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Sex-dependent association between circulating irisin levels and insulin resistance in healthy adults

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ABSTRACT

Background: Irisin, a myokine, expressed by muscle and adipose tissue, has been reported to stimulate conversion of white into brown adipose tissue. The beneficial health effects of exercise are thought to be mediated in part, via increased production of irisin.
Objective: The primary aim of this study was to assess the association between plasma irisin levels glycaemic indices in healthy adults. Associations between irisin and lipid levels, CRP and body composition were explored as secondary outcomes.
Methods: A cross-sectional sample of forty nine (n = 49) free living healthy males (n = 28) and females (n = 21), between the ages of 18 and 65, with body mass index (BMI) within the healthy range, were recruited. Body weight, height, and body composition measurements were taken. Fasting blood samples were collected for the analysis of glucose, insulin and irisin levels. Insulin resistance score, HOMA-IR, was calculated using fasting blood glucose and insulin values. The relationship between plasma irisin levels and anthropometric measurements, glucose, insulin and HOMA-IR was determined using Spearman's bivariate correlation test.
Results: A significant inverse relationship was found between plasma irisin levels and insulin($r = -0.380$; $P = 0.007$) and HOMA-IR($r = -0.362$; $P = 0.011$). This relation was further strengthened in males when the data was stratified by gender. Circulating irisin levels were positively correlated with HDL-C ($r = 0.39$; $P = 0.05$) in male participants. Additionally, there was a significant negative correlation between percent body fat ($r = -0.43$, $P < 0.05$) and body fat mass ($r = -0.47$, $P < 0.05$) and circulating irisin levels in male participants.
Conclusions: This study reports a sex-dependent inverse relationship between plasma irisin levels and insulin resistance in healthy subjects.

1. Introduction

Insulin resistance is the pathological constellation of metabolic abnormalities such as impaired glucose uptake, increased hepatic glucose output and subclinical inflammation, often allied with physical inactivity [1]. The escalating prevalence of insulin resistance worldwide has greatly increased the interest in the metabolic and physiological role of hormones secreted by muscle [2]. Insulin resistance, being a component of metabolic syndrome, is a trigger for pathological conditions like type 2 diabetes and cardiovascular abnormalities [3,4]. Sedentary lifestyle is a major contributor for the development of insulin resistance, obesity and type 2 diabetes. Transient changes in physical inactivity tend to modulate the hormones associated with the metabolic processes leading to the accumulation of visceral adipose tissue and loss of muscle mass [5,6]. Scientific literature in recent years cites skeletal muscle as a key organ playing an important role in exhibiting resistance or sensitivity to insulin [2,7]. Advances in research examining the role of skeletal muscle in insulin resistance has highlighted the secretory function of skeletal muscle, releasing myokines during or post

Abbreviations: BMI, Body Mass Index; CRP, c-Reactive Protein; FFM, Fat Free Mass; FNDC5, Fibronectin type III Domain Containing protein 5; HDL-C, High Density Lipoprotein cholesterol; HOMA –IR, Homeostatic Model Assessment for Insulin Resistance; IPAQ, International Physical Activity Questionnaire; LDL-C, Low Density Lipoprotein cholesterol; PBF, Percentage Body Fat; PGC1α, Proliferator activated receptor-γ Co-activator 1; SMM, Skeletal Muscle Mass.

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muscular activity. The depiction of skeletal muscle as an endocrine organ suggests it may modify insulin resistance by modulation of myokines [2,8].

In 2012, Bostrom et al. discovered a novel myokine, irisin, modulated by peroxisome proliferator activated receptor-γ co-activator 1 (PGC1α) and released upon proteolytic cleavage from fibronectin type III domain containing protein 5 (FNDC5) [9]. Irisin is believed to be involved in browning of white adipose tissue and salutary effects of physical activity [10]. Since the discovery of irisin, a large volume of literature relating its physiological effects, browning effect and metabolic function [9,11,12] has been published. Administration of irisin through adenoviral delivery system exhibited browning of white adipose tissue at specific points associated with modest but significant weight loss [10]. The lower levels of circulatory irisin have been reported in type 2 diabetes individuals and positively correlated with age, BMI, cholesterol and blood pressure in individuals without diabetes [13,14].

Although several studies have been carried out in mice and humans to determine the therapeutic efficacy of irisin in obesity and diabetes, there is a need for further research to identify the role of irisin as a biomarker to predict metabolic disease in healthy individuals.

The aim of this study was to examine the association between the plasma irisin levels and glycaemic indices (fasting blood glucose and insulin levels) along with other metabolic markers, including lipid levels, CRP, physical activity and body composition in healthy adults.

2.. Subjects and methods

2.1. Subjects

his was a cross-sectional pilot study including 49 healthy adults (28 male and 21 female) between the ages of 18–65 years who were enrolled for an ongoing study. Participants were also asked to complete a medical questionnaire, International Physical Activity Questionnaire (IPAQ) and a 3 day food diary. Written consent was obtained from all the participants. Subjects with diagnosed hyperlipidaemia, diabetes mellitus, gastrointestinal disorders, currently on fructose/sugar restricted diet, vegan diet or weight loss program, who had undergone any surgical procedure for obesity, pregnant or lactating mothers, currently taking lipid-lowering drugs, anti-inflammatory drugs and BMI >30 kg/m^2 were excluded from the study. Fasting blood samples obtained from the participants were used to analyse the associations between circulating irisin levels and physical activity, body weight, height and body composition, blood lipids (triglyceride, LDL-C, HDL-C, Total/HDL-C), inflammation (CRP) and nutrient intake data. The study protocol was approved by the University of Newcastle Human Research Ethics Committee.

2.2. Methods

2.2.1. Anthropometry, body composition and nutrient intake

Standing height was measured to the nearest 0.1 cm using a stadiometer. Body weight, BMI, waist: hip ratio, body fat mass (BFM) and muscle mass (MM) in the fasting state were measured using direct segmental multi-frequency bioelectrical impedance (InBody 230, Biospace Co., Ltd. Seoul, Korea). Participants were asked to refrain from physical exertion and alcohol consumption for 24 h prior to testing. Physical activity (metabolic equivalent/week) was calculated from the International Physical Activity Questionnaire (IPAQ). 3 day food records were collected. Food records collected from participants were entered into FoodWorks Version 7.0.291 database (Xyris Software Pty Ltd, Queensland, Australia) to analyse daily energy and nutrient intake of participants.

2.2.2. Biochemical analysis

Blood samples were collected into tubes pre-coated with EDTA, lithium heparin and sodium fluoride by venipuncture. EDTA blood tubes were centrifuged for 10 min at 3000 g at 4 °C for separation of plasma and stored at −80 °C for further use. The lithium heparin tubes for CRP and blood lipids; sodium fluoride tubes for blood glucose and insulin measurement were analysed by the accredited Hunter New England Area Pathology Services.

Homeostatic model assessment for insulin resistance (HOMA-IR), an index of insulin resistance was calculated by using fasting blood glucose and insulin values as follows: HOMA-IR = (FBG × Insulin)/22.5, where insulin is in lU/mL and fasting blood glucose is in (mmol/L).

2.2.3. Hormone assays

Irisin levels were measured by competitive Enzyme Linked-Immunosorbent Assay (ELISA) for quantitative determination of irisin in human plasma (obtained from centrifugation of EDTA blood tubes) (Adipogen; Liestal, Switzerland, detection limit 1 ng/ml). Serum insulin levels were analysed by Hunter New England Area Pathology services.

2.2.4. Statistical analysis

All data are presented as mean ± SEM. The relationship between plasma irisin levels and anthropometric measurements, body composition, glucose, insulin and HOMA-IR was determined using Spearman's bivariate correlation test. All statistical analyses were carried out with SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). A probability level of $p < 0.05$ was adopted throughout to determine statistical significance unless otherwise mentioned.

3. Results

3.1. Participant anthropometric characteristics and nutrient intake

The mean age of the all participants was 36.0 ± 1.7 and the mean BMI (kg/m^2) was 24.3 ± 0.5 (Table 1). There was no significant difference between the BMI levels of males (25.0 ± 0.57) and females (23.5 ± 0.8) in this study group. Males had significantly higher levels of skeletal muscle mass (kg) (29.8 ± 1.1 vs 24.5 ± 1.5), fat free mass (kg) (59.5 ± 1.8 vs 42.1 ± 1.4), but lower levels of percent body fat (21.1 ± 1.4 vs 30.7 ± 1.8) and body fat mass (kg) (16.1 ± 1.2 vs 19.0 ± 1.5) than females. The daily energy intake of males (2121.6 ± 127.0 kcal) was significantly higher than females (1813.4 ± 65.7 kcal). Males consumed significantly higher levels of protein and fat (monounsaturated fat) when compared with the intake of females (Table 2). Physical activity of the participants was measured using IPAQ questionnaire. The mean physical activity of all participants was 1083.8 ± 116.4 MET minutes/week with females (1198.7 ± 199.7 MET minutes/week) slightly more physically active than males (997.7 ± 139.0 MET minutes/week).

3.2. Clinical and hormonal characteristics

There were no significant differences in clinical characteristics (Table 1) including glucose (4.8 ± 0.06 vs 4.9 ± 0.08 mmol/L), cholesterol (5.1 ± 0.18 vs 4.6 ± 0.19 mmol/L), and triglycerides (1.12 ± 0.11 vs 0.94 ± 0.01 mmol/L) between the male and female participants. But the LDL-C and total/HDL ratio was significantly higher in male participants (3.23 ± 0.17; 4.2 ± 0.24) than female participants (2.71 ± 0.18; 3.3 ± 0.22). There were no noteworthy differences in the levels of irisin and insulin between the males

Table 1
Anthropometric measurements, blood biomarkers & energy and nutrients intakes of study participants.

n	Total	Males	Females	P values
	49	28	21	
Weight (kg)	67.8 ± 2.2	74.6 ± 2.3	58.7 ± 3.1	**<0.05**
Age (yrs)	36.0 ± 1.7	37.1 ± 2.4	34.5 ± 2.4	N.S.
BMI (kg/m^2)	24.3 ± 0.4	25.0 ± 0.5	23.5 ± 0.7	N.S.
SMM (kg)	29.8 ± 1.1	33.8 ± 1.1	24.5 ± 1.4	**<0.05**
FFM (kg)	52.0 ± 1.7	59.5 ± 1.8	42.1 ± 1.4	**<0.05**
PBF (%)	25.1 ± 1.8	21.1 ± 1.3	30.7 ± 1.8	**<0.05**
BFM	17.3 ± 0.9	16.1 ± 1.2	19.0 ± 1.4	N.S.
Waist: hip	0.9 ± 0.01	0.9 ± 0.01	0.9 ± 0.01	N.S.
Glucose (mmol/L)	4.8 ± 0.06	4.9 ± 0.08	4.8 ± 0.08	N.S.
Cholesterol (mmol/L)	4.9 ± 0.1	5.1 ± 0.1	4.6 ± 0.2	N.S.
Triglyceride (mmol/L)	1.04 ± 0.09	1.1 ± 0.1	0.9 ± 0.1	N.S.
LDL-C (mmol/L)	3.01 ± 0.1	3.2 ± 0.1	2.7 ± 0.1	**<0.05**
HDL-C (mmol/L)	1.40 ± 0.06	1.3 ± 0.09	1.4 ± 0.08	N.S.
Total/HDL ratio	3.8 ± 0.1	4.2 ± 0.2	3.3 ± 0.2	**<0.05**
Insulin (mIU/L)	7.5 ± 0.5	7.2 ± 0.7	7.9 ± 0.7	N.S.
CRP (mg/L)	1.6 ± 0.2	1.3 ± 0.2	2.0 ± 0.4	N.S.
HOMA-IR	1.6 ± 0.1	1.5 ± 0.1	1.7 ± 0.1	N.S.
Irisin (mcg/mL)	6.8 ± 0.3	7.1 ± 0.4	6.6 ± 0.4	N.S.
Physical activity (MET-minutes/week)	1084 ± 116	998 ± 139	1199 ± 199	N.S.

Mean values ± Standard Error of Mean.
BMI, Body mass index; SMM, Skeletal muscle mass, FFM, Fat Free Mass; PBF, Percentage Body Fat; BFM, Body fat mass; LDL-C, Low Density Lipoprotein cholesterol; HDL-C, High Density Lipoprotein cholesterol; CRP, c-Reactive Protein; HOMA IR Homeostatic model assessment for insulin resistance; N.S., non-significant.
The values are represented in bold to highlight the significant correlation between the circulating irisin levels and other parameters.

Table 2
Daily energy and nutrient intake of study participants.

Daily intake	Total	Males	Females	P values
	49	28	21	
Energy (kcal)	1990 ± 80	2122 ± 127	1813 ± 66	<0.05
Protein (g)	86 ± 5.1	97 ± 8.0	71.51 ± 4.1	<0.05
Fat (g)	78 ± 4.5	85 ± 6.0	66.21 ± 6.0	<0.05
Saturated Fat (g)	29 ± 1.8	32 ± 2.5	24.62 ± 2.4	N.S.
Polyunsaturated fat (g)	12 ± 0.9	13 ± 1.5	10.42 ± 1.1	N.S.
Monounsaturated fat (g)	28 ± 1.8	31 ± 2.4	23.79 ± 2.6	<0.05
Fibre (g)	25 ± 1.5	25 ± 2.3	23.66 ± 1.9	N.S.
Cholesterol (mg)	274 ± 41	333 ± 63	196 ± 41	N.S.
Carbohydrate (g)	232 ± 11.2	235 ± 18	226 ± 11	N.S.
Sugar (g)	83 ± 5.7	84 ± 8.4	82 ± 7.5	N.S.

(7.10 ± 0.46; 7.2 ± 0.71 mIU/L) and females (6.63 ± 0.41; 7.9 ± 0.78 mIU/L). The HOMA-IR and CRP levels were not significantly different between males and females (Table 1).

3.3. Correlation of irisin with physical activity and anthropometric measurements

The physical activity (MET min/week) data of all study participants obtained from IPAQ were positively correlated with the serum irisin levels ($r = 0.326$, $P < 0.05$) (Table 3). The correlation between serum irisin levels and anthropometric measurements using the Spearman's bivariate correlation test showed gender differences. There was a significant negative correlation between circulating irisin levels and both percent body fat ($r = -0.43$, $P < 0.05$) and body fat mass ($r = -0.47$, $P < 0.05$) in male participants only (Fig. 3- A & B).

There were no significant associations between serum irisin levels and other anthropometrical parameters (Table 3) including weight, BMI, SMM, FFM and waist hip ratio, in the total group, or in males or females alone.

3.4. Correlation of irisin with clinical and hormonal parameters

A significant inverse relationship was found between plasma irisin levels and HOMA-IR ($r = -0.29$; $P = 0.045$) and insulin ($r = -0.34$; $P = 0.016$) in all study participants (Fig. 1- A&B). Plasma irisin levels were negatively correlated with insulin levels in the low physically active participants ($r = -0.608$, $p < 0.05$) (Table 4). No significant relationship was apparent between irisin and blood glucose level, triglycerides, cholesterol and CRP (Table 3). When data was stratified into males and females, the inverse relationships between plasma irisin levels and HOMA-IR ($r = -0.47$; $P = 0.011$) and insulin ($r = -0.46$; $P = 0.014$) were further strengthened in males (Fig. 2- A&B). Interestingly, irisin level was also found to have a positive correlation with HDL-C ($r = 0.39$; $P = 0.039$) in males (Fig. 3 – C).

4. Discussion

This is the first cross-sectional study to demonstrate an inverse relationship between plasma irisin levels and insulin or HOMA-IR scores in healthy individuals. The principal findings of our study are the associations between circulating irisin and metabolic parameters, which are different by sex. The significant inverse association between irisin and both insulin and HOMA-IR levels was evident in males but not females. Interestingly we also found a significant correlation between irisin and HDL-C in male participants only. Parallel to these observations, plasma irisin levels were negatively associated with percent body fat (PBF) and body fat mass (BFM) in men but not women. Small sample size in this pilot study might attribute to difficulties in finding associations between the irisin and other parameters. The relationship between irisin and physical activity level appears to be a determinant of the relationship between plasma irisin and fasting insulin levels with a negative relationship in participants whose physical activity level was low.

Previous studies involving obese individuals and people with metabolic syndrome or type 2 diabetes have shown differences in the association between serum irisin and insulin or HOMA-IR scores. Some studies have reported a positive correlation [12,15] while others reported either no correlation [14,16] or even a negative correlation [17,18] between serum irisin and HOMA-IR scores. Serum irisin levels were negatively correlated with insulin and HOMA-IR in our study participants. This might be explained by the fact that all participants in our study were metabolically

Table 3
Spearman's correlation between irisin levels and anthropometric and clinical parameters.

n	Total		Males		Females	
	49		28		21	
	r*	P	r*	P	r*	P
Weight (kg)	−0.58	N.S.	−0.32	N.S.	0.27	N.S.
BMI (kg/m^2)	0.02	N.S.	−0.22	N.S.	0.31	N.S.
SMM (kg)	−0.12	N.S.	−0.02	N.S.	−0.29	N.S.
FFM (kg)	−0.18	N.S.	−0.04	N.S.	−0.08	N.S.
PBF (%)	−0.16	N.S.	**−0.43**	**<0.05**	0.28	N.S.
BFM	−0.17	N.S.	**−0.47**	**<0.05**	0.34	N.S.
Waist: hip	0.03	N.S.	−0.09	N.S.	0.17	N.S.
Glucose (mmol/L)	0.07	N.S.	−0.12	N.S.	0.29	N.S.
Cholesterol (mmol/L)	0.27	N.S.	0.36	N.S.	0.06	N.S.
Triglyceride (mmol/L)	−0.14	N.S.	−0.19	N.S.	−0.13	N.S.
LDL-C (mmol/L)	0.28	N.S.	0.32	N.S.	0.19	N.S.
HDL-C (mmol/L)	0.23	N.S.	**0.39**	**<0.05**	0.02	N.S.
Total/HDL ratio	0.01	N.S.	−0.14	N.S.	0.14	N.S.
Insulin (mIU/L)	**−0.34**	**<0.05**	**−0.46**	**<0.05**	−0.09	N.S.
CRP (mg/L)	−0.11	N.S.	−0.25	N.S.	0.05	N.S.
HOMA-IR	**−0.29**	**<0.05**	**−0.47**	**<0.05**	0.04	N.S.
Physical activity (MET minutes/week)	**0.32**	**<0.05**	0.26	N.S.	0.4	N.S.

r*, Spearman correlation coefficient; Level of significance given as $P \leq 0.05$.
BMI, Body mass index; SMM, Skeletal muscle mass, FFM, Fat Free Mass; PBF, Percentage Body Fat; BFM, Body fat mass; LDL-C, Low Density Lipoprotein cholesterol; HDL-C, High Density Lipoprotein cholesterol; CRP, c-Reactive Protein; HOMA-IR, homeostatic model assessment; N.S., non-significant; MET metabolic equivalents.
The values are represented in bold to highlight the significant correlation between the circulating irisin levels and other parameters.

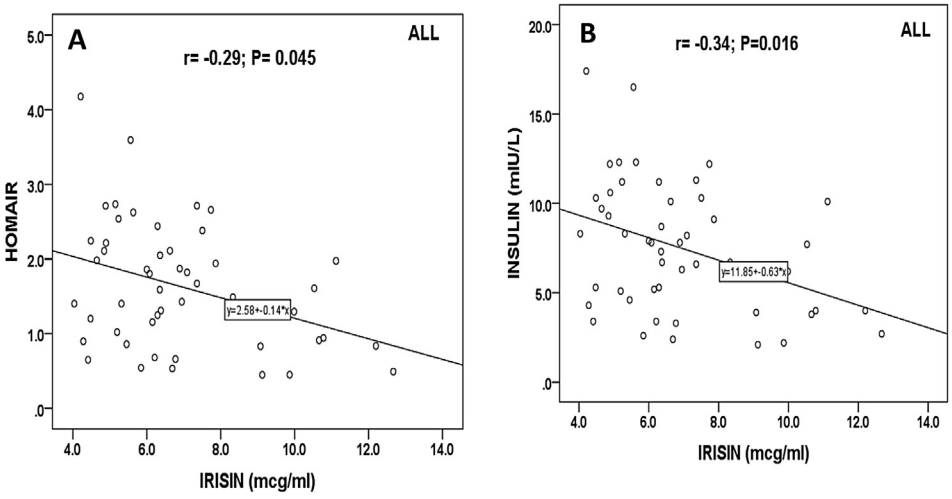

Fig. 1. Correlation of serum irisin with HOMA IR (A) and insulin (B).

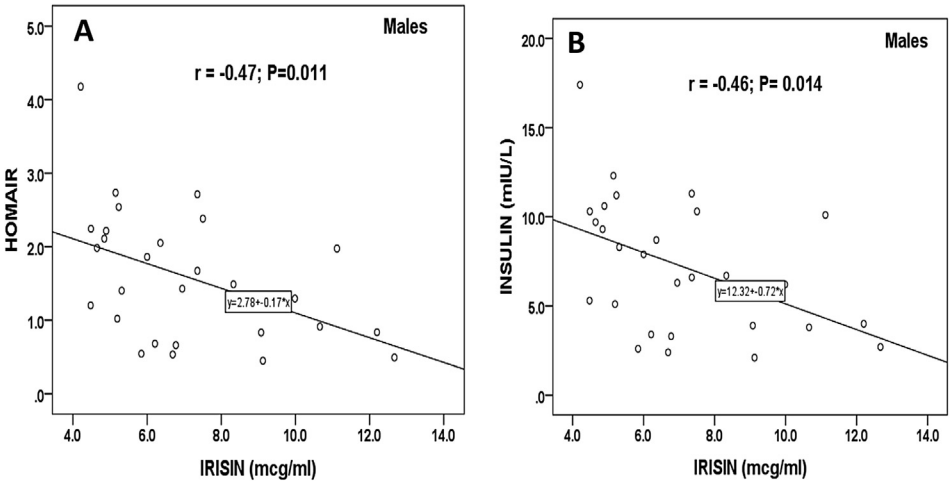

Fig. 2. Correlation of serum irisin with HOMA −IR (A) and insulin (B) in males.

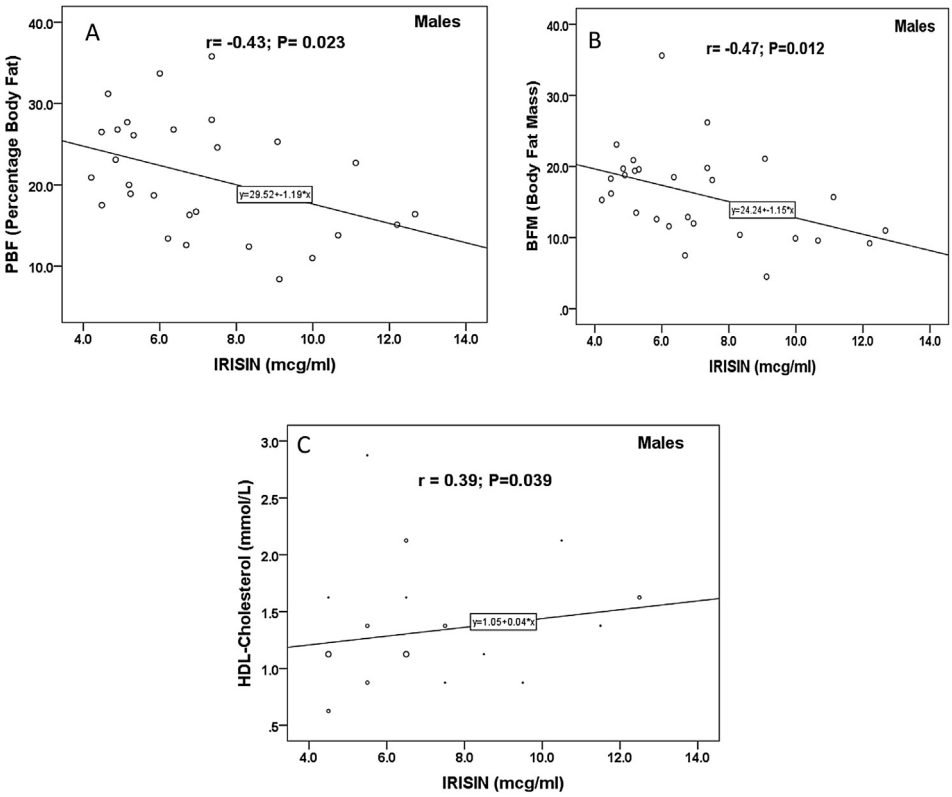

Fig. 3. Correlation of serum irisin with percent body fat (A), body fat mass (B) and HDL-C (C).

Table 4
Spearman's correlation between irisin and insulin or HOMA-IR in low, moderate and high physical activity.

Irisin	HOMA-IR		Insulin	
	r	P	r	P
Low Phy act (N = 12)	−0.538	0.071	**−0.608***	**0.036**
Moderate Phy act (N = 27)	−0.162	0.421	−0.236	0.235
High Phy act (N = 10)	−0.212	0.556	−0.382	0.276

Phy act – Physical activity; N = Number of participants; r* spearman correlation coefficient; P – significance; **Category 1** = Low Individuals who do not meet criteria for Categories 2 or 3 are considered "low". **Category 2** = Moderate 3 or more days of vigorous-intensity activity of at least 20 min per day (OR) 5 or more days of moderate-intensity activity and/or walk of at least 30 min per day (OR) 5 or more days of any combination of walking, moderate -intensity or vigorous-intensity activities achieving a minimum total physical activity of at least 600 MET-minutes/weeks; **Category 3** = High Vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week (OR) 7 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum total physical activity of at least 3000 MET-minutes/week.
The values are represented in bold to highlight the significant correlation between the circulating irisin levels and other parameters.

healthy with BMI, blood lipids, fasting glucose and insulin levels, all in the normal range. Correlation between irisin and insulin resistance is supported by the hypothesised involvement of the p-38-PGC1α-irisin-betatrophin pathway [33]. The UCP-1 mediated action of irisin promotes the expression of betatrophin and beta cell regeneration thereby reducing insulin resistance [33]. These results therefore suggest that irisin may be a sensitive biomarker of insulin resistance in healthy individuals, however additional studies are needed to confirm this observations.

Our study demonstrates an association of irisin with insulin or HOMA-IR, percent body fat, body fat mass and HDL-C with gender differences. The differences in the distribution of fat (white and brown) in males and females might explain the gender differences [19,20]. Irisin released after exercise induces profound changes in the subcutaneous adipose tissue to increase the UCP-1 expression and browning effect [10]. Previous studies reported the expression of the brown adipocyte marker gene UCP-1 was higher in subcutaneous adipose tissue from women than men [19]. This hypothesis might provide a basis for sex based variations in circulating irisin levels. Another plausible explanation may be the hormonal differences in males and females. Estradiol, a primary female sex hormone, has been shown to be positively correlated with circulating irisin levels, while there was no significant relationship with free testosterone levels [12]. Moreover, the skeletal muscle mass (biceps circumference) has been shown to be positively correlated with serum irisin levels. Muscle mass is considered to be a main predictor of circulating irisin concentration underlying its association with metabolic variables. It has been shown that in male mice, testosterone induces an increase in energy expenditure derived from elevated PGC1-α mediated mitochondrial biogenesis, which is reported to stimulate FNDC5/irisin production in skeletal muscle. Testosterone levels are known to be several folds higher in men than pre-menopausal women. The variations in hormonal levels between males and females might affect the levels of circulating irisin levels producing gender specific effects. Hormonal influences on the production, secretion and functions of irisin are worthy of further investigation in order to clarify the observed sex differences in the association between irisin and insulin or HOMA-IR.

Physical activity level has been identified as an indicator and non-pharmacological intervention for prevention of insulin resistance [21,22]. A moderate increase in physical activity has been correlated with improvements in metabolic profile [23,24], however the mechanisms underlying the beneficial effects of physical activity are not clearly understood. Irisin is considered as one of the

myokines which regulate the beneficial effects of the physical activity [10]. Irisin levels have been previously shown to be higher in young athletes compared to middle aged women [12]. Acute aerobic exercise (treadmill running, cycling, sprinting) has been reported to result in elevated irisin levels [25–27]. Consistent with these studies, a positive correlation between plasma irisin and physical activity levels has been previously reported [10,12,26]. Notably the inverse relationship between plasma irisin and insulin or HOMA-IR in the present study is further strengthened when the data is stratified on the basis of physical activity levels. Taken together these results suggest that plasma irisin levels may predict insulin resistance in physically inactive, but otherwise healthy, individuals.

A recent review article has highlighted the controversy surrounding the relationship between irisin and anthropometric measurements [9]. Some previous studies reported a positive correlation of irisin and BMI [12,14] while negative correlations [28,29] have been described in other studies. In this study, no associations were observed between circulating irisin levels and anthropometric measurements including body weight, waist to hip ratio and BMI, which is consistent with the published reports [17,27]. However, in contrast to the previous studies [12,26], we found an inverse relationship of irisin with percent body fat and body fat mass in males, but not females. The heterogeneity of the data may be due to the different physiological and experimental conditions and health status of the individuals. These results can be justified by the fact that the participants included in this study were healthy with no metabolic abnormalities, which differs from the characteristics of participants from previous studies.

Limited scientific literature on the relationships between blood glucose levels and irisin have produced controversial results. Liu et al. reported a positive correlation between serum irisin and fasting plasma glucose [14], whereas Choi et al. demonstrated a negative correlation with OGTT and HbA1c [16]. In the present study we found there was no significant relationship between glucose, triglycerides and cholesterol levels, which is consistent with some studies [17,30,31] but not others [12,14,15,32]. The variations in the associations between circulating irisin and metabolic characteristics like glycaemic profile (glucose and insulin) and lipid profile (triglycerides and cholesterol) in the present study with other studies might be explained due to the variation in experimental conditions, differences in the assays used in analysis of irisin levels, confounding variables like age and gender, physical activity and the variation in health status of study populations.

Small sample size with a higher number of male participants might be a limiting factor in the present study. However to our knowledge, no previous studies have examined the association between irisin and metabolic parameters in healthy adults, making it difficult to accurately determine appropriate sample size.

In conclusion, we demonstrate a sex-dependent inverse relationship between plasma irisin levels and fasting insulin and HOMA-IR values. The outcomes of this study may be used as a reference for further studies to determine the role of irisin in the pathogenesis of insulin resistance using a larger sample size and including equal number of male and female participants.

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Disclosure

none.

Author's contributions

MLG and LGW designed the project; FJ and BP conducted research; FJ analysed data; RT, MLG and FJ wrote the paper; FJ and RT had primary responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest

None.

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