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META-ANALYSIS

Relationship between circulating irisin levels and overweight/obesity: A meta-analysis

Jue Jia, Fan Yu, Wei-Ping Wei, Ping Yang, Ren Zhang, Yue Sheng, Yong-Qin Shi

ORCID number: Jue Jia (0000-0003-1871-5015); Fan Yu (0000-0003-2009-3702); Wei-Ping Wei (0000-0002-2774-0354); Ping Yang (0000-0003-3555-847X); Ren Zhang (0000-0003-4783-5243); Yue Sheng (0000-0002-4001-6993); Yong-Qin Shi (0000-0002-7334-3130).

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Jue Jia, Fan Yu, Wei-Ping Wei, Ping Yang, Yue Sheng, Yong-Qin Shi, Affiliated Hospital of Jiangsu University, Zhenjiang 212001, Jiangsu Province, China

Ren Zhang, Department of Library of Jiangsu University, Zhenjiang 212001, Jiangsu Province, China

Corresponding author: Jue Jia, MD, Lecturer, Associate Chief Physician, Affiliated Hospital of Jiangsu University, No. 438, Jiefang North Road, Jingkou District, Zhenjiang 212001, Jiangsu Province, China. 1000011436@ujs.edu.cn
Telephone: +86-511-85031120
Fax: +86-511-85019237

Abstract

BACKGROUND

Currently, the findings about irisin as a novel myokine related to obesity are inconsistent in overweight/obese people. To our knowledge, no systematic analysis has been conducted to evaluate the relationship between irisin levels and overweight/obesity.

AIM

To evaluate the association between circulating irisin levels and overweight/obesity.

METHODS

The Cochrane Library, MEDLINE, SCOPUS, and the ISI Web of Science were searched to retrieve all of the studies associated with circulating irisin levels and overweight/obesity. Standard mean difference values and 95% confidence intervals (CI) were estimated and pooled using meta-analysis methodology.

RESULTS

A total of 18 studies were included in our meta-analysis containing 1005 cases and 1242 controls. Our analysis showed that the circulating irisin level in overweight/obese people was higher than that in overall healthy controls (random effects MD = 0.63; 95%CI: 0.22-1.05; $P = 0.003$). In the subgroup analysis by ethnicity, the irisin level was higher in overweight/obesity people than that in controls in Africa (random effects MD = 3.41; 95%CI: 1.23-5.59; $P < 0.05$) but not in European, Asian, or American populations. In addition, in a subgroup analysis by age, the results showed that obese children exhibited a higher irisin level than controls (random effects MD = 0.86; 95%CI: 0.28-1.43; $P < 0.05$).

CONCLUSION

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This meta-analysis provides evidence that circulating irisin is higher in obese individuals compared to healthy controls and it is important to identify the relationship between circulating irisin levels and overweight/obesity in predicting overweight/obesity.

Key words: Irisin; Overweight/obesity; Myokines; Body mass index

Core tip: This study is the first meta-analysis that systematically assessed circulating irisin in overweight/obese people. This meta-analysis showed that circulating irisin levels were higher in obese individuals than in healthy controls. It also suggested that circulating irisin levels were higher in obese people in Africa than in controls. This meta-analysis further suggested that obese children exhibited a higher irisin level than controls.

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INTRODUCTION

The definition of obesity is the increase of fat mass which could cause serious health problems[1]. Guidelines of obesity treatment defined that body mass index (BMI) ≥ 25 is overweight and greater than 30 is obesity in adults. For children, age needs to be considered when defining overweight and obesity[2]. Over the past three decades, obesity has been a worldwide epidemic and a serious threat to human health for the steady rising of global obesity rate as well as no-declined prevalence rates[3]. Accumulating evidence suggests that overweight/obesity has been identified as an independent risk factor for chronic diseases, including metabolic syndrome, cardiovascular disease, and diabetes mellitus, leading to a negative effect on health-related quality of life and a heavy pressure on the health care system[4-6]. Hence, identification of overweight/obesity-oriented factors that are potential biomarkers that could be used to predict obesity and related complications is important.

It is well known that muscle tissues can secrete some cytokines and other peptides named myokines that are essential for maintaining metabolic homeostasis[7]. Irisin is a novel myokine produced by proteolytical cleavage of fibronectin type III domain-containing 5 (FNDC5) both in mice and humans, and it can also be secreted by adipose tissue and the liver in a small amounts[8]. Recent meta-analysis reported that circulating irisin levels were associated with polycystic ovary syndrome and coronary artery diseases[9,10], and it was considered a critical myokine related to body metabolism. Interestingly, irisin can promote white adipose tissue browning, which dissipates energy to produce heat and decreases the appearance of cellulite[11]. Recently, a growing number of studies suggested that circulating irisin levels in plasma or serum may be related to overweight/obesity in different groups of people[7]; however, this relationship remains controversial due to conflicting results that have been reported[12-18]. A clinical study involving 94 obese patients who participated in a weight loss program showed that obese subjects had a higher circulating irisin level than controls[12]. These findings are consistent with other studies[13-16]. Puzzlingly, although most studies support a role for irisin in forecasting obesity, several studies do not have a consistent trend and concluded that circulating irisin levels were lower in the obese group compared to the control group[17-19]. Moreover, in obese *vs* healthy children, boys, or girls, results regarding circulating irisin were also incompatible[20-22].

To our knowledge, no systematic analysis has been conducted to evaluate the relationship between irisin levels and overweight/obesity. As a result, the objective of this study was to analyze all of the available data to perform a quantitative assessment of the association and deepen our understanding of the role of circulating irisin levels in the development of obesity *via* a meta-analysis.

MATERIALS AND METHODS

Search strategies

Databases including the Cochrane Library, PUBMED, and the ISI Web of Science were searched in English to identify studies published up to April 1, 2018, which addressed both irisin and overweight/obesity. Our overall search terms were irisin OR frcp2 OR fibronectin type III domain containing protein 5 OR fndc5 AND fat OR MS OR metabolic syndrome OR overweight/obesity. The reference lists of identified articles were also reviewed for more studies.

Selection criteria

To be considered for the meta-analysis, the studies had to be case-control or cohort studies that reported irisin levels in overweight/obese patients compared with healthy controls regardless of age or gender. We incorporated overweight into the obese group. Conference abstracts were also included if they contained sufficient information to extract effect estimates. Literature reviews, articles of research on the drug, articles in which the mean and standard deviation (SD) could not be calculated, and studies with no healthy control group were excluded.

Data extraction

The titles and abstracts of all eligible studies were reviewed by two authors independently. To settle disagreements, a third author was consulted. The following information was collected from each study: The first author, publication year, study design, study location, numbers of cases and controls, age, BMI, types of blood sample, assays for irisin measurement, study quality, and circulating irisin levels (means and standard deviations).

Data synthesis and analysis

The primary variables, circulating irisin levels in patients with obesity, were reported as standard mean differences (SMD) and the corresponding 95% confidence intervals (CIs). The SMD for circulating irisin levels were calculated for all of the studies that were identified for the meta-analysis, and the results were combined using fixed- or random-effects modeling, as appropriate. Publication bias was assessed using Begg's funnel plot and Egger's test[22,23]. Heterogeneity in the results of the different studies was examined using χ^2 tests for significance (a P-value < 0.1 was considered statistically significant) and the I^2 test (I^2 > 50%: significant heterogeneity; I^2 < 25%: insignificant heterogeneity), which can be interpreted as the percentage of total variation across several studies owing to heterogeneity[24,25]. A sensitivity analysis was performed to assess whether the summary results had been significantly influenced by removing one study that investigated the association between circulating irisin levels and obesity. Subgroup analyses were conducted by geographic area and age. All statistical analyses were performed with Review Manager 5.2 and Stata version 11.0. P < 0.05 was considered statistically significant.

RESULTS

Description of the studies

The literature search identified 1295 possible relevant articles. From these, 507 were duplicates, 788 were excluded after reading the title or abstract for obvious irrelevance, and 51 were finally included for further full-text evaluation. Of the 51 articles, five were excluded because they were reviews. Fifteen articles were excluded because they did not include healthy controls. Eight articles were excluded because data were represented by the median. Five articles were excluded because they did not contain detailed data. Finally, a total of 18 studies (1005 cases and 1242 controls) were included in our meta-analysis.

Figure 1 displays the flow chart describing the process of study inclusion/exclusion. Among the 18 studies, six were conducted in Europe, six in Asia, four in America, and two in Africa. The main characteristics of the included studies are presented in Table 1. Serum samples were used in 11 studies for irisin measurement, while plasma samples were used in the others. The sample size for each study ranged from 10 to 618. All of the irisin levels were measured with ELISA kits.

There were nine studies utilizing irisin ELISA kits from Phoenix Pharmaceuticals (Burlingame, CA, United States), three from BioVendor (Brno, Czech Republic), two from Bio Vision (Milpitas, United States), and one each from CUSABIO Life Science (Wuhan, China), Bioscience (Santa Clara, California, United States), Mercodia AB (Uppsala, Sweden), and MyBioSource (San Diego, United States). The details of

Table 1 Characteristics of included studies

Ref.	Country	Blood sample	Participants' age, years (case-control)	Cases/controls, *n*	Irisin assay	BMI (kg/m²) (case-control)	ELISA kit
Moreno-Navarrete *et al*[7], 2013	Spain	Plasma	52.41 ± 10.99-47.28 ± 10.15	51/18	ELISA	28.98 ± 3.17-23.33 ± 1.2	SK00170-01; Aviscera Bioscience Inc, Santa Clara, California
Stengel *et al*[13], 2013	Germany	Plasma	47.17 ± 11.91-48.5 ± 12.16	24/8	ELISA	50.63 ± 15.27-22.6 ± 2.55	Phoenix Pharmaceuticals, Inc., Burlingame, CA, United States
Crujeiras *et al*[12], 2014	Spain	Plasma	49.4 ± 9.4-35.71 ± 8.8	94/48	ELISA	35.6 ± 4.5-22.9 ± 2.2	Mercodia, AB (Uppsala, Sweden)
Hou *et al*[18], 2015	China	Serum	33 ± 9-31 ± 7	41/40	ELISA	30.8 ± 3.8-21.3 ± 1.8	Phoenix Pharmaceuticals, Inc., Burlingame, CA, United States
Palacios-González *et al*[20], 2015	Mexico	Serum	9.07 ± 0.88-9.0 ± 0.86	60/25	ELISA	-0.25 ± 0.67-2.11 ± 0.77[1]	CUSA-BIO BIOTECH
Viitasalo *et al*[26], 2016[26]	Finland	Plasma	7.71 ± 0.4-7.6 ± 0.4	55/388	ELISA	20.21 ± 1.52-15.5 ± 1.3	Phoenix Pharmaceuticals, Inc., Burlingame, CA, United States
Belviranli *et al*[17], 2016	Turkey	Plasma	34.40 ± 10.60-28.70 ± 6.82	10/10	ELISA	32.65 ± 3.04-23.00 ± 2.23	BioVendor, Czech Republic
Chen *et al*[14], 2016	China	Serum	34.4 ± 7.6-32.8 ± 7.8	30/20	ELISA	33.3 ± 4.2-21.1 ± 2.0	PHOENIX PHARMACEUTICAL
Fagundo *et al*[15], 2016	Spain	Plasma	44.49 ± 11.50-29.04 ± 6.22	65/49	ELISA	42.83 ± 6.63-21.61 ± 1.54	EK-067-52; Phoenix Pharmaceuticals, INC, CA
Mehrabian *et al*[27], 2016	Iran	Serum	28.76 ± 4.67-29.23 ± 4.50	38/26	ELISA	22.26 ± 1.23-20.88 ± 1.28	Biovendor, Laboratory Medicine, Modrice Czech Republic
Rizk *et al*[28], 2016	Egypt	Serum	45.45 ± 8.30-44.25 ± 10.46	20/20	ELISA	32.54 ± 1.80-22.85 ± 1.68	BioVendor, Bmo, Czechrepublic (cat. No. RAG018R)
Shoukry *et al*[29], 2016	Egypt	Serum	47.06 ± 4.76-45.12 ± 4.72	119/31	ELISA	34.72 ± 5.68-23.27 ± 0.50	BioVision, Milpitas, CA
Elizondo-Montemayor *et al*[21], 2017	Mexico	Plasma	8.0 (6–11)-8.5 (6-12)	5/5	ELISA	98 (98-99)-66 (35-73)	Phoenix Pharmaceuticals, Inc., Burlingame, CA, United States
Jang *et al*[30], 2017	South Korea	Serum	13.7 ± 0.7-13.5 ± 0.5	248/370	ELISA	31.4 ± 3.8-19.4 ± 1.5	Cat#EK-067-52; Phoenix, Pharmaceuticals, Belmont, CA
Liu *et al*[19], 2017	China	Serum	35.20 ± 6.51-35.01 ± 7.09	51/75	ELISA	27.80 ± 3.04-22.62 ± 2.52-	Bio Vision, Milpitas, CA95035, United States
Nigro *et al*[22], 2017	Italy	Serum	9.7 ± 2.7-8 ± 2.4	27/13	ELISA	2.7 ± 0.5-—0.46 ± 1.2	Phoenix Pharmaceuticals, Belmont, CA, United States
Tibana *et al*[16], 2017	Brazil	Serum	66.5 ± 5.0-68.0 ± 6.2	26/23	ELISA	30.9 ± 3.1-24.3 ± 3.6	MyBioSource Inc., San Diego, CA, United States

Sahin-Efe *et al*[31], 2018	United States	Serum	69.4 ± 8.6-69.5 ± 9.2	41/73	ELISA	30.5 (29.6–31.5)-24.0 (23.3–24.7)	CAT#EK-067-52; Phoenix Pharmaceuticals, Burlingame, CA

[1]BMI z-score. Data are presented as the mean ± SD for continuous parametric variables or median (interquartile range) for continuous nonparametric variables. ELISA: Enzyme-linked immunosorbent assay.

characteristics related to the included studies are shown in Table 1.

Main analysis

A meta-analysis of 18 studies involving a total of 2247 subjects (1005 cases and 1242 controls) was performed. Among them, four studies showed that obese individuals expressed lower irisin levels than healthy controls[7,17-19], while nine articles observed the opposite outcome where significantly higher irisin levels were exhibited in obese individuals compared to healthy controls. The results of the remaining four studies had no significance. Data were all described as the means ± SD. The *P*-value of heterogeneity between studies was significant ($P < 0.05$, Figure 2), so we used the random effects model and found that the overall effect was significant (random effects MD = 0.63; 95%CI: 0.22-1.05; $P = 0.003$). The effect size revealed that the irisin level was higher in obese people compared to healthy people.

In the subgroup analysis by ethnicity, the irisin level was higher in obese people in Africa than in controls and the test for overall effect was significant ($I^2 = 91\%$; random effects MD = 3.41; 95%CI: 1.23-5.59; $P < 0.05$). While the irisin levels in European ($I^2 = 90\%$, random effects MD = 0.57; 95%CI: -0.02-1.15), Asian ($I^2 = 93\%$; random effects MD = -0.05; 95%CI: -0.67-0.58), and American populations ($I^2 = 91\%$; random effects MD = 0.61; 95%CI: -0.38-1.61) were not higher in obese individuals than in healthy controls, and the test for overall effect was not significant ($P = 0.06$, 0.89, and 0.31, respectively) (Figure 3).

Furthermore, we performed a subgroup analysis by age. Five studies included children. Three of these studies suggested that obese children exhibited a higher irisin level than controls, and another two studies showed different outcomes. The *P*-value of heterogeneity between studies was significant ($P < 0.05$, Figure 4), then we used the random effects model and found that the overall effect was significant (random effects MD = 0.86; 95%CI: 0.28-1.43; $P = 0.004$). The effect size revealed that the irisin levels were higher in obese children than in controls. Conversely, the irisin levels in adult patients were not significantly different from controls and the total effect was not significant ($I^2 = 95\%$; random effects MD = 0.57; 95%CI: -0.03-1.18; $P = 0.06$) (Figure 4).

We omitted one study at a time and calculated the pooled SMD for the remainder of the studies to conduct a sensitivity analysis. There was no considerable change in the direction of the effect when omitting each of the studies.

We also conducted analyses by the Begg's test and Egger's test. Begg's funnel plot had the expected funnel shape (Figure 5). Begg's test ($Z = 0.61$, $P = 0.544$) and Egger's test for publication bias ($t = 0.46$, $P = 0.65$) indicated that there was no publication bias in our analysis.

DISCUSSION

This meta-analysis showed that circulating irisin levels in obese individuals were higher than those in overall healthy controls. It also suggested that circulating irisin levels were higher in obese people than in healthy controls in Africa, while studies in other regions showed a negative result. This meta-analysis further suggested that obese children exhibited higher irisin levels than controls.

First, the overall result of this meta-analysis is positive that circulating irisin levels increased in obesity compared with health controls, although some studies did not draw the same conclusion. When it comes to underlying mechanisms, it is speculated that the rising circulating irisin level in obesity is an accommodative compensatory response to obesity-induced metabolic dysfunction, such as a decline of insulin levels or "irisin resistance"[32] as has already been established for leptin or insulin in obesity. Second, the results suggest that age may be a factor for the increasing circulating irisin levels in obese children compared to controls. It is deduced that diet habits and lifestyle are also related factors. Due to their growth and development needs, children differ from adults in the above-mentioned factors. In addition, there are other differences such as exercise and underlying diseases[33-37]. Recent studies explored that baseline irisin levels were lower in the old compared to the young participants for age-related decline in muscle function[38,39]. Third, in the subgroup analysis by

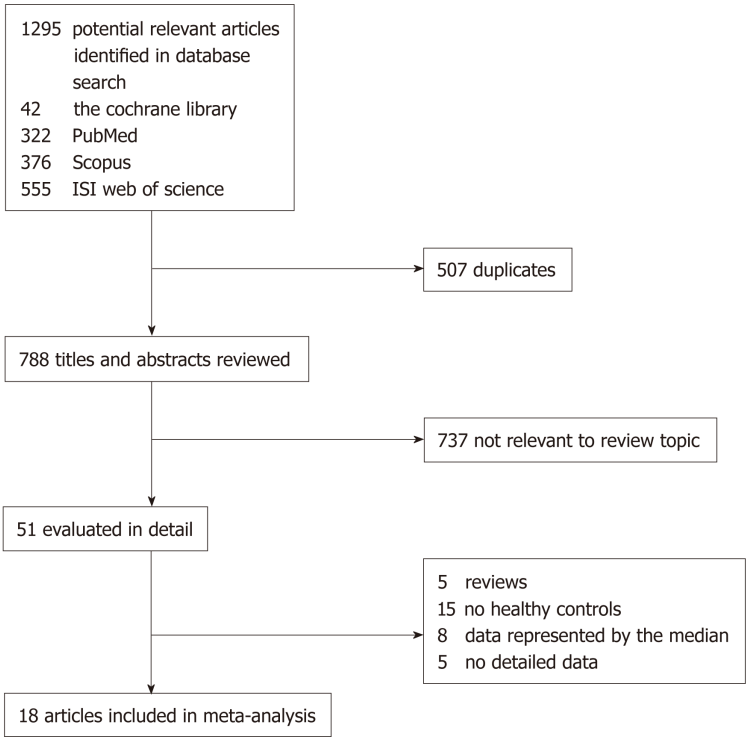


Figure 1 Flow chart of article selection for meta-analysis.

ethnicity, the irisin level was only higher in obese individuals than in controls in Africa, while there were no significant differences in European, Asian, or American populations. These results indicate that genetic differences can influence specific hormone levels such as those of irisin. Weight stratification in the Asian population based on different BMI criteria from other regions may also lead to no significance of the subgroup analysis. Besides the above, gender is another interesting aspect. Murawska-Cialowicz *et al*[38] found that the level of irisin at baseline was higher in men than in women and after a 3-mo CrossFit training program, the changes of irisin level between women and men did not have a uniform trend[38], while in obese children, there was no evidence for differences of irisin levels between genders[37].

To our knowledge, this study is the first meta-analysis that systematically assessed circulating irisin in obese people, yet some limitations should be noted. First, in the above articles, how to choose the criteria to judge obesity is still in question. Although most studies chose to use BMI as the criterion of obesity, Mehrabian *et al*[27] suggested that body fat percentage is a better indicator of total adiposity compared to BMI for some individuals with normal weight obesity. Second, due to different methods, we cannot analyze whether the quality of serum or plasma samples has a decisive impact on the test results. For human FNDC5 does not have a canonical ATA translation start and some reports questioned that many human irisin antibodies used in commercial ELISA kits may lack necessary specificity[40], it is hard to determine the reliability of the results detected with the kits of many brands, although mass spectrometry has clearly demonstrated the existence of human irisin. Third, there were differences in the number of research subjects in different regions or countries; the majority of those surveyed were in Asia and Europe, while relatively few were in Africa. A larger sample survey is needed in the future for a more reliable result. Additionally, influences of the intensity and time of exercise on circulating irisin levels are also of interest, since irisin is a myokine associated with exercise. Future studies are required to investigate whether circulating irisin could predict the risk of obesity. Moreover, studies on the effects of exercise, lifestyle, and weight loss on the irisin level and related prospective studies are also needed.

In conclusion, our meta-analysis provides evidence that circulating irisin is higher in obese individuals compared to healthy controls and that circulating irisin levels seem to be affected by ethnicity and age. More investigations are necessary to clarify the association between the circulating irisin levels and overweight/obesity.

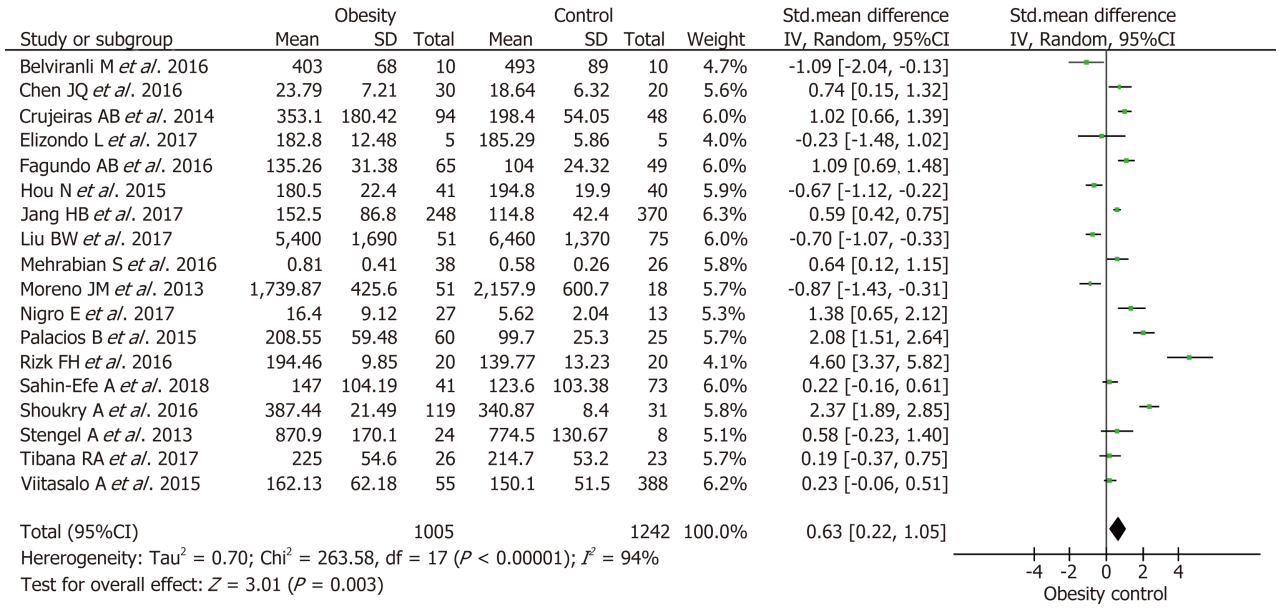


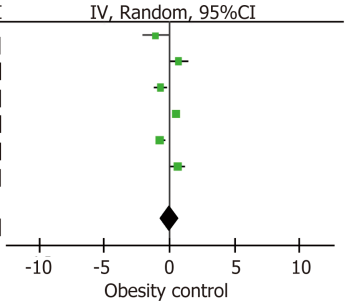
Figure 2 Forest plot of meta-analysis of the association between irisin and obesity.

A

Study or subgroup	Obesity Mean	Obesity SD	Obesity Total	Control Mean	Control SD	Control Total	Weight	Std.mean difference IV, Random, 95%CI
Belviranli M *et al*. 2016	403	68	10	493	89	10	13.2%	-1.09 [-2.04, -0.13]
Chen JQ *et al*. 2016	23.79	7.21	30	18.64	6.32	20	16.3%	0.74 [0.15, 1.32]
Hou N *et al*. 2015	180.5	22.4	41	194.8	19.9	40	17.3%	-0.67 [-1.12, -0.22]
Jang HB *et al*. 2017	152.5	86.8	248	114.8	42.4	370	18.7%	0.59 [0.42, 0.75]
Liu BW *et al*. 2017	5,400	1,690	51	6,460	1,370	75	17.8%	-0.70 [-1.07, -0.33]
Mehrabian S *et al*. 2016	0.81	0.41	38	0.58	0.26	26	16.8%	0.64 [0.12, 1.15]
Total (95%CI)			418			541	100.0%	-0.05 [-0.67, 0.58]

Hererogeneity: Tau^2 = 0.54; Chi^2 = 70.24, df = 5 (P < 0.00001); I^2 = 93%

Test for overall effect: Z = 0.14 (P = 0.89)

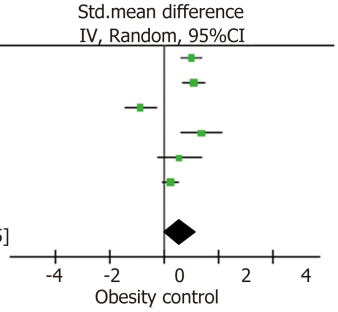


B

Study or subgroup	Obesity Mean	Obesity SD	Obesity Total	Control Mean	Control SD	Control Total	Weight	Std.mean difference IV, Random, 95%CI
Crujeiras AB *et al*. 2014	353.1	180.42	94	198.4	54.05	48	18.1%	1.02 [0.66, 1.39]
Fagundo AB *et al*. 2016	135.26	31.38	65	104	24.32	49	17.8%	1.09 [0.69, 1.48]
Moreno JM *et al*. 2013	1,739.87	425.6	51	2,157.9	600.7	18	16.5%	-0.87 [-1.43, -0.31]
Nigro E *et al*. 2017	16.4	9.12	27	5.62	2.04	13	14.9%	1.38 [0.65, 2.12]
Stengel A *et al*. 2013	870.9	170.1	24	774.5	130.67	8	14.1%	0.58 [-0.23, 1.40]
Viitasalo A *et al*. 2015	162.13	62.18	55	150.1	51.5	388	18.6%	0.23 [-0.06, 0.51]
Total (95%CI)			316			524	100.0%	0.57 [-0.02, 1.15]

Hererogeneity: Tau^2 = 0.46; Chi^2 = 48.17, df = 5 (P < 0.00001); I^2 = 90%

Test for overall effect: Z = 1.90 (P = 0.06)

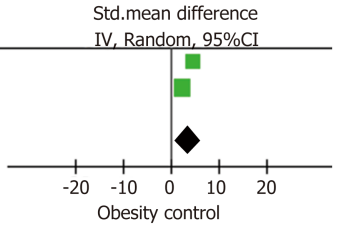


C

Study or subgroup	Obesity Mean	Obesity SD	Obesity Total	Control Mean	Control SD	Control Total	Weight	Std.mean difference IV, Random, 95%CI
Rizk FH *et al*. 2016	194.46	9.85	20	139.77	13.23	20	46.6%	4.60 [3.37, 5.82]
Shoukry A *et al*. 2016	387.44	21.49	119	340.87	8.4	31	53.4%	2.37 [1.89, 2.85]
Total (95%CI)			139			51	100.0%	3.41 [1.23, 5.59]

Hererogeneity: Tau^2 = 2.25; Chi^2 = 10.95, df = 1 (P < 0.00009); I^2 = 91%

Test for overall effect: Z = 3.07 (P = 0.002)



D

Study or subgroup	Obesity Mean	Obesity SD	Obesity Total	Control Mean	Control SD	Control Total	Weight	Std.mean difference IV, Random, 95%CI
Elizondo L *et al*. 2017	182.8	12.48	5	185.29	5.86	5	19.8%	-0.23 [-1.48, 1.02]
Palacios B *et al*. 2015	208.55	59.48	60	99.7	25.3	25	26.3%	2.08 [1.51, 2.64]
Sahin-Efe A *et al*. 2018	147	104.19	41	123.6	103.38	73	27.6%	0.22 [-0.16, 0.61]
Tibana RA *et al*. 2017	225	54.6	26	214.7	53.2	23	26.3%	0.19 [-0.37, 0.75]
Total (95%CI)			132			126	100.0%	0.61 [-0.38, 1.61]

Hererogeneity: Tau^2 = 0.90; Chi^2 = 33.61, df = 3 (P < 0.00001); I^2 = 91%

Test for overall effect: Z = 1.21 (P = 0.23)

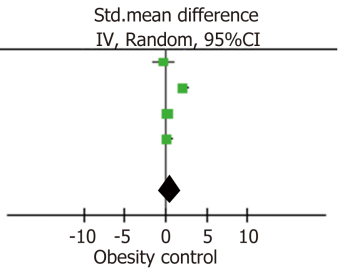


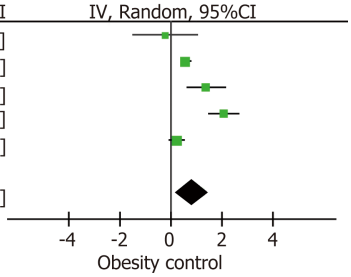
Figure 3 Forest plot of irisin in obese patients in different racial groups. A: Forest plot of irisin in obese patients in Asia; B: Forest plot of irisin in obese patients in Europe; C: Forest plot of irisin in obese patients in Africa; D: Forest plot of irisin in obese patients in America.

A

Study or subgroup	Obesity Mean	SD	Total	Control Mean	SD	Total	Weight	Std.mean difference IV, Random, 95%CI
Elizondo L *et al*. 2017	182.8	12.48	5	185.29	5.86	5	11.7%	-0.23 [-1.48, 1.02]
Jang HB *et al*. 2017	152.5	86.8	248	114.8	42.4	370	25.3%	0.59 [0.42, 0.75]
Nigro E *et al*. 2017	16.4	9.12	27	5.62	2.04	13	18.2%	1.38 [0.65, 2.12]
Palacios B *et al*. 2015	208.55	59.48	60	99.7	25.3	25	20.6%	2.08 [1.51, 2.64]
Viitasalo A *et al*. 2015	162.13	62.18	55	150.1	51.5	388	24.3%	0.23 [-0.06, 0.51]
Total (95%CI)			395			801	100.0%	0.89 [0.28, 1.43]

Hererogeneity: Tau^2 = 0.33; Chi^2 = 38.95, df = 4 (P < 0.00001); I^2 = 90%

Test for overall effect: Z = 2.92 (P = 0.004)



B

Study or subgroup	Obesity Mean	SD	Total	Control Mean	SD	Total	Weight	Std.mean difference IV, Random, 95%CI
Belviranli M *et al*. 2016	403	68	10	493	89	10	6.9%	-1.09 [-2.04, -0.13]
Chen JQ *et al*. 2016	23.79	7.21	30	18.64	6.32	20	7.8%	0.74 [0.15, 1.32]
Crujeiras AB *et al*. 2014	353.1	180.42	94	198.4	54.05	48	8.1%	1.02 [0.66, 1.39]
Fagundo AB *et al*. 2016	135.26	31.38	65	104	24.32	49	8.1%	1.09 [0.69, 1.48]
Hou N *et al*. 2015	180.5	22.4	41	194.8	19.9	40	8.0%	-0.67 [-1.12, -0.22]
Liu BW *et al*. 2017	5,400	1,690	51	6,460	1,370	75	8.1%	-0.70 [-1.07, -0.33]
Mehrabian S *et al*. 2016	0.81	0.41	38	0.58	0.26	26	7.9%	0.64 [0.12, 1.15]
Moreno JM *et al*. 2013	1,739.87	425.6	51	2,157.9	600.7	18	7.8%	-0.87 [-1.43, -0.31]
Rizk FH *et al*. 2016	194.46	9.85	20	139.77	13.23	20	6.2%	4.60 [3.37, 5.82]
Sahin-Efe A *et al*. 2018	147	104.19	41	123.6	103.38	73	8.1%	0.22 [-0.16, 0.61]
Shoukry A *et al*. 2016	387.44	21.49	119	340.87	8.4	31	7.9%	2.37 [1.89, 2.85]
Stengel A *et al*. 2013	870.9	170.1	24	774.5	130.67	8	7.3%	0.58 [-0.23, 1.40]
Tibana RA *et al*. 2017	225	54.6	26	214.7	53.2	23	7.8%	0.19 [-0.37, 0.75]
Total (95%CI)			610			441	100.0%	0.57 [-0.03, 1.18]

Hererogeneity: Tau^2 = 1.13; Chi^2 = 221.15, df = 12 (P < 0.00001); I^2 = 95%

Test for overall effect: Z = 1.87 (P = 0.06)

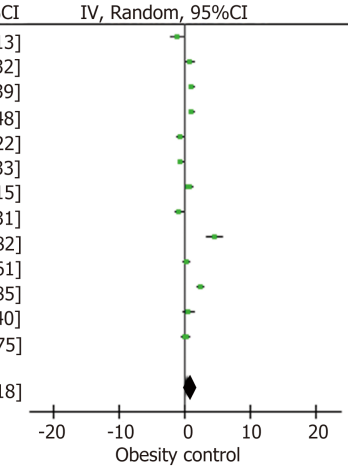


Figure 4 Forest plot of irisin in obese patients in children and adults. A: Forest plot of irisin in obese children *vs* nonobese children; B: Forest plot of irisin in obese adults *vs* nonobese adults.

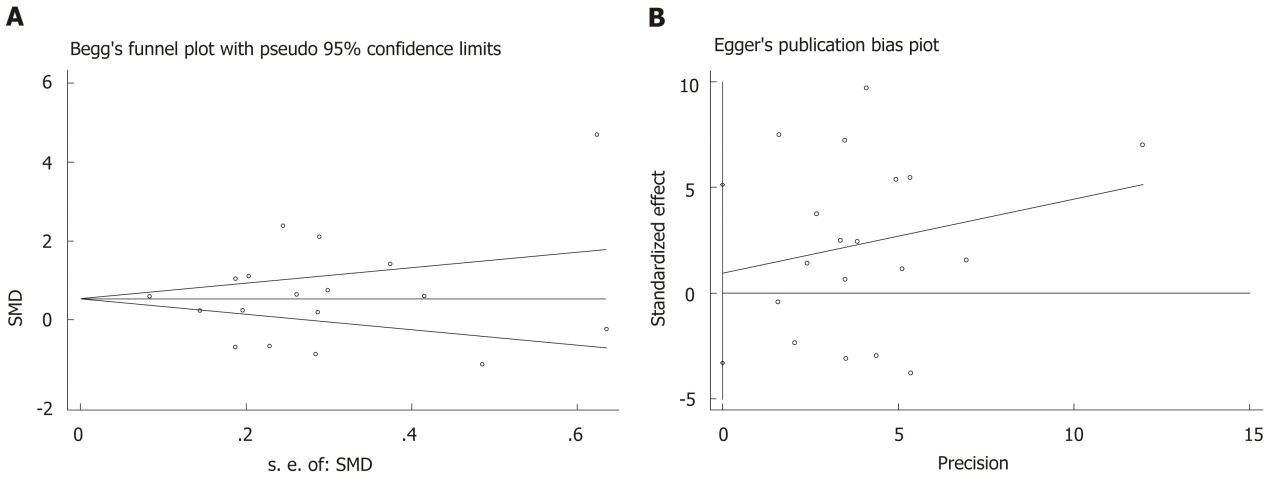


Figure 5 Analysis of publication bias. A: Begg's funnel plot had the expected funnel shape (Begg's test P = 0.544); B: Egger's publication bias plot (Egger's test P = 0.65).

ARTICLE HIGHLIGHTS

Research background

Overweight/obesity has been a global health challenge and irisin as a novel myokine is reported to play an important role in the development of metabolism dysfunction and obesity, however, the exact relationship between irisin and overweight/obesity remains unclear.

Research motivation

Many studies on the results of circulating irisin levels in overweight/obesity people are incon-

sistent, which has puzzled us in confirming the role of irisin in overweight/obesity, thus, it is necessary to do such an analysis to clarify the relationship between them.

Research objectives
The main objective was to extract available data from studies and clarify the relationship between irisin and overweight/obesity.

Research methods
We searched Cochrane Library, MEDLINE, SCOPUS, and the ISI Web of Science to retrieve all of the studies associated with circulating irisin levels and overweight/obesity. We estimated standard mean difference values and 95% confidence intervals and used meta-analysis methodology to get final results.

Research results
A total of 18 studies were included in this meta-analysis containing 1005 cases and 1242 controls. The overall analysis showed that the circulating irisin level in overweight/obese people was higher than that in overall healthy controls. In the subgroup analysis by ethnicity, the irisin level was higher in overweight/obese people than that in controls in Africa. In addition, in a subgroup analysis by age, the results showed that obese children exhibited a higher irisin level than controls. Studies of larger population samples are needed to better explore the relationship between irisin and overweight/obesity.

Research conclusions
This study integrated the existing data to show that the circulating irisin levels in overweight/obese people was higher than those in healthy controls overall, and explored the potential of irisin as a predictive factor for overweight/obesity.

Research perspectives
More studies on the effects of exercise, lifestyle, and weight loss on the irisin level and related prospective studies are needed.

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