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ORIGINAL RESEARCH

# Gender-Specific Association of Handgrip Strength with Type 2 Diabetes Mellitus in Chinese Han Older Adults

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**Purpose:** We aimed to analyze the relationship between handgrip strength/relative handgrip strength among older Han adults with type 2 diabetes mellitus (T2DM) by gender to determine the optimal cut-off value of grip strength for older adults.

**Methods:** A multi-stage sampling method was used to conduct a questionnaire survey and physical examination of 6128 older adults in Anhui Province. Chi-squares tests, *t*-tests, analysis of variance, and logistic regression analysis were used to analyze the association between handgrip strength/relative handgrip strength and T2DM between the sexes. The decision tree model (CRT) was used to explore the predictive value of handgrip strength /relative handgrip strength on T2DM.

**Results:** There was an association between handgrip strength and T2DM (P = 0.006, OR = 0.985, 95% CI = 0.975, 0.996), which was found in females (P = 0.013, OR = 0.978, 95% CI = 0.961, 0.995) but not in males (P = 0.125, OR = 0.989, 95% CI = 0.976, 1.003). Relative handgrip strength was also correlated with T2DM (P = 0.014, OR = 0.730, 95% CI = 0.568, 0.939), which was found in females (P = 0.003, OR = 0.534, 95% CI = 0.352, 0.809) but not in males (P = 0.432, OR = 0.879, 95% CI = 0.638, 1.212). The incidence of T2DM in elderly females with hypertension who were uneducated and with a handgrip strength of <17.350 kg was 24.3% (115 cases), whereas that in elderly females with hypertension and a relative handgrip strength of <0.240 was 29.0% (127 cases).

**Conclusion:** According to our results, handgrip strength and relative handgrip strength were associated with T2DM. People with hypertension had a higher risk of T2DM in women with a handgrip strength of  $\leq 17.350$ kg and a relative grip strength of  $\leq 0.240$ . Further research is needed to validate the effectiveness of this cut-off for implementing interventions and avoiding risks. **Keywords:** diabetes mellitus, handgrip strength, gender, older adult

#### Introduction

Diabetes mellitus (DM) is a serious chronic endocrine and metabolic disease that is caused by insufficient insulin secretion and defective insulin action because of multiple pathogenic factors.<sup>1</sup> The prevalence of DM is as high as 11.2% in China, of which 90% are of type 2 diabetes mellitus (T2DM).<sup>2</sup> The prevalence of T2DM in Chinese adults 60 years and older is close to 20%, placing a heavy burden on individuals, families, and society.<sup>2</sup>

T2DM is most common in older adults (ie, aged 60 years or older),<sup>3</sup> resulting in complications such as kidney failure, amputation, vision loss, and nerve damage that directly affect quality of life.<sup>4,5</sup> The problem of global aging has become increasingly prominent. The 2021 China Census reported 264 million people over the age of 60. According to the World Health Organization, the global aging population (ie, aged 60 years and older) will increase to 1.4 billion by 2030 and 2.1 billion by 2050.<sup>6</sup> Thus, T2DM has become a serious public health problem, and it is important to adopt scientific methods to evaluate and prevent diabetes.

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Previous studies have shown lower muscle strength is one of the risk factors for T2DM,<sup>7</sup> as it can lead to a reduction in surface area for glucose delivery, which increases insulin resistance (ie, the inability of insulin to stimulate glucose disposal) and triggers T2DM.<sup>8,9</sup> As an indicator of muscle strength, handgrip strength has been proposed and used to screen T2DM,<sup>10</sup> with decreased handgrip strength being associated with an increased prevalence of T2DM.<sup>11</sup> Meanwhile, studies have found that muscle strength is higher among males than among females at any age.<sup>12</sup> Furthermore, abdominal fat can lead to a greater loss of muscle strength through neuroendocrine dysregulation and may result in different rates of muscle strength decline in older adults of different genders.<sup>13</sup> Another major cause of T2DM is obesity, as obese populations demonstrate a higher risk of T2DM,<sup>13,14</sup> with body mass index (BMI) being the most commonly used indicator of obesity.<sup>15</sup>

In summary, the relationship between obesity, muscle strength, and T2DM is complex. At present, some scholars have explored the relationship between grip strength or relative grip strength normalized according to BMI and hypertension.<sup>16</sup> However, we have not found a study that explores the relationship between BMI-standardized handgrip strength and T2DM. Hence, this study proposed that the effect of handgrip strength on T2DM may be influenced by BMI and gender. We explored the relationship between grip strength or relative grip strength and T2DM in terms of gender to determine the optimal cut-off value of grip strength or relative grip strength for older adults.

## **Materials and Methods**

#### Study Population

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Anhui Medical University. The data came from the Anhui Healthy Longevity Survey (AHLS), the details of which have been reported elsewhere.<sup>17</sup> The multi-stage sampling method and the principle of randomization were used in this survey. In the first stage, according to geographical location, cities were selected from the east, west, south, and north of Anhui Province. In the second stage, three to five urban communities were randomly selected among all others in each sample city, and three to five rural communities were selected in each sample city following the same principle. In the third stage, within the selected communities, a face-to-face questionnaire survey with 750 samples each in urban and rural areas was completed following the principle of random and voluntary participation. The study population was adults aged 60 or over, living in Anhui Province for at least half a year, with good cognitive ability to cooperate with the investigation. A questionnaire was conducted among 6128 older adults of the Chinese Han population, and the investigators were recruited from teachers and students at Anhui Medical University. After excluding individuals with missing demographic characteristics or handgrip strength values, the final sample size was 5864 (95.7%).

## Questionnaire Survey

A face-to-face questionnaire survey was conducted by investigators who had been uniformly trained and passed an assessment. The inspector checked each questionnaire on the same day it was taken to ensure its quality. The questionnaire included questions about age, gender (male or female), education level (uneducated, primary school, junior school, high school, and above), income (<6500, 6500–15,000, 15,000–24,000, >24,000 RMB),<sup>18</sup> smoking history (yes or no), alcohol history (yes or no), hypertension (yes or no), and T2DM (yes or no) (diagnosis by medical institutions at or above the county level).

## **Physical Measurements**

Handgrip strength was measured using an electronic dynamometer, whose usage was demonstrated to the participants by the investigator before the measurement. All participants were asked to stand upright with their feet apart, their elbows bent at right angles, and their wrists in a neutral position. The participants were asked to squeeze the dynamometer handle with a maximum force for 2-3 seconds, with three measurements each for the left and right hands in turn. The study used the maximum handgrip strength value of the dominant hand for statistical analysis. The dynamometer was calibrated prior to measurement to ensure that the error was within  $0.1 \text{ kg.}^{19}$  The investigators gave verbal

encouragement during the measurements to elicit the maximum performance of the participants. Relative grip strength was used for assessment, which is the patient's grip strength divided by their BMI.

Height was measured with a steel tape measure. The participants were asked to take off their shoes and caps. During the measurement, the patient's torso was naturally straight, the head was straight, and both eyes were looking straight ahead. The heel, sacrum, and shoulder blades were in contact with an upright post, and the patient assumed a "three-point, one-line" standing posture. The investigator's eyes were at the same height as the horizontal pressure plate when taking the height measurement.

Body weight was measured using an electronic weight meter. The weight meter was corrected before measurement to ensure that the error was not greater than 0.1 kg. During the measurement, the weight meter was placed on level ground, and the participant was asked to stand barefoot in its center. The participants were then grouped into the following BMI categories: thin (BMI < 18.5 kg/m<sup>2</sup>), normal (18.5  $\leq$  BMI  $\leq$  24.9 kg/m<sup>2</sup>), overweight (25.0  $\leq$  BMI  $\leq$  29.9 kg/m<sup>2</sup>), and obese (BMI  $\geq$  30.0 kg/m<sup>2</sup>).

#### Statistical Analysis

Epi Data software (version 3.1) was used for data entry and double check. Statistical analyses were performed using SPSS software (version 25.0). Continuous variables were presented as means  $\pm$  standard deviations, and categorical variables were expressed as proportions. The distribution differences of gender, age, education level, smoking history, drinking history, hypertension history, BMI, handgrip strength, and relative handgrip strength between the diabetic group and the non-diabetic group were analyzed by chi-squared tests or *t*-tests. The distribution differences of gender, age, education level, smoking history, drinking history, hypertension history, and BMI in handgrip strength or relative handgrip strength were analyzed by variance analyses (ANOVA) and *t*-tests. The relationship between T2DM and handgrip strength or relative handgrip strength was analyzed using binary logistic regression. The dependent variable was T2DM, and the covariates were age, gender, education level, annual average personal income, smoking history, drinking history, and hypertension. Handgrip strength and age were continuous variable data, and the other variables were categorical variable data. Based on single-factor and multi-factor studies, the decision tree model (CRT) was further used to explore the influence of different factors and the prediction of T2DM. The significant level was set at 0.05 ( $\alpha = 0.05$ ).

## Results

## General Characteristics of the Study Population

A total of 5864 individuals were included in this study. Of these, 45.5% (2666) were male (mean age: 70.96 $\pm$ 6.99 years, mean BMI: 23.87 $\pm$ 3.45 kg/m<sup>2</sup>) and 54.5% (3198) were female (mean age: 70.97 $\pm$ 7.15 years, mean BMI: 24.47 $\pm$ 3.81 kg/m<sup>2</sup>). The prevalence of T2DM was 15.59%. There were statistical differences in education level, income, smoking, hypertension, and BMI (*P*<0.05), whereas there were no statistical differences in gender, age, and alcohol use (*P*>0.05) (Table 1).

## Handgrip Strength with Different Demographic Characteristics

There were statistical differences in handgrip strength and relative handgrip strength between different genders (all P < 0.001). Similarly, handgrip strength and relative handgrip strength showed statistical differences among different education level, income, alcohol use, smoking, hypertension, and BMI groups (all P < 0.001) (Table 2).

## Association Between Handgrip Strength/Relative Handgrip Strength and T2DM

The data showed an association between handgrip strength/relative handgrip strength and T2DM (OR=0.985, 95% CI=0.975, 0.996; OR=0.730, 95% CI=0.568, 0.939). The results showed that in the older adult population, highly educated, high-income, and hypertensive patients were at higher risk of T2DM. Sex-stratified analyses showed that the association between handgrip strength and T2DM had statistical differences in women (OR=0.978, 95% CI=0.961, 0.995; OR=0.534, 95% CI=0.352, 0.809) but not in men (OR=0.989, 95% CI=0.976, 1.003/ OR=0.879, 95% CI=0.638, 1.212) (Table 3 and Table 4).

Various	Ν	T2I	DM	t/χ²	P-value	
		Yes	No			
Gender						
Male	2666(45.5)	395(43.2)	2271(45.9)	2.205	0.138	
Female	3198(54.5)	519(56.8)	2679(54.1)			
Education level						
Uneducated	2884(49.2)	399(43.7)	2485(50.2)	19.559	<0.001	
Primary school	1641(28)	280(30.6)	1361(27.5)			
Junior school	832(14.2)	130(14.2)	702(14.2)			
High school and above	507(8.6)	105(11.5)	402(8.1)			
Income						
<6500	3540(60.4)	502(54.9)	3038(61.4)	20.115	<0.001	
6500-15,000	908(15.5)	139(15.2)	769(15.5)			
15,000-24,000	465(7.9)	88(9.6)	377(7.6)			
>24,000	951(16.2)	185(20.2)	766(15.5)			
Alcohol use						
No	3590(61.2)	579(63.3)	3011(60.8)	2.063	0.151	
Yes	2274(38.8)	335(36.7)	1939(39.2)			
Smoking						
No	4626(78.9)	747(81.7)	3879(78.4)	5.246	0.022	
Yes	1238(21.1)	167(18.3)	1071(21.6)			
Hypertension						
No	2888(49.2)	213(23.3)	2675(54)	291.62	<0.001	
Yes	2976(50.8)	701(76.7)	2275(46)			
BMI						
Thin	309(5.2)	39(4.3)	270(5.5)	12.784	0.005	
Moderate	3237(54.1)	468(51.2)	2769(55.9)			
Overweight	1967(32.9)	340(37.2)	1627(32.9)			
Obesity	351(5.9)	67(7.3)	284(5.7)			
Age	5864	70.86±6.88	70.98±7.11	0.477	0.633	
Handgrip strength	5864	20.70±8.98	21.38±9.14	2.068	0.039	
Relative handgrip strength	5864	0.86±0.390	0.90±0.39	3.154	0.002	

Table I	General	Characteristics	of Participants	[n	(%)	1
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Abbreviations: T2DM, type 2 diabetes mellitusin; BMI, body mass index.

## Prediction of Handgrip Strength/Relative Handgrip Strength on T2DM

A predictive decision tree model of handgrip strength toward T2DM in females is shown in Figure 1, which showed an average accuracy of 84.0%. The proportion of T2DM in those with hypertension was 25.0% (296 cases). Among those with hypertension, 21.7% (168 cases) were uneducated, and 24.3% (115 cases) were uneducated and with a handgrip strength of  $\leq$  17.350 kg.

A predictive decision tree model of relative handgrip strength toward T2DM in females is shown in Figure 2, which showed an average accuracy of 84.3%. Among those with hypertension, 24.3% (291 cases) had T2DM, and 29.0% (127 cases) had a relative handgrip strength of  $\leq 0.240$  kg. Handgrip strength/relative grip strength had no significant predictive value in the male decision tree model. Thus, hypertension, education level, income, and grip strength/relative grip strength were important influencing factors. We can also conclude from the results that high-income people are at greater risk of T2DM than low-income people, and hypertensive patients are at greater risk than non-hypertensive patients. Among the female patients with hypertension, those with a grip strength of  $\leq 17.250$  kg and a relative grip strength of < 0.296 kg are at greater risk of T2DM.

Various	Hand	grip Stren	gth	Relative Handgrip Strength			
	M±SD	t/F	P-value	M±SD	t/F	P-value	
Gender							
Male	26.87±8.98	50.177	<0.001	1.14±0.38	51.535	<0.001	
Female	16.61±6.10			0.69±0.26			
Education level							
Uneducated	18.55±8.04	240.587	<0.001	0.78±0.35	226.133	<0.001	
Primary school	22.16±8.99			0.94±0.39			
Junior school	25.95±9.19			1.08±0.39			
High school and above	26.24±9.40			1.09±0.38			
Income							
<6500	19.43±8.56	138.498	<0.001	0.82±0.37	115.847	<0.001	
6500-15,000	23.1±9.05			0.97±0.40			
15,000-24,000	24.1±9.37			0.98±0.40			
>24,000	25.03±9.18			1.05±0.39			
Alcohol use							
Yes	25.08±9.13	26.362	<0.001	1.05±0.39	25.325	<0.001	
No	18.87±8.24			0.79±0.36			
Smoking							
Yes	25.97±9.27	20.346	<0.001	1.13±0.40	23.561	<0.001	
No	20.02±8.65			0.83±0.36			
Hypertension							
Yes	20.93±9.20	2.946	0.003	0.85±0.38	8.082	<0.001	
No	21.63±9.01			0.93±0.39			
BMI							
Thin	17.9±7.75	29.214	<0.001	1.03±0.44	88.892	<0.001	
Moderate	20.88±8.91			0.94±0.40			
Overweight	22.53±9.51			0.84±0.36			
Obesity	20.86±8.67			0.65±0.28			

Table 2 Han	dgrip Strength	with Different	Demographic	Characteristics
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Abbreviations: T2DM, type 2 diabetes mellitusin; BMI, body mass index.

 Table 3 Binary Logistic Regression Analysis of Handgrip Strength and T2DM

Various			Total		Male			Female		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Handgrip strength		0.985	0.975–0.996	0.006	0.989	0.976-1.003	0.125	0.978	0.961-0.995	0.013
Age		0.989	0.978-1.001	0.061	0.998	0.980-1.015	0.782	0.983	0.968-0.998	0.023
Gender	Male	1.000								
	Female	1.010	0.824-1.238	0.924						
Education level	Uneducated	0.631	0.475-0.838	0.001	0.629	0.428-0.923	0.018	0.635	0.409-0.986	0.043
	Primary school	0.836	0.633-1.105	0.208	0.770	0.537-1.104	0.156	0.948	0.608-1.48	0.815
	Junior school	0.757	0.561-1.021	0.068	0.761	0.523-1.105	0.151	0.752	0.455-1.241	0.265
	High school and above	1.000			1.000			1.000		
Income	<6500	0.732	0.587-0.913	0.006	0.641	0.476-0.862	0.003	0.886	0.631-1.244	0.485
	6500-15,000	0.849	0.652-1.107	0.227	0.701	0.488-1.007	0.054	1.103	0.741-1.642	0.630
	15,000-24,000	1.070	0.792-1.444	0.661	1.007	0.654-1.550	0.976	1.208	0.787-1.855	0.387
	>24,000	1.000			1.000			1.000		
Alcohol use	Yes	0.947	0.800-1.121	0.530	0.870	0.693-1.093	0.231	1.07	0.837-1.368	0.588
	No	1.000			1.000			1.000		
Smoking	Yes	0.918	0.746-1.130	0.419	0.962	0.764-1.211	0.742	0.788	0.474-1.310	0.358
	No	1.000			1.000			1.000		
Hypertension	Yes	3.907	3.315-4.605	<0.001	3.549	2.783-4.527	<0.001	4.265	3.406-5.340	<0.001
	No	1.000			1.000			1.000		
	1	1	1	1	1	1	1	1	1	1

Various	Total				Male			Female		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	
Relative handgrip strength	0.730	0.568–0.939	0.014	0.879	0.638-1.212	0.432	0.534	0.352-0.809	0.003	
Age	0.990	0.980-1.002	0.092	1.000	0.983-1.018	0.971	0.982	0.968–0.997	0.019	
Gender										
Male	1.000									
Female	1.026	0.837-1.257	0.807							
Education level										
Uneducated	0.634	0.478-0.842	0.002	0.640	0.436-0.940	0.023	0.628	0.404–0.975	0.038	
Primary school	0.843	0.638-1.113	0.228	0.783	0.547-1.121	0.182	0.941	0.602-1.469	0.788	
Junior school	0.758	0.562-1.022	0.069	0.763	0.525-1.108	0.155	0.753	0.456-1.244	0.269	
High school and above	1.000			1.000			1.000			
Income										
<6500	0.738	0.592-0.919	0.007	0.655	0.487–0.879	0.005	0.880	0.627-1.237	0.463	
6500-15,000	0.852	0.654-1.110	0.235	0.708	0.493-1.016	0.061	1.095	0.735-1.630	0.657	
15,000-24,000	1.065	0.789-1.438	0.680	1.002	0.651-1.543	0.992	1.196	0.779–1.836	0.414	
>24,000	1.000			1.000			1.000			
Alcohol use										
Yes	0.940	0.794–1.112	0.469	0.862	0.686-1.081	0.199	1.069	0.837-1.366	0.592	
No	1.000			1.000			1.000			
Smoking										
Yes	0.929	0.755-1.144	0.490	0.966	0.767-1.217	0.771	0.806	0.485-1.339	0.404	
No	1.000			1.000			1.000			
Hypertension										
Yes	3.843	3.259-4.531	<0.001	3.520	2.758-4.492	<0.001	4.153	3.315-5.204	<0.001	
No	1.000			1.000			1.000			

Table 4 Binary Logistic Regression Analysis of Relative Handgrip Strength and T2DM

## Discussion

According to previous research, obesity affects muscle strength, which is an important risk factor for T2DM.<sup>20–23</sup> More importantly, BMI is related to handgrip strength and T2DM.<sup>24,25</sup> Therefore, we considered that BMI may be a confounding factor in the relationship between handgrip strength and T2DM and used BMI to standardize handgrip strength to explore this effect. The results of the study showed the following: first, the grip strength of the Han elderly was related to T2DM, similar to the results of previous studies of other races. Second, there was also a correlation between relative grip strength and T2DM. Third, there were obvious gender differences in the above correlation.

The results showed that the risk of T2DM was negatively correlated with handgrip strength or relative handgrip strength, consistent with Merchant RA's research results.<sup>20</sup> In our study, the risk of T2DM decreased by 1.5% for each unit increase in handgrip strength, and by 27.0% with each unit increase in relative handgrip strength. Possible causes for this relationship are decreased muscle strength, which may lead to impaired glucose tolerance and inflammation, affecting glucose metabolism and insulin resistance.<sup>26,27</sup> Furthermore, reduced insulin signaling could lead to decreased protein synthesis and increased activation of protein degradation pathways, leading to muscle strength loss.<sup>28</sup> Therefore, the increased risk of T2DM was not only the outcome of muscle strength loss but also its cause.<sup>29</sup>

Interestingly, being overweight and obese are not only risk factors for T2DM but also consequences of T2DM. First, being overweight and obese will cause a low-grade chronic inflammatory state and mitochondrial dysfunction in the human body in response to overnutrition, which produces insulin resistance and promotes the development of T2DM.<sup>22</sup> Second, weight gain may result if T2DM patients are treated with insulin therapy, which may be the result of insulin inhibiting protein metabolism and stimulating lipid production to increase fat accumulation.<sup>30</sup> Third, overweight and obese older adult diabetes patients often lack daily activity, which can lead to a reduction in muscle strength, deterioration in glycemic control, and may further exacerbate physical inactivity.<sup>28</sup> Meanwhile, the logistics results of this study show that highly educated, high-income, and hypertensive patients were at higher risk of diabetes. It may be that people



Figure I The predictive decision tree model of handgrip strength to T2DM in females.

with high levels of education and income have better medical treatment levels, stronger health awareness, and higher treatment rates for chronic diseases than others.<sup>2</sup> Moreover, patients with hypertension often exhibit insulin resistance, so they are at greater risk of developing diabetes than normotensive individuals.<sup>31</sup>





As there was an association between gender and handgrip strength, a categorical analysis of gender in older adults was performed.<sup>32</sup> It was found that the association between handgrip strength or relative handgrip strength and T2DM in women was not found in men. In women, the risk of T2DM decreased by 2.2% for every unit increase in handgrip strength, and 46.6% for every unit increase in relative handgrip strength. This gender difference may be related to factors such as sex hormones, glucose balance, and body composition.<sup>33,34</sup> First, in older adults, Fetuin-A (a protein primarily secreted by the liver that regulates insulin signaling) levels are higher in women than in men, increasing the former's risk of T2DM.<sup>35</sup> Second, a decline in sex hormone levels can aggravate the impaired glucose metabolism of women as they age.<sup>33</sup> Third, higher androgen activity may be present after menopause in women, resulting in impaired glucose tolerance and the promotion of insulin resistance.<sup>36</sup> Finally, older men have high concentrations of anabolic hormones, which stimulate muscle protein synthesis by increasing lean muscle mass, leading to greater strength than in women.<sup>37</sup> Other studies have found that increasing muscle strength to reduce the risk of death from various causes seems to be more important for older women than for men.<sup>37</sup> Therefore, it is necessary to consider the effect of gender when analyzing the association between handgrip strength and T2DM.

T2DM has become a serious threat with increasingly aging populations. Therefore, taking appropriate measures to prevent, screen, and control the occurrence and development of diabetes can promote healthy aging. At the same time, it is also conducive to promote the combination of health management and medical services for old adults, establish a medical and health service system, promote the prevention and treatment of chronic diseases, and improve the health level of older adults. From the results of this study, we recommend that elderly women with hypertension, especially uneducated women, should pay attention to control blood glucose when their grip strength is less than 17.350 kg or their relative grip strength is less than 0.296.

Our study has several strengths, such as a large sample size obtained by multi-stage stratified sampling. Second, income in our study differs from classifications in general research. Instead, it was classified according to the average income and expenditure in the Survey Report on the Living Conditions of China's Urban and Rural Older Persons (2018), which can better meet the particularity of the research object for the old adults. However, there were still some limitations that should be considered. This study was cross-sectional and could not explore the causal association between handgrip strength and T2DM. Meanwhile, a history of hypertension may affect an individual's metabolic levels, which can affect the results. However, combined with the results of previous studies, we can conclude that handgrip strength is related to the prevention and control of T2DM. Gender factors should be considered when using handgrip strength to screen for T2DM. Future studies could adopt a prospective cohort study to explore the causal relationship between handgrip strength and T2DM.

## **Data Sharing Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## **Ethics Statement**

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Anhui Medical University, Hefei, China (no. 2020H011).

## **Acknowledgments**

Thanks to all participants who voluntarily participated in the study. We would like to thank the editors of this manuscript and Charlesworth for English language editing. Qian Huang and Xing Chen are co-first authors for this study. Dong Mei Zhang and Gui Mei Chen are co-correspondence authors for this study.

## **Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

# Funding

This study was funded by the Anhui Natural Science Foundation (No. 1808085QH252). The funder has no role in the conduct of the research or the decision to submit this report.

## **Disclosure**

The authors report no conflicts of interest in this work.

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