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Irisin is more strongly associated with leisure-time physical activity than resistin and high-density lipoprotein cholesterol are

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ABSTRACT

Objectives: Irisin is a myokine with a potential role in cardiometabolic diseases, but previous studies have described inconsistencies between serum irisin and physical activity (PA). Our aim was to analyze the relationship between serum irisin and leisure-time PA (LTPA) in a large sample of the general adult population, and secondarily, to evaluate its relationship with two PA-related biomarkers (HDL cholesterol and resistin).
Design: A cross-sectional study was nested in the "CDC of the Canary Islands" cohort participants (n = 3827, 18–75 years, 60% women).
Methods: PA was collected by administering the Minnesota leisure-time physical activity questionnaire, and physical examination and blood tests (irisin, resistin, HDL-cholesterol) were performed.
Results: Irisin inversely correlated with BMI ($p < 0.001$ in women) and resistin ($p = 0.038$ in women, $p = 0.004$ in men), and directly with HDL cholesterol ($p < 0.001$in women). There was a direct association of irisin with leisure-time and energy expenditure in light, moderate and vigorous LTPA, which was stronger in women than men. The distribution of leisure-time and PA variables across irisin quintiles showed a significant trend, except for light LPTA in men. Adjusting for age, sex and BMI, the association of irisin with leisure-time and LTPA variables was stronger than the association of these variables with resistin and HDL cholesterol, reaching the strongest association for irisin with the 80th percentile of time of LTPA (OR = 2.57; 95% CI = 2.00–3.31).
Conclusions: There is a direct and independent association between serum irisin levels and LTPA in the general adult population, which is stronger than other biomarkers of PA. Findings on exercise-related irisin support the possibility of irisin health benefits.

1. Introduction

Physical inactivity contributes to the global noncommunicable disease epidemic because almost one in three adults are physically inactive.[1] There is a widespread public health policy and scientific consensus that regular physical activity (PA) is an essential component of successful ageing. It has been reported that prolonged sedentary leisure-time is associated with a significantly decreased survival time.[2] PA is also associated with a lower risk of all-cause mortality; the greater the intensity of PA, the lower the risk.[3] This capacity is partly mediated by the secretion of myokines, whose synthesis and release is promoted by the activation of skeletal muscle during exercise.[4]

Irisin is a myokine which was only discovered a decade ago with thermogenic and energy expenditure regulating capacity[4]; it is released from myocytes during PA, and it can be considered as a link between muscles and other tissues and organs.[5] As a mediator of PA, irisin binds to adipose tissue and induces the browning of it.[4,6] The association of this myokine with a lower risk of developing

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obesity-related conditions has been described, such as arteriosclerosis, insulin resistance, and type 2 diabetes.[6]

Irisin, with its beneficial and pleiotropic properties, may be a potential biomolecule to promote health and prevent or treat some diseases,[5] but some findings on the effect of exercise and PA on serum irisin levels have been inconsistent. The effect of exercise on irisin has been reported,[7] and this might be affected by training mode,[8,9] but other studies did not find any effect.[10] These controversial findings may be due in part to the fact that most of the studies have only analyzed small samples.

Regarding PA, to our knowledge there are no studies of the relationship between irisin and the intensity of PA in men and women in a large sample of the general population. One study described the association of irisin with habitual PA in 858 individuals, but it did not analyze the results by sex or intensity of PA.[11] However, another study analyzed data of 300 participants and concluded that serum irisin concentration was not related to measures of PA and physical fitness in healthy humans under resting conditions.[12]

Focusing on leisure-time physical activity (LTPA) could provide an accurate view of association between irisin and PA in the real-life conditions of most people compared to clinical trials with short-term and tailored exercise programs. This approach could overcome the lack of scientific data on irisin association with well-known PA-related biomarkers, such as high density lipoprotein (HDL) cholesterol[13] and resistin.[14] Given that PA can have significant anti-inflammatory effects depending on the type of exercise,[15,16] the relationship between irisin, types of PA and known biomarkers of PA and inflammation - such as resistin - is a potentially productive area for research. This raises the possibility that studies in large population-based samples may provide conclusive evidence of the relationship between LTPA and irisin levels in people with different levels of PA (light, moderate or vigorous leisure time activities).

Therefore, the first aim of this study was to analyze the relationship between serum irisin levels and LTPA in a large sample of the general adult population, and the second aim was to compare this relationship with well-known PA-related variables such as HDL cholesterol and resistin. We hypothesized that serum irisin should be directely related to LTPA at least as strongly as resistin (inversely) and HDL-cholesterol (directely) do.

2. Methods

2.1. Design and participants

This is a cross-sectional study of the general adult population cohort called “CDC of the Canary Islands” (CDC means Cardiovascular, Diabetes, Cancer). This cohort consists of a random sample from the adult population of the Canary Islands (Spain): 6729 participants (18–75 years, 45% men and 55% women). A randomly selected subsample (n = 3827 participants) of the cohort was analyzed for this study. They were recruited during the period 2000–2005, and have been followed up until the present. All participants gave their informed consent and the project was evaluated and approved by the Ethics Committee of the University Hospital Nuestra Señora de Candelaria.

2.2. Measurements

The methodology was described in detail.[17] Briefly, each participant underwent a physical examination (BMI, was obtained after weighting and measuring the height of the participants, and expressed in kg/m^2), and trained interviewers administered an extensive questionnaire about their lifestyle (such as smoking, alcohol use, PA, diet, etc.). Furthermore, a fasting venous blood sample was extracted to determine biochemical parameters (such as serum lipids, blood glucose levels, etc.) and serum aliquots were stored at −80 °C. HDL cholesterol concentrations were recorded for all participants within 24 h after the blood was obtained, and measurements were made with a Hitachi1 917 autoanalyzer and expressed as mg/dL.

As mentioned above, serum samples were frozen and stored at −80 °C, and a serum aliquot was later thawed in 2012 to measure resistin by enzyme linked immunosorbent assay (ELISA), which was expresed in ng/mL (Bio-Vendor, Heidelberg, Germany; between-assay coefficient of variation, 7.72%; within-assay coefficient of variation, 2.22%).

A new serum aliquot was thawed in 2021 to determine irisin concentration; ELISA kits (RAG018R. BioVendor, Brno, Czech Republic) were also used and the results refer to the standard used by the manufacturer and are expressed in μg/mL. The samples were run diluted so that the irisin concentration was within the assay range (0.001 μg/mL - 5 μg/mL). The intra-assay and inter-assay coefficients of variation were 20.2% and 35.1%, respectively. In order to obtain these values, a serum pool of 600 participants from the autoimmunity laboratory was prepared, which were aliquoted and kept at −80 °C until use. The determinations were performed with a Triturus autoanalyzer (Grifols, Barcelona, Spain), in the Immunology laboratory. For funding reasons, irisin measurements were not taken for the entire cohort participants (n = 6729), but in a subsample of it (n = 3827).

Participants were interviewed to obtain responses to a questionnaire on their health-related antecedents. Data on LTPA were recorded with the Spanish version of the Minnesota Leisure-Time Physical Activity Questionnaire.[18] This was described in detail.[19] Each PA reported by the participants was assigned a metabolic equivalent task (MET) score which expresses its intensity based on the ratio between the metabolic rate during activity and the basal metabolic rate. One MET reflects an individual's energy consumption at rest, equivalent to approximately 1 kcal (4.184 kJ) per kg body weight per hour.[20] Measurements of MET during leisure-time did not consider usual housework activities. Weekly total leisure time was calculated, and hours of LTPA. PA was classified in three categories: light (MET<3.5), moderate (MET 3.5 to 6) or vigorous (MET>6). Energy expenditure was expressed in MET-hours per week (MET-h/week) following the formula: Energy expenditure = intensity (MET) x weekly frequency x duration (average time spent in each session in hours and minutes).[20]

2.3. Statistical analysis

Serum irisin was summarized with the mean ± standard deviation for each sex. Irisin associations with leisure-time and PA continuous variables were analyzed using the non-parametric Spearman correlation coefficients, stratified by sex, and also partial age-adjusted correlations. In addition, these associations were explored with linear multivariate regression models adjusted for age and sex. Furthermore, an ANOVA of the distribution of leisure-time and PA variables across the irisin quintiles was performed, and an analysis of trends was performed for the 80th percentile (p80) distribution of these same variables across the irisin quintiles.

The effect of leisure-time and LTPA variables on irisin was analyzed using logistic regression models, adjusted for age, sex and BMI. The dependent variable was the p80 of irisin, and quintiles of leisure-time and PA were included as independent variables; the odds ratios (OR) and their 95% confidence intervals (95% CI) were thereby obtained. The logistic analysis was repeated substituting p80 of irisin for p80 of HDL cholesterol and p80 of resistin as the dependent variable.

All hypothesis contrast tests used were two-tailed and p-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS statistical software (version 26.0 for Windows; SPSS Inc., Chicago, IL).

3. Results

3.1. Irisin and sex

Mean serum irisin levels of the 3827 participants were 35 ± 14.5 μg/mL in women, and 32.3 ± 14 μg/mL in men. In women (n = 2298), irisin inversely correlated with age (rho = −0.12; p < 0.001), BMI (rho = −0.13; p < 0.001), and resistin (rho = −0.04; p = 0.04), and directly correlated with HDL cholesterol (rho = 0.16; p < 0.001). In men (n = 1529), irisin inversely correlated with resistin (rho = −0.08; p < 0.01), but there was no correlation with age (rho = 0.00; p = 0.99), BMI (rho = 0.03; p = 0.30), or HDL cholesterol (rho = 0.05; p = 0.08).

3.2. Irisin and PA

Table 1 shows the significant association (p < 0.001) of irisin with total leisure-time, hours of LTPA, energy expenditure and MET spent on the three categories of PA, even after adjusting for age and sex. The non-parametric correlations between irisin and PA were direct, and stronger in women than in men.

The distribution of leisure-time and the different PA variables across the irisin quintiles is shown in Table 2. The increase in mean levels was significant (p < 0.001) for all the analyzed variables in women, and the results were similar in men except for the distribution of MET spent on light LTPA that was not significant (p = 0.18). The trend analysis of the p80 distribution of the leisure-time and PA variables across the irisin quintiles (supplementary table) produced significant results (p for trend <0.001) for all of them in women, while in men this was not significant for the p80 of METs spent on light LTPA (p for trend = 0.28).

Fig. 1 shows the percentage of women (p for trend<0.001) and men (p for trend<0.001) reaching the p80 of irisin across the quintiles of the hours of LTPA.

3.3. Irisin and PA biomarkers

Table 3 summarizes eighteen logistic models adjusted for age, sex, and BMI, one per cell in each column: six models for p80 of irisin, six models for p80 of HDL cholesterol, and six models for p80 of resistin. Irisin was directly associated with all the analyzed independent variables, reaching its strongest association with p80 of time of LTPA (OR = 2.57; 95% CI = 2.00–3.31). In turn p80 of resistin was inversely associated with all the variables analyzed except with p80 of METs in light LTPA, also reaching its strongest association with p80 of time of LTPA (OR = 0.74; 95% CI = 0.63–0.87). However, p80 of HDL cholesterol only showed an association with p80 of METs in moderate (OR = 1.29; 95% CI = 1.01–1.65) and vigorous (OR = 1.53; 95% CI = 1.20–1.94) LTPA.

4. Discussion

The present study found a direct association of leisure-time and PA with serum irisin in the general adult population. The association of irisin levels were corroborated for light, moderate, and vigorous LTPA in women, and only for moderate and vigorous LTPA in men. Furthermore, after adjustment for age, sex, and BMI this association between LTPA variables and irisin was stronger than the association between LTPA and resistin or HDL cholesterol, which are considered as good biochemical correlates of PA.

To the best of our knowledge, this study has measured serum irsin in the largest sample to date of adults from the general population. We have explored the relationship between irisin, leisure-time, and the different domains of LTPA. The results showed the existence of a direct correlation, which was stronger in women than men. The analysis of variance showed a significant and growing distribution of time and METs invested in all types of LTPA across irisin quintiles; this association was similar in both sexes, although significant differences were not found in men at the light level of LTPA. This pattern was corroborated in the trend analysis of p80 values of LTPA across irisin quintiles. Previous studies on the relationship between exercise and irisin detected increases of this myokine in aged adults when training is demanding and progressive in terms of intensity[21]; and, as mentioned above, irisin increases during high-intensity interval training in healthy young individuals.[7] Therefore, the present study corroborates this relationship not only in old or young people but in any adult age and, furthermore, shows that the relationship of irisin is not only with exercise but also with the PA that the population normally performs in their leisure time. As frequently happens when correlating a biomarker values with data obtained with a questionnaire the correlation coefficients were weak, but they can no longer be explained by chance; in addition, after categorizing the irisin values (p80) the multivariate adjustment produced moderate and strong odds ratios.

Several benefits have been particularly linked to LTPA compared to other types of PA. LTPA has been associated with greater cardiorespiratory and metabolic benefits when compared to occupational PA, which would be due to the characteristics of this type of activity: it is often high-intensity, dynamic, aerobic exercise, performed over short periods of time and with recovery time afterwards.[22] All this has even led to irisin being proposed as a biomarker with potential as a predictor for vigorous-intensity PA.[23] It has also been found that exercise in outdoor environments induces an increase in irisin levels compared to the same exercise practiced indoors at higher temperatures.[24] These observations are in line with the association found in the present study, because LTPA is generally practiced mostly in an outdoor environment, particularly in the Canary Islands, which is where the studied population resides, and whose environmental temperature is comfortable throughout the year.

Table 1
Partial age-adjusted correlations of irisin with leisure-time and physical activity variables in all participants (A). Non parametric correlations in each sex (B. C). Standardized regression coefficients, adjusted for age and sex (D).

	A. Irisin in all participants n = 3827	B. Irisin in women n = 2298	C. Irisin in men n = 1529	D. Irisin in all participants n = 3827
Hours of leisure-time	r = 0.12; (p < 0.001)	r = 0.12; (p < 0.001)	r = 0.09; (p < 0.001)	r = 0.11; (p < 0.001)
Hours of LTPA	r = 0.12; (p < 0.001)	r = 0.13; (p < 0.001)	r = 0.10; (p < 0.001)	r = 0.12; (p < 0.001)
MET-hours/week during LTPA	r = 0.12; (p < 0.001)	r = 0.12; (p < 0.001)	r = 0.09; (p < 0.001)	r = 0.11; (p < 0.001)
METs in light LTPA	r = 0.11; (p < 0.001)	r = 0.10; (p < 0.001)	r = 0.06; (p = 0.02)	r = 0.09; (p < 0.001)
METs in moderate LTPA	r = 0.07; (p < 0.001)	r = 0.09; (p < 0.001)	r = 0.08; (p = 0.003)	r = 0.08; (p < 0.001)
METs in vigorous LTPA	r = 0.07; (p < 0.001)	r = 0.10; (p < 0.001)	r = 0.08; (p = 0.002)	r = 0.08; (p < 0.001)

Table 2
Distribution of leisure-time, hours of leisure-time physical activity (LTPA), LTPA energy expenditure and MET spent in the three categories of PA, across irisin quintiles in women and men. The mean with 95% CI is given.

	Irisin in women (μg/mL) n = 2298				
	Q1	Q2	Q3	Q4	Q5
	16.91 (16.59–17.23)	24.99 (24.81–25.17)	32.01 (31.81–32.21)	39.99 (39.74–40.24)	56.39 (55.57–57.21)
Hours of leisure-time	0.47 (0.43–0.50)	0.48 (0.43–0.53)	0.61 (0.54–0.69)	0.63 (0.56–0.71)	0.72 (0.63–0.81)
Hours of LTPA	0.77 (0.71–0.82)	0.80 (0.73–0.88)	1.03 (0.91–1.14)	1.14 (1.00–1.27)	1.20 (1.08–1.33)
MET-hours/week during LTPA	11.00 (10.10–11.89)	11.51 (10.17–12.84)	15.17 (13.24–17.11)	15.55 (13.58–17.53)	17.91 (15.61–20.20)
METs in light LTPA	1.00 (0.92–1.08)	0.99 (0.88–1.10)	1.18 (1.03–1.32)	1.23 (1.08–1.39)	1.39 (1.21–1.56)
METs in moderate LTPA	0.48 (0.39–0.57)	0.57 (0.45–0.69)	0.80 (0.66–0.95)	0.83 (0.68–0.98)	0.93 (0.76–1.10)
METs in vigorous LTPA	0.10 (0.06–0.14)	0.17 (0.11–0.24)	0.26 (0.19–0.33)	0.28 (0.20–0.37)	0.35 (0.27–0.44)
	Irisin in men (μg/mL) **n=1529**				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	16.24 (15.86–16.61)	25.14 (24.93–25.34)	31.72 (31.50–31.94)	40.04 (39.70–40.38)	55.87 (54.69–57.05)
Hours of leisure-time	0.29 (0.24–0.33)	0.34 (0.28–0.40)	0.32 (0.25–0.39)	0.40 (0.32–0.48)	0.46 (0.36–0.56)
Hours of LTPA	0.62 (0.52–0.71)	0.79 (0.65–0.93)	0.68 (0.56–0.80)	0.87 (0.71–1.02)	1.00 (0.81–1.19)
MET-hours/week during LTPA	9.26 (7.65–10.88)	10.92 (8.87–12.96)	10.87 (8.45–13.29)	13.36 (10.59–16.13)	15.77 (11.99–19.54)
METs in light LTPA	0.13 (0.08–0.17)	0.13 (0.09–0.18)	0.16 (0.09–0.23)	0.22 (0.13–0.32)	0.21 (0.11–0.31)
METs in moderate LTPA	0.96 (0.76–1.17)	1.21 (0.95–1.47)	1.26 (0.96–1.56)	1.32 (1.01–1.63)	1.69 (1.27–2.11)
METs in vigorous LTPA	0.40 (0.29–0.51)	0.40 (0.26–0.53)	0.56 (0.37–0.76)	0.60 (0.42–0.78)	0.80 (0.47–1.13)

MET = metabolic equivalent, LTPA = leisure-time physical activity.

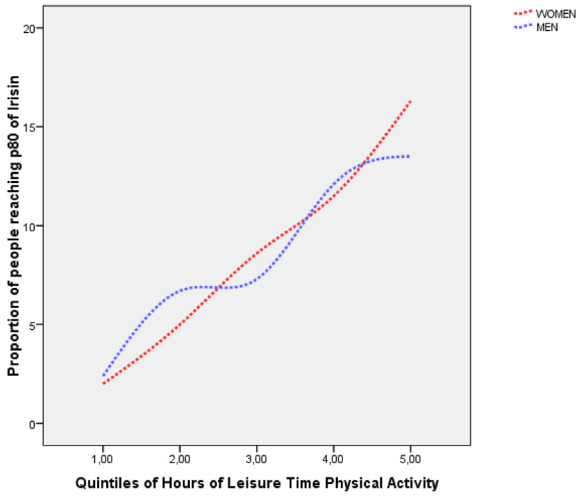

Fig. 1. Percentage of women (p for trend<0.001) and men (p for trend<0.001) reaching p80 of irisin across the quintiles of the hours of LTPA.

The mechanisms by which PA can induce a change in irisin concentration are generated by muscle contraction-promoted overexpression of the FNDC5 gene,[4] and irisin may directly modulate muscle metabolism through AMPK activation.[25] These mechanisms are influenced by aspects related to the exercise itself, such as type, amount, intensity, duration and environmental temperature.[5] As mention above, some results on the association of exercise and PA on serum irisin have been inconsistent. This can probably be explained by the great variation in study populations (such as age, sex, body composition, physical fitness and health status), exercise programs (such as endurance versus high-intensity interval training), and the fact that most of the studies analyzed small samples. It should be noted that most of the previous publications include clinical trials conducted on a few dozen participants undergoing short-term physical training programmes, althought most people in their real lives do not usually perform such programmes or practice sport so strictly.

The serum concentration of resistin and HDL cholesterol are known as good biochemical correlates of PA,[14] which is why they have been used here as a reference to compare the association between serum irisin and LTPA. The association of resistin with PA has previously been described as stronger than the association of

Table 3
Summary of eighteen logistic models adjusted by age, sex, and BMI. Six models for irisin, six model for resistin, and six models for HDL cholesterol in all participants. Odds ratios (95% CI) are given for different measurements of leisure and LTPA.

EXPOSURE	DEPENDENT VARIABLE	DEPENDENT VARIABLE	DEPENDENT VARIABLE
	Irisin p80	resistin p80	HDL-cholesterol p80
Leisure-time p80	2.27 (1.74–2.95)	0.81 (0.69–0.95)	0.93 (0.69–1.27)
Hours of LTPA p80	2.57 (2.00–3.31)	0.74 (0.63–0.87)	1.19 (0.90–1.57)
MET-hours/week during LTPA p80	2.17 (1.68–2.80)	0.83 (0.71–0.98)	1.08 (0.81–1.43)
METs in light LTPA p80	1.79 (1.41–2.27)	0.87 (0.74–1.02)	1.24 (0.97–1.59)
METs in moderate LTPA p80	1.49 (1.17–1.89)	0.83 (0.71–0.96)	1.29 (1.01–1.65)
METs in vigorous LTPA p80	1.69 (1.34–2.14)	0.86 (0.75–1.00)	1.53 (1.20–1.94)

*p80 = 80th Percentile, MET = metabolic equivalent, LTPA = leisure-time physical activity.

HDL cholesterol with PA, making resistin a potentially useful biomarker of PA.[14] As expected, given the physiological origin of both molecules, we have found an inverse correlation of irisin with resistin in both sexes. But, regardless of the direction of such associations, it should be noted that the association of irisin with the variables of time and intensity of LTPA was stronger than that detected for resistin and for HDL cholesterol, which is plausible if we consider that irisin is a myokine, that is, a direct product of muscle.

A direct association was only detected between irisin and HDL cholesterol in women, but it was not far from also being significant in men. However, findings from the previous general population study showed no association between this lipid fraction and irisin in either men or women, despite detecting favourable associations of irisin with the rest of the lipid profile[13]; the authors of this study consider that perhaps they lacked statistical power and that studies with larger population samples would be necessary, as is the case of the present study.

As for the sex differences in the results of irisin with age, BMI, HDL cholesterol, or light LTPA, a possible reason has been argued considering the different levels of sex hormones, and the sexual dimorphism in body composition with a higher lean and lower fat mass in men as well as differences in transcription of FNDC5.[4] Furthermore, some polymorphisms of this gene encoding irisin appear to be associated with increased dyslipidemia in women with diabetes but not in men.[26] In addition, it has been suggested that gender differences in the relationship between betatrophin and irisin indicate a cytokine-mediated crosstalk between the liver, adipose tissue and skeletal muscle.[27] In any case, the cause of the difference is not yet proven.

A possible limitation is that self-reported data on amount of PA might introduce some memory bias. However, validated methods were used to measure anthropometric data, biochemical variables and PA/LTPA; measuring PA, particularly LTPA, with a validated questionnaire is closer to the reality of daily life in the general population.[15] There is also a further limitation due to the cross-sectional design of the present study, which impedes establishing causal associations. The main strength of the study is that it was conducted on a large and randomly selected sample of the general adult population; so, it is, by some distance, the study with the highest number of irisin determinations performed.

5. Conclusions

There is a direct and independent association between LTPA and serum irisin levels in the general adult population, where the amount and intensity of LTPA is concerned. The association between elevated irisin levels and LTPA was found to be independent of age, sex and adiposity, but it seems to be stronger in women. The study also corroborated a direct association of irisin with HDL cholesterol and an inverse association with resistin, but the association of irisin with LTPA is stronger than that of those biomarkers. The findings on exercise-related irisin support the possibility of irisin health benefits.

6. Practical implications

- There is a direct and independent association between light, moderate and vigorous LTPA and serum irisin levels in the general adult population.
- The association between elevated irisin levels and LTPA is independent of age, sex and adiposity, but it is stronger in women.
- There is a direct association of irisin with HDL cholesterol and an inverse association with resistin, but the association of irisin with LTPA is stronger than that of those biomarkers.

Contributors

Antonio Cabrera de León planned the original study and wrote the final manuscript. María del Cristo Rodríguez-Pérez and Titta Katariina Kontro drafted the manuscript. Delia Almeida González directed all the laboratory procedures and quality control of the data. Itahisa Marcelino Rodríguez y Beatriz Gómez Álvarez analyzed the data and revised the manuscript. All authors contributed to study design, and accepted the final version of the manuscript.

MET = metabolic equivalent, LTPA = leisure-time physical activity.

Supplementary table
Distribution of the p80 of leisure and PA variables across the serum irisin quintiles. Percentages are given.

	Irisin in women (μg/mL)n = 2298					p for trend
	Q1	Q2	Q3	Q4	Q5	
Leisure-time p80	5.3	10.5	19.9	26.3	38.0	<0.001
Hours of LTPA p80	4.1	10.7	19.4	27.0	38.8	<0.001
MET-hours/week during LTPA p80	4.7	11.5	21.4	26.6	35.9	<0.001
METs in light LTPA p80	3.6	8.5	20.6	27.9	39.4	<0.001
METs in moderate LTPA p80	12.4	13.5	23.6	23.6	26.9	<0.001
METs in vigorous LTPA p80	7.2	11.8	21.7	25.3	33.9	<0.001
	Irisin in men (μg/mL)**n=1529**					**p for trend**
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	
Leisure-time p80	8.3	21.7	20.0	25.8	24.2	<0.001
Hours of LTPA p80	7.0	18.3	18.3	27.8	28.7	<0.001
MET-hours/week during LTPA p80	7.9	21.4	19.8	26.2	24.6	<0.001
METs in light LTPA p80	20.2	21.7	22.9	15.9	19.4	0.28
METs in moderate LTPA p80	13.2	19.9	21.3	22.1	23.5	0.001
METs in vigorous LTPA p80	17.4	17.4	21.1	23.7	20.5	0.003

*MET = metabolic equivalent, LTPA = leisure-time physical activity.

Ethical approval

This study was conducted according to good clinical and scientific practice and the Declaration of Helsinki. The authors declare that the results of this study are presented honestly, and without inappropriate data manipulation. Approval for questionnaire data collection was given by the Ethics Committee of the University Hospital Nuestra Señora de Candelaria. All the participants gave informed consent by returning the questionnaire, which were accompanied by a cover letter explaining the purpose of the study.

Data sharing

The data, the Bioethics Committee approval and the analysis plan that support the findings of this study are available on request from the corresponding author.

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Declaration of competing interest

None.

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References

1. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W. Ekelund U and lancet physical activity series working group. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380:247–257.
2. Larsson SC, Wolk A. Sedentary leisure-time in relation to mortality and survival time. *J Sci Med Sport*. 2019;22:562–567.
3. Wang Y, Nie J, Ferrari G, Rey-Lopez JP, Rezende LFM. Association of physical activity intensity with mortality A national cohort study of 403 681 US adults. *JAMA Intern Med*. 2021;181:203–211.
4. Boström P, Wu J, Jedrychowski MP, et al. PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481:463–468.
5. Korta P, Pocheć E, Mazur-Biały A. Irisin as a multifunctional protein: implications for health and certain diseases. *Medicina (Kaunas)*. 2019;55:485.
6. Mazur-Bialy AI, Pochéc E, Zarawski M. Anti-Inflammatory properties of irisin, mediator of physical activity are Connected with TLR4/MyD88 signaling pathway activation. *Int J Mol Sci*. 2017;18:701.
7. Anastasilakis AD, Polyzos SA, Saridakis ZG, et al. Circulating irisin in healthy, young individuals: day-night rhythm, effects of food intake and exercise, and associations with gender, physical activity, diet and body composition. *J Clin Endocrinol Metab*. 2014;99:3247–3255.
8. Qiu S, Bosnyák E, Treff G, et al. Acute exercise-induced irisin release in healthy adults: associations with training status and exercise mode. *Eur J Sport Sci*. 2018;18:1226–1233.
9. Colpitts BH, Rioux BV, Eadie AL, Brunt KR, Sénéchal M. Irisin response to acute moderate intensity exercise and high intensity interval training in youth of different obesity statuses: a randomized crossover trial. *Phys Rep*. 2022;10, e15198.
10. Norheim F, Langleite TM, Hjorth M, et al. The effects of acute and chronic exercise on PGC-1α, irisin and browning of subcutaneous adipose tissue in humans. *FEBS J*. 2014;281:739–749.
11. Buscemi S, Corleo D, Vasto S, et al. Factors associated with circulating concentrations of irisin in the general population cohort of the ABCD study. *Int J Obes*. 2018;42, 398-04.
12. Biniaminov N, Bandt S, Roth A, Haertel S, Neumann R, Bub A. Irisin, physical activity and fitness status in healthy humans: No association under resting conditions in a cross-sectional study. *PLoS One*. 2018;13, e0189254.
13. Oelmann S, Nauck M, Völzke H, Bahls M, Friedrich N. Circulating irisin concentrations are associated with a favourable lipid profile in the general population. *PLoS One*. 2016;11, e0154319.
14. Marcelino-Rodríguez I, Almeida González D, Alemán-Sánchez JJ, et al. Inverse association of resistin with physical activity in the general population. *PLoS One*. 2017;12, e0182493.
15. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercisemodalities and independent of weight loss. *Nutr Metabol Cardiovasc Dis*. 2010;20:608–617.
16. Hopps E, Canino B, Caimi G. Effects of exercise on inflammation markers in type 2 diabetic subjects. *Acta Diabetol*. 2011;48, 183-39.
17. Cabrera de León A, Rodríguez Pérez MC, Almeida González D, et al. Presentation of the "CDC de Canarias" cohort: objectives, design and preliminary results. *Rev Esp Salud Publica*. 2008;82:519–534.
18. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota leisure time physical activity questionnaire in Spanish men. The MARATHOM investigators. *Am J Epidemiol*. 1994;139, 1197-09.
19. Serrano-Sánchez JA, Fernández, Rodríguez MJ, et al. Domain and intensity of physical activity are associated with metabolic syndrome: a population-based study. *PLoS One*. 2019;14, e0219798.
20. Ainsworth BE, Haskell WL, Herrmann SD, et al. Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43:1575–1581, 2011.
21. Cosio PL, Crespo-Posadas M, Velarde-Sotres A, Pelaez M. Effect of chronic resistance training on circulating irisin: systematic review and meta-analysis of randomized controlled trials. *Int J Environ Res Publ Health*. 2021;18:2476.
22. Holtermann A, Krause N, van del Beek AJ, Strakee L. The physical activity paradox: six reasons why occupational physical activity (OPA) does not confer the cardiovascular health benefits that leisure time physical activity does. *Br J Sports Med*. 2018;52:149–150.
23. Morelli C, Avolio E, Galluccio A, et al. Impact of vigorous-intensity physical activity on body composition parameters, lipid profile markers, and irisin levels in adolescents: a cross-sectional study. *Nutrients*. 2020;12:742.
24. Ozbay S, Ulupınar S, Şebin E, Altınkaynak K. Acute and chronic effects of aerobic exercise on serum irisin, adropin, and cholesterol levels in the winter season: indoor training versus outdoor training. *Chin J Physiol*. 2020;63:21–26.
25. Huh JY, Mougios V, Kabasakalis A, et al. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. *J Clin Endocrinol Metab*. 2014;99:E2154–E2161.
26. Brondani LA, Boelter G, Assmann TS, Leitão CB, Canani LH, Crispim D. Irisin-encoding gene (FNDC5) variant is associated with changes in blood pressure and lipid profile in type 2 diabetic women but not in men. *Metabolism*. 2015;64:952–957.
27. Xie X, Gao T, Yang M, et al. Associations of betatrophin levels with irisin in Chinese women with normal glucose tolerance. *Diabetol Metab Syndrome*. 2015;7:26.