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Irisin plays an important role in the outcomes of newly diagnosed prediabetes in adults in Guiyang, China

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ABSTRACT

Aims/Introduction: To explore the potential role of irisin in the outcomes of newly diagnosed prediabetes.

Materials and Methods: Data were obtained from the Guiyang subcenter of the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study. A total of 2,530 participants had newly diagnosed prediabetes at baseline and completed follow up. The nested 1:1 case–control study included 161 participants who developed diabetes mellitus at follow up, and 161 age- and sex-matched controls. The follow-up study included 86 matched case–control pairs. Fasting serum irisin levels were measured using enzyme-linked immunosorbent assay.

Results: Baseline serum irisin levels were higher in the cases than in the controls ($P = 0.002$); high baseline serum irisin levels were an independent risk factor for the development of diabetes (odds ratio 1.235, 95% confidence interval 1.025–1.488). After adjustment for age, sex, body mass index, glycated hemoglobin (HbA1c), smoking, exercise, and family history of diabetes, subjects in the highest quartile of irisin levels had a higher risk of diabetes than those in the lowest quartile (odds ratio 3.065, 95% confidence interval 1.511–6.218). The extent of decrease in irisin levels during follow-up was greater in the cases than in the controls ($P < 0.001$). Baseline serum irisin levels were positively correlated with the extent of decrease in irisin during follow-up ($r = 0.773$, $P < 0.001$). After adjustment for confounding factors, subjects with a decrease of irisin above the median had much higher risk for diabetes (odds ratio 5.077, 95% confidence interval 2.112–12.206).

Conclusions: Irisin might play an important role in the outcomes of newly diagnosed prediabetes in adults in Guiyang, and can predict the risk for developing diabetes in these individuals.

INTRODUCTION

Patients with diabetes mellitus are increasing in number in China with the acceleration of population aging and changes in lifestyle. Diabetes has become a severe challenge for public health in China and around the world. The prevalence of diabetes in Chinese adults has risen to 11.6% according to recent epidemiology surveys, and the prevalence of prediabetes has reached 50.1%. It was found that one out of every four people with diabetes around the world was Chinese[1,2]. If we could identify those individuals who tend to develop diabetes and take effective interventions, it would be possible to redress abnormal glucose metabolism and prevent the disease.

Irisin is a kind of myokine relying on peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α), which can upregulate the expression of fibronectin type III domain-containing protein 5. The *FNDC5* gene encodes a protein secreted as irisin after being proteolytically cleaved[3]. Many studies have shown that irisin could increase the expression of uncoupling protein 1, induce the browning of white adipose cells, and increase thermogenesis and energy expenditure[3,4]. Furthermore,

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investigators have shown that irisin increases glucose uptake in muscle cells, inhibits hepatic gluconeogenesis and glycogenolysis, and promotes glycogen synthesis[5–7]. Thus, irisin is considered to be able to contribute to glucose homeostasis.

However, findings on whether irisin is related to the development of diabetes are not consistent. Several studies showed that circulating irisin levels in patients with diabetes were lower than in individuals without diabetes[8–11]. In contrast, other studies showed that circulating irisin levels were higher in diabetes patients than in individuals without diabetes[12–14], and were positively correlated with fasting plasma glucose levels[15,16]. In addition, other investigators showed that high circulating irisin levels indicated high risks of insulin resistance and diabetes[17,18], whereas another study showed that irisin levels did not predict the risk of diabetes[19]. The inconsistency of these studies highlights the need for a more accurate detection method for irisin and a well-designed prospective study to ascertain its role in the development of diabetes[20]. To date, there has been no study to clarify the relationship between irisin and the outcomes of newly diagnosed prediabetes, and whether it can be a predictor of diabetes in these individuals. Based on this objective, the present study includes two parts: (i) a nested case–control study, to show the underlying role of irisin in the development of diabetes; and (ii) a follow-up study, to investigate the changes of serum irisin levels in different outcomes.

METHODS

Study design

The present study was embedded in the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study, which is a large community-based prospective cohort study in people aged ≥40 years[21]. Our participants came from the Guiyang research subcenter. A total of 10,140 adults were recruited from the Yunyan community, Guiyang, China, from May to August 2011. Of those, 10,015 participants completed physical examination, laboratory measurements and questionnaires including medical history, physical activities, and smoking and alcohol drinking status, and 7,570 (75.59%) of these participants were followed up in July 2014. The study was approved by the Human Research Ethics Committee of the Affiliated Hospital of Guizhou Medical University, and conformed to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Nested case–control study

A total of 2,530 participants were newly diagnosed with prediabetes at baseline and completed the 3-year follow up. Participants with a history of hypertension, stroke, cardiovascular disease, liver or kidney dysfunction, cancer, autoimmune diseases, acute or chronic infection, or any medication use at baseline were excluded. Of the remaining 1,238 participants, 169 developed diabetes at follow up. Finally, 161 participants were included in the case group due to eight participants lacking samples. We randomly matched a control for each case from risk sets who had not developed diabetes at follow up. Case–control pairs were individually matched by sex and age (±2 years).

Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L or 2-h post-load plasma glucose ≥11.1 mmol/L. Prediabetes included impaired fasting glucose and impaired glucose tolerance. Impaired fasting glucose was defined as fasting plasma glucose 6.1–6.9 mmol/L and 2-h post-load plasma glucose <7.8 mmol/L; impaired glucose tolerance was defined as fasting plasma glucose <7.0 mmol/L and 2-h post-load plasma glucose 7.8–11.0 mmol/L, according to the 1999 World Health Organization criteria[22,23].

Follow-up study

For 161 matched case–control pairs, those pairs were excluded as long as one of them had cardiovascular disease, stroke, hypertension, liver or kidney dysfunction, cancer, autoimmune diseases, acute or chronic infection, or any medication use during the 3-year follow-up period, or lacked samples. Finally, 86 pairs were included in the follow-up study.

Demographic factors and anthropometric measurements

Information on smoking, including the average number of cigarettes per day and duration, was collected from the self-reported data of each participant. Smoking was defined as having smoked ≥100 cigarettes in one's lifetime, regardless of "ever" or "current" smoking[24]. Alcohol drinking was defined as consuming ≥30 grams per week of alcohol for at least 1 year[25]. Exercise was defined as moderate-intensity activities ≥150 min per week or vigorous-intensity activities ≥75 min per week or moderate- and vigorous-intensity activities ≥150 min per week[26].

Anthropometric measurements including height, weight, waist circumference, hip circumference and blood pressure were evaluated by uniformly trained staff. Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). The waist-to-hip ratio was calculated by dividing the waist circumference by hip circumference. Blood pressure was measured three times after 5 min of rest, and the results were averaged.

Biochemical measurements

Venous blood was collected from all participants after at least 10 h overnight fast, and subsequently, a 75-g oral glucose tolerance test was carried out. Blood samples were obtained again 2 h later. Plasma glucose was determined by the hexokinase method within 4 h (ADVIA2400, Siemens, Erlangen, Germany). Within 1 h, serums were separated, and then aliquoted and stored at −80°C until further analysis. Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels were determined using an autoanalyzer (ARCHITECT ci16200l Abbott Laboratories, Chicago, IL, USA). The 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation was used to calculate the estimated glomerular filtration rate. Fasting insulin levels were determined by the chemiluminescence method.

Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as follows: fasting plasma glucose level (mmol/L) × fasting insulin level (mU/L) / 22.5. Homeostatic model assessment of β-cell function (HOMA-β) was calculated as follows: 20 × fasting insulin level (mU/L) / (fasting plasma glucose level (mmol/L) − 3.5).

Serum irisin measurement

Fasting serum irisin levels were measured using the enzyme-linked immunosorbent assay kit (EK-067-29, Phoenix Pharmaceuticals Inc, Burlingame, CA, USA) considered to be the best available irisin enzyme-linked immunosorbent assay kit[20]. The detection range was 0.1–1,000 ng/mL, and the intra- and interassay variations were <10% and <15%, respectively.

Statistical analysis

SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used to carry out the statistical analyses. The normality of distributions was evaluated with the Shapiro–Wilk test. Data are presented as the mean ± standard deviation or median (interquartile range). In the nested case–control study, comparison between the cases and controls was carried out with paired Student's *t*-test or paired Wilcoxon signed-rank test for continuous variables, and McNemar's test for categorical variables. The Mann–Whitney test was carried out to compare the difference in serum irisin levels between the two different exercise statuses. Spearman's rank correlation was carried out to evaluate the associations between serum irisin levels and clinical parameters. Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the independent risk factors for the development of diabetes in newly diagnosed prediabetes, and the risk of diabetes in relation to baseline irisin quartiles. In the follow-up study, repeated measures analysis of variance (ANOVA) was used to compare the changes in serum irisin levels between cases and controls and over time. The difference in the levels of serum irisin between the baseline and follow up in each group was compared using paired Student's *t*-test or paired Wilcoxon signed-rank test. Spearman's rank correlation was carried out to evaluate the association between baseline serum irisin levels and the extent

Table 1 | Characteristics of participants at baseline

	Cases (n = 161)	Controls (n = 161)	P
Age (years)	59.2 ± 6.8	59.1 ± 6.8	0.262
Male, n (%)	41 (25.5%)	41 (25.5%)	1.000
BMI (kg/m^2)	24.7 ± 3.1	23.8 ± 3.0	0.009
Waist circumference (cm)	85.5 ± 8.5	83.7 ± 8.4	0.042
Hip circumference (cm)	93.0 (88.6–96.9)	92.0 (87.6–96.2)	0.343
Waist-to-hip ratio	0.92 (0.88–0.96)	0.91 (0.87–0.94)	0.077
Systolic blood pressure (mmHg)	119 (110–133)	117 (109–126)	0.040
Diastolic blood pressure (mmHg)	76 (72–83)	75 (70–82)	0.180
Fasting plasma glucose (mmol/L)	6.1 (5.7–6.5)	6.3 (6.2–6.5)	<0.001
2-h post-load plasma glucose (mmol/L)	9.3 (8.3–10.0)	7.0 (6.2–7.6)	<0.001
Creatinine (μmol/L)	66.1 (57.7–72.9)	65.7 (58.0–72.1)	0.644
eGFR (mL·min^{-1}·[1.73 m^2]$^{-1}$)	92.5 (84.1–99.2)	92.3 (84.1–100.6)	0.596
HDL cholesterol (mmol/L)	1.2 (1.0–1.4)	1.2 (1.0–1.5)	0.548
LDL cholesterol (mmol/L)	2.7 ± 1.0	2.5 ± 0.9	0.023
Total cholesterol (mmol/L)	4.8 (4.1–5.7)	4.5 (3.6–5.3)	0.020
Triglycerides (mmol/L)	1.5 (1.1–2.3)	1.2 (0.9–1.9)	0.003
ALT (IU/L)	20.0 (13.0–27.0)	16.0 (11.0–21.5)	0.001
AST (IU/L)	22.0 (16.0–27.0)	18.0 (14.0–23.0)	<0.001
HbA1c (%)	6.2 (6.0–6.5)	6.1 (5.9–6.4)	0.002
Fasting insulin (mU/L)	9.0 (6.7–11.4)	8.1 (6.2–11.1)	0.173
HOMA-IR	2.42 (1.82–3.21)	2.29 (1.71–3.04)	0.477
HOMA-β	68.03 (50.94–89.73)	60.13 (43.80–79.00)	0.001
Irisin (ng/mL)	11.434 (9.373–13.224)	10.236 (8.429–12.403)	0.002
Smoking	27 (16.8%)	34 (21.1%)	0.265
Drinking	13 (8.1%)	19 (11.8%)	0.307
Exercise	33 (20.5%)	34 (21.1%)	1.000
Family history of diabetes	32 (19.9%)	30 (18.6%)	0.892

Data are expressed as the mean ± standard deviation or median (interquartile range) for continuous variables, and n (%) for categorical variables.
ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance index; LDL, low-density lipoprotein.

of decrease in irisin during follow up. The ORs and 95% CIs for the development of diabetes in relation to the extent of decrease in serum irisin levels were assessed using binary logistic regression analysis. A two-sided *P*-value <0.05 was considered significant.

RESULTS

Nested case–control study

Characteristics of participants at baseline

Characteristics of participants at baseline are presented in Table 1. No differences in age, sex, hip circumference, waist-to-hip ratio, diastolic blood pressure, serum creatinine, estimated glomerular filtration rate, HDL cholesterol, fasting insulin levels, HOMA-IR, smoking, alcohol drinking, exercise or family history of diabetes were observed between the two groups. BMI, waist circumference, systolic blood pressure, and levels of 2-h post-load plasma glucose, LDL cholesterol, total cholesterol, triglycerides, alanine transaminase, aspartate aminotransferase, glycated hemoglobin (HbA1c), HOMA-β and irisin were higher in the cases than in controls ($P < 0.05$ or $P < 0.01$), whereas fasting plasma glucose levels were lower in the cases ($P < 0.001$). In addition, no differences in serum irisin levels between the two different exercise statuses were observed in the case group, the control group or total participants (Figure S1).

Correlations of serum irisin levels with clinical parameters at baseline

Spearman's correlation analyses showed that serum irisin levels were positively correlated with age ($r = 0.191$, $P = 0.001$), systolic blood pressure ($r = 0.134$, $P = 0.016$) and 2-h post-load plasma glucose ($r = 0.161$, $P = 0.004$; Figure 1). Irisin was not associated with BMI, waist circumference, hip circumference, waist-to-hip ratio, diastolic blood pressure, estimated glomerular filtration rate or levels of fasting plasma glucose; creatinine; HDL, LDL or total cholesterol; triglycerides; alanine transaminase; aspartate aminotransferase; HbA1c; fasting insulin; or HOMA-IR or HOMA-β. Furthermore, the cases and controls were analyzed separately. It was found that the correlation between serum irisin levels and age was not significant in the case group ($P = 0.228$), whereas their positive relationship was closer in the control group ($r = 0.281$, $P < 0.001$).

Analysis of independent risk factors for diabetes

The independent risk factors for the development of diabetes in newly diagnosed prediabetes are presented in Figure 2. Conditional logistic regression analysis indicated that BMI, 2-h post-load plasma glucose, aspartate aminotransferase and irisin were independent risk factors.

Serum irisin levels and risk of diabetes

The risk of diabetes according to irisin quartiles is presented in Table 2. Conditional logistic regression analysis showed that participants with higher levels of serum irisin had a significantly higher risk of diabetes. This association remained significant after adjustment for age, sex, BMI, HbA1c, smoking, exercise, family history of diabetes (OR 3.065, 95% CI 1.511–6.218) and stratification by exercise status (Table S2).

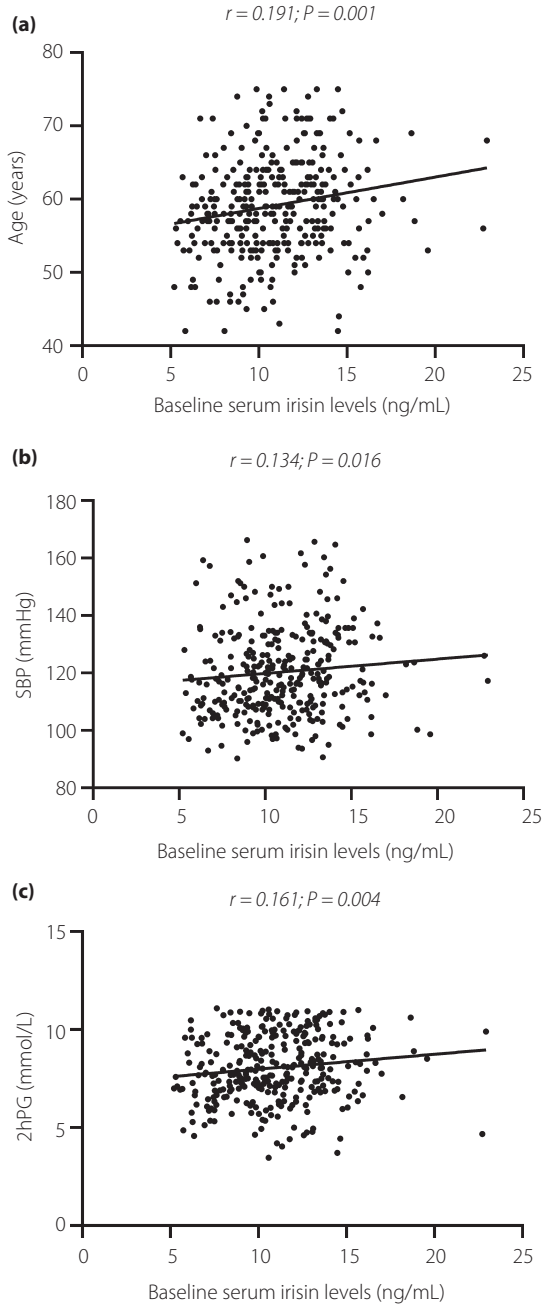

Figure 1 | Correlations of serum irisin levels with age, systolic blood pressure (SBP) and 2-h post-load plasma glucose (2hPG) at baseline.

Follow-up study

Changes in serum irisin levels between the cases and controls

The changes in serum irisin levels between the cases and controls are presented in Figure 3a. Repeated measures ANOVA showed a significant difference between the two groups; the

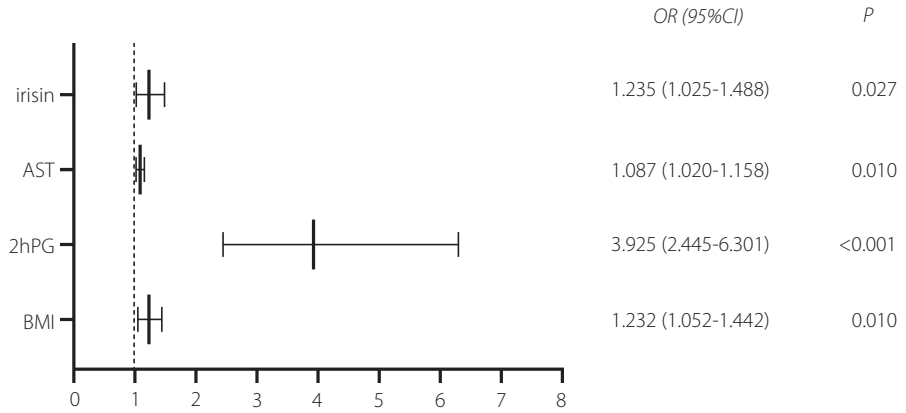

Figure 2 | Analysis of independent risk factors for diabetes. 2hPG, 2-h post-load plasma glucose; AST, aspartate aminotransferase; BMI, body mass index.

Table 2 | Odds ratios and 95% confidence intervals for the development of diabetes in relation to serum irisin quartiles

	Irisin (ng/mL)				
	Q1 (n = 80) 5.206–8.944	Q2 (n = 80) 8.945–10.749	Q3 (n = 82) 10.750–12.815	Q4 (n = 80) 12.816–22.927	P for trend
Model 1	1	1.474 (0.778–2.794)	2.143 (1.140–4.028)*	2.786 (1.405–5.523)**	0.011
Model 2	1	1.474 (0.778–2.794)	2.143 (1.140–4.028)*	2.786 (1.405–5.523)**	0.011
Model 3	1	1.523 (0.791–2.931)	2.089 (1.103–3.954)*	3.065 (1.511–6.218)**	0.008

Model 1 was unadjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, body mass index, glycated hemoglobin, smoking, exercise, and family history of diabetes. *P < 0.05. **P < 0.01.

extent of decrease in serum irisin levels in the cases was greater than that in the controls (P < 0.001). Serum irisin levels were significantly lower in the cases at follow up (P < 0.001). Furthermore, the controls were divided into two subgroups according to the state of glucose tolerance at follow up: either remaining prediabetic or reverting to normal glucose tolerance. A significant decrease was observed only in those controls remaining prediabetic (P < 0.001), not in the other subgroup (P = 0.661; Figure 3b).

Correlation of baseline serum irisin levels with the extent of decrease in irisin during the follow-up period

Serum irisin levels in a total of 134 participants decreased at follow up. Spearman's correlation analysis showed that baseline serum irisin levels were positively correlated with the extent of decrease in irisin during the follow-up period (r = 0.773, P < 0.001; Figure 4).

The extent of decrease in irisin and the risk of diabetes

A total of 134 participants who experienced a decrease in serum irisin levels during the follow-up period were divided into two equal groups according to the median of the decrease – the significant group and the non-significant group. Binary logistic regression analysis showed that participants in the significant group had a higher risk for developing diabetes than the non-significant group, even after adjustment for age, sex and the change values of BMI; waist circumference; HbA1c; systolic and diastolic blood pressure; HDL, LDL and total cholesterol; and triglycerides (OR 5.077, 95% CI 2.112–12.206, P < 0.001; Table S1).

DISCUSSION

In the present study, we found that baseline serum irisin levels were higher in diabetes-developing cases compared with controls in individuals with newly diagnosed prediabetes. High irisin levels were an independent risk factor for diabetes development. In addition, the decrease of irisin in diabetes-developing cases was greater than that in controls during the follow-up period, and baseline serum irisin levels were positively correlated with the extent of decrease in irisin. These findings suggest that irisin is related to the outcomes of newly diagnosed prediabetes.

In 2012, Boström *et al.*[3] found a new hormone containing 112 amino acids. This hormone was confirmed to improve the glucose tolerance of mice with obesity and insulin resistance induced by a high-fat diet[3]. Since then, more investigators have paid attention to the relationship between this hormone and energy metabolism. Recent studies have shown that irisin

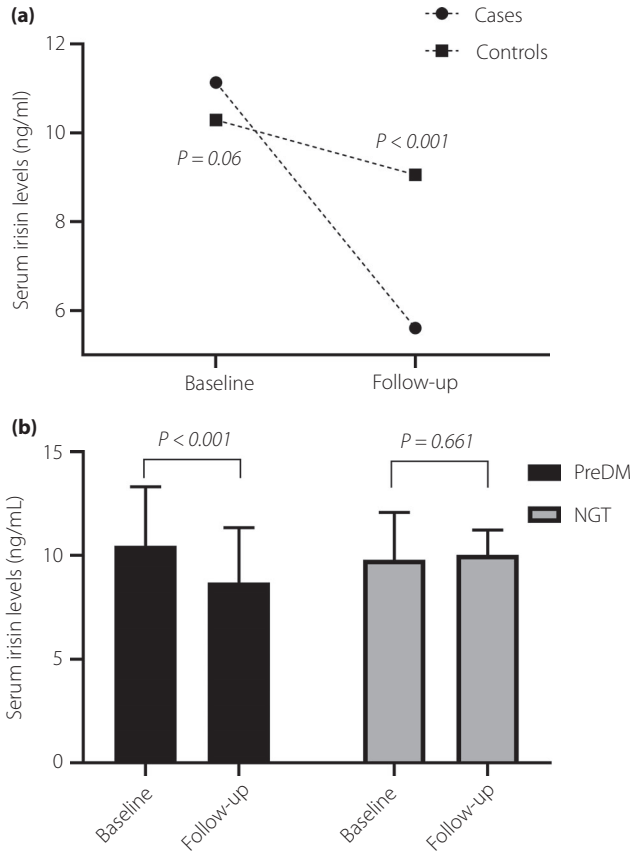

Figure 3 | Changes in serum irisin levels in each group. (a) The changes in serum irisin levels between cases and controls. (b) Comparison of serum irisin levels between baseline and follow-up in subjects remaining prediabetic (PreDM; $n = 63$), and in individuals reverting to normal glucose tolerance (NGT; $n = 23$) using the paired Wilcoxon signed-rank test and paired Student's *t*-test, respectively.

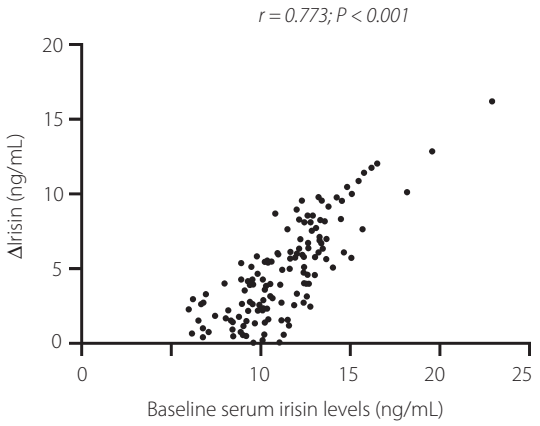

Figure 4 | Correlation of baseline serum irisin levels with the extent of decrease in irisin during the follow-up period.

improved insulin sensitivity, promoted pancreatic β-cells' survival and protected them from apoptosis, induced insulin synthesis and secretion, and increased the expression of anorexigenic genes in mice models[6,27,28]. Thus, irisin was considered as a potential target for diabetes intervention. A dietary intervention study carried out in obese patients including two sequential periods, a 2-month dietary intervention period and a 4-month follow-up period, showed that HOMA-IR in participants with circulating irisin levels above the median was higher than in those with lower circulating irisin levels, whether at baseline or follow up. Furthermore, higher baseline circulating irisin levels predicted a higher risk of insulin resistance at the second period[17]. A study in Korea showed that a high serum irisin level at baseline was an independent risk factor for the development of diabetes[18]. Another cross-sectional study including 151 white Americans and African Americans found that circulating irisin levels in individuals with metabolic syndrome (MetS) were higher than those without MetS, and higher circulating irisin levels indicated higher risks for MetS and elevated fasting plasma glucose, which is a component of MetS[15]. However, a nested case–control study from the Veterans Affairs Normative Aging Study cohort showed that irisin was not a predictor for diabetes[19]. These inconsistent conclusions might be due to different races. There are differences in muscle mass and body fat content among different races[29]. Furthermore, skeletal muscle and adipose tissue are the main sources of irisin. In addition, there are differences in body composition due to sex. Women have a higher proportion of fat, whereas men have a higher proportion of muscle[30]. The study in Korea included just 37.6% men, whereas the nested case–control study from the Veterans Affairs Normative Aging Study cohort was all men. Therefore, the difference of sex composition might also lead to the inconsistent conclusions. In addition, the blood glucose level, degree of obesity, accompanying disease status and concomitant medications might also cause the inconsistency of conclusions in these studies.

The present findings showed that high baseline serum irisin levels are an independent risk factor for diabetes in newly diagnosed prediabetes, and that serum irisin levels are positively correlated with systolic blood pressure and 2-h post-load plasma glucose at baseline, similar to the findings of previous studies[15,16,18]. It is speculated that high serum irisin levels at baseline are likely a compensatory increase in order to maintain glucose homeostasis[15,17,31]. Interestingly, we observed that serum irisin levels are positively correlated with age, a finding different from the results of several previous studies[8,32–34], but similar to that found by Jang *et al.*[16] and Hisamatsu *et al.*[35] Another study compared the serum irisin levels of healthy centenarians, young healthy controls and young patients with acute myocardial infarction, and found that the serum irisin levels of healthy centenarians were highest[36]. Although muscle mass and bone are gradually lost with aging[37], aging does not affect the secretion of irisin[5,32]. It was found that irisin could induce hypertrophy and improve grip strength of uninjured muscle, increase regeneration of injured muscle and decrease the loss of

skeletal muscle mass[38]. A recent study showed that irisin is a marker of muscle function improvement in elderly individuals[39]. Therefore, we assume that serum irisin levels increasing with age might be an adaptive response to overcome age-related muscle atrophy. However, this adaptive response might be related to the pathophysiological state of subjects, because when we analyze the control group alone, we found that the positive correlation between serum irisin levels and age is closer, whereas their relationship was not significant in the case group. We also found that irisin was not related to fasting insulin levels or HOMA-IR, which agrees with several previous studies[40,41], although one study showed that circulating irisin levels were positively correlated with fasting insulin levels and HOMA-IR in individuals with or without diabetes[42]. This discrepancy might be due to the different states of glucose metabolism and obesity. This might also show that the extrapancreatic role of irisin is more important than its effect on pancreatic β-cells in glucose homeostasis. Furthermore, the present study found that the extent of decrease in serum irisin levels in participants who subsequently developed diabetes was greater than that in controls during the 3-year follow-up period, although their baseline levels were higher; as in previous studies, serum irisin levels were significantly lower in patients with diabetes than in controls at follow up[8,42–45]. Further analysis showed that the extent of decrease in irisin during follow up was positively correlated with the levels of serum irisin at baseline, and participants with a significant decrease in irisin had much higher risk for diabetes compared with those with a non-significant decrease. In addition, levels of serum irisin decreased only in controls who remained prediabetic at follow up, but not in those reverting to normal glucose tolerance, when the controls were divided into the above subgroups. These findings suggest that high serum irisin levels at baseline are a compensatory increase, and the occurrence of diabetes might be related to impaired compensatory ability.

In the present study, we observed the relationship between irisin and the outcomes of newly diagnosed prediabetes, and different changes of serum irisin levels in different outcomes. One strength of the present study is that selection bias was reduced and comparability was increased, because cases and controls were nested from the same cohort. In addition, we controlled for confounding factors, such as cardiovascular disease, stroke, hypertension, liver and kidney dysfunction, and medication. Nevertheless, there are also several limitations. First, causal inference strength is weaker than in a cohort study. Second, the sample size of the follow-up study was relatively small, and with a short follow-up time. Third, body compositions were not measured. Finally, the present participants were all Chinese, so it is not clear whether the results are applicable to other populations. Therefore, the role of irisin in the outcomes of prediabetes needs to be further clarified in larger prospective cohort studies.

In summary, irisin might play an important role in the outcomes of newly diagnosed prediabetes and can predict the risk for developing diabetes mellitus. This finding has promising implications for diabetes intervention.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Comparisons of baseline serum irisin levels between the two different exercise statuses. (a) Case group. (b) Control group. (c) Total participants.

Table S1 | Odds ratios and 95% confidence intervals for the development of diabetes in relation to the extent of decrease in serum irisin levels during the follow-up period.

Table S2 | Odds ratios and 95% confidence intervals for the development of diabetes in relation to baseline serum irisin levels stratified by exercise status.