diabetes medications, which can lower TG and raise HDL-C, thus impacting VAI calculations (37). The small sample size may have influenced the mean VAI values and reduced the

**TABLE 5.** Correlation coefficients between biochemical indicators, irisin and cardiometabolic syndrome indices of the study participants

| Indicator     | FBS | HDL-C  | LDL     | TC      | TG      | Irisin   | VAI      |
|---------------|-----|--------|---------|---------|---------|----------|----------|
| <b>FBG</b>    |     |        |         |         |         |          |          |
| Total (n=300) | 1   | -0.032 | 0.058   | 0.131*  | 0.245** | -0.266** | 0.271**  |
| Men (n=150)   | 1   | -0.101 | 0.086   | 0.007   | 0.258** | -0.180*  | 0.355**  |
| Women (n=150) | 1   | 0.001  | 0.051   | 0.236** | 0.249** | -0.335** | 0.221**  |
| <b>HDL-C</b>  |     |        |         |         |         |          |          |
| Total (n=300) |     | 1      | 0.165** | 0.308** | -0.128* | 0.041    | -0.462** |
| Men (n=150)   |     | 1      | 0.319** | 0.432** | -0.039  | 0.114    | -0.464** |
| Women (n=150) |     | 1      | 0.152   | 0.235** | -0.180* | -0.061   | -0.554** |
| <b>LDL</b>    |     |        |         |         |         |          |          |
| Total (n=300) |     |        | 1       | 0.662** | 0.218** | -0.009   | 0.022    |
| Men (n=150)   |     |        | 1       | 0.748** | 0.169*  | -0.039   | -0.006   |
| Women (n=150) |     |        | 1       | 0.564** | 0.252** | 0.062    | 0.116    |
| <b>TC</b>     |     |        |         |         |         |          |          |
| Total (n=300) |     |        |         | 1       | 0.399** | 0.019    | 0.154**  |
| Men (n=150)   |     |        |         | 1       | 0.353** | 0.124    | 0.104    |
| Women (n=150) |     |        |         | 1       | 0.446** | -0.084   | 0.236**  |
| <b>TG</b>     |     |        |         |         |         |          |          |
| Total (n=300) |     |        |         |         | 1       | -0.091   | 0.825**  |
| Men (n=150)   |     |        |         |         | 1       | -0.147   | 0.832**  |
| Women (n=150) |     |        |         |         | 1       | -0.022   | 0.829**  |
| <b>Irisin</b> |     |        |         |         |         |          |          |
| Total (n=300) |     |        |         |         |         | 1        | -0.068   |
| Men (n=150)   |     |        |         |         |         | 1        | -0.118   |
| Women (n=150) |     |        |         |         |         | 1        | -0.043   |
| <b>VAI</b>    |     |        |         |         |         |          |          |
| Total (n=300) |     |        |         |         |         |          | 1        |
| Men (n=150)   |     |        |         |         |         |          | 1        |
| Women (n=150) |     |        |         |         |         |          | 1        |

\*Significant at  $P < 0.05$ ; \*\*Significant at  $P < 0.01$ ; \*\*\*Significant at  $P < 0.001$ . \*BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, WHpR: Waist to hip ratio, WHtR: Waist to height ratio, FBG: Fasting blood glucose, HDL-C: High density lipoprotein cholesterol, LDL: Low density lipoprotein, TC: Total cholesterol, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

**TABLE 6.** Area under the curve for identifying cardiometabolic syndrome risk indices in the study participants

| Indicators | AUC/men | AUC/women | AUC/total |
|------------|---------|-----------|-----------|
| WC         | 0.788   | 0.768     | 0.781     |
| WHpR       | 0.730   | 0.713     | 0.717     |
| WHtR       | 0.783   | 0.746     | 0.748     |
| BMI        | 0.788   | 0.767     | 0.775     |
| DBP        | 0.628   | 0.776     | 0.712     |
| SBP        | 0.695   | 0.754     | 0.731     |
| HDL-C      | 0.437   | 0.412     | 0.437     |
| FBG        | 0.730   | 0.858     | 0.805     |
| TG         | 0.660   | 0.686     | 0.677     |
| Irisin     | 0.230   | 0.347     | 0.230     |
| VAI        | 0.683   | 0.695     | 0.679     |

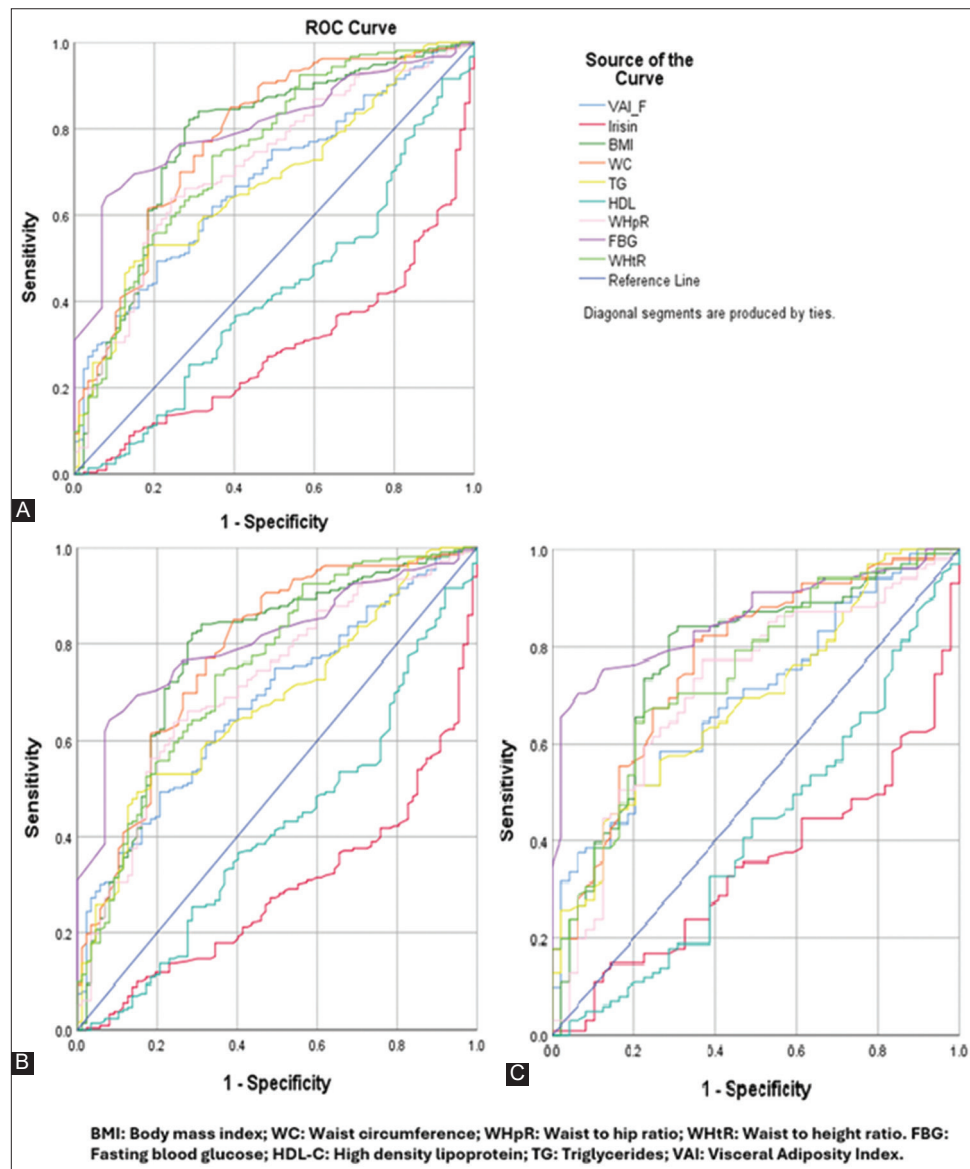
BMI: Body mass index, WC: Waist circumference, WHpR: Waist to hip ratio, WHtR: Waist to height ratio, FBG: Fasting blood glucose, HDL-C: High density lipoprotein, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, VAI: Visceral adiposity index, AUC: Area under the curve. For irisin and HDL-C, AUC values  $< 0.5$  indicate inverse associations; thus,  $(1 - \text{AUC})$  was considered for interpretation

statistical power. While VAI significantly correlated with several biochemical indicators of CMS, including FBG, TG, and HDL-C, it did not correlate with irisin, consistent with a previous study in Jordan (25). Comparisons with other studies revealed mixed results; some research

supported VAI as a reliable predictor of visceral adiposity and cardiometabolic risk (14,23), while other studies from a recent review (38) indicated limited predictive value. Indeed, heterogeneity of study populations may explain the discrepancy in the results of these studies.

Strong negative correlations were found between WHtR and irisin, as well as between irisin and key anthropometric measures and metabolic risk factors like SBP and FBG. These results align with recent studies indicating a negative relationship between irisin and glucose metabolism markers (36,39). Some studies have shown that sex does not significantly influence the associations mentioned, indicating that the relationship between irisin and metabolic risk factors is similar for both men and women (36,40). The broader body of evidence suggests that variations in assay techniques, physical activity intensity, comorbidities, and chronic medication exposure represent important sources of heterogeneity that may underline the inconsistent associations reported between irisin and metabolic outcomes.

Logistic regression analysis further supported these findings. Among anthropometric measures, BMI emerged as a significant predictor of CMS ( $\text{OR} = 1.15$ ,  $p < 0.009$ ). This result is consistent with that reported elsewhere (27,28), but contrasts with that reported by Lee et al. (33). This disparity may be attributed to the limitations of the BMI, which does not distinguish between excess fat and excess



**FIGURE 2.** Receiver operating characteristic Curves of Anthropometric and Biochemical Indices, along with the visceral adiposity index and Irisin, for Identifying Subjects with Cardiometabolic Syndrome among All Study Participants (A), Men (B), and Women (C).

muscle mass. As a result, individuals of similar weight and height may be classified as at greater risk for cardiovascular disease, even if their body composition differs (27). In terms of biochemical predictors, FBG was strongly associated with CMS ( $OR = 1.07, p < 0.001$ ). Notably, irisin was inversely related to CMS ( $OR = 0.995, p < 0.003$ ), suggesting a potential protective role. These results are consistent with reported evidence that irisin is affected by cardiometabolic and inflammatory processes, but the direction of this relationship can vary in different clinical conditions (41). Both logistic regression and ROC analyses emphasize the significance of traditional anthropometric and metabolic markers, while also highlighting the potential of irisin as an innovative biomarker for predicting the risk of CMS.

The present study design and systematic random sampling technique enabled a comprehensive characterization of the participants, including demographic, anthropometric, biochemical, and clinical measures, which strengthens the internal validity of the findings. Both irisin and VAI were evaluated as potential predictive biomarkers for CMS, providing clinically relevant insights into their utility in

identifying individuals at increased cardiometabolic risk. Moreover, the careful measurement of biochemical parameters and the use of standardized ELISA protocols for irisin quantification enhanced the reliability of the data. By integrating both novel biomarkers and established anthropometric indices, this study provides valuable evidence to the emerging literature on the role of irisin and visceral adiposity in predicting cardiometabolic risk. Undoubtedly, the results of this study will pave the way for a better understanding of disease risks and for creating advanced targeted educational strategies that address the prevention and management of obesity and diabetes (42).

This study employed a cross-sectional design; the associations observed reflect relationships at a single point in time; thus, it does not follow individuals over time. While this means that causality cannot be established, cross-sectional studies remain a reliable design for identifying clinically relevant associations and generating evidence that can guide further research (40). Some participants reported using medicines to manage dyslipidemia or hyperglycemia. Nonetheless, such treatments may have influenced

biochemical parameters involved in VAI calculation, potentially affecting its estimation (37). In the current study, diet was not evaluated, which may limit the ability to account for its potential effects on anthropometric measures (43) and, consequently, on irisin and related metabolic outcomes.

## CONCLUSION

The findings suggest that circulating irisin may serve as a valuable biomarker for assessing the risk of CMS and related disorders among Jordanian adults. The observed inverse relationship between irisin levels and key metabolic markers, such as FBG and WHtR, indicates its potential utility in early detection, especially in populations with high obesity and T2D rates. In contrast, the VAI has limited predictive power compared to irisin and other established measurements. These results highlight the need to integrate novel biomarkers like irisin into risk assessment models for better early detection and prevention of CMS. Further longitudinal studies are needed to clarify irisin's predictive value and its role in CMS development.

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## DECLARATION OF INTERESTS

Authors declare no conflict of interest.

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