

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Details of the BRAVO Collaborative Group

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eMethods 2. The details of inclusion and exclusion criteria

Participants meeting the following 3 criteria will be included:

1. Participants aged ≥ 18 years.
2. Participants with obesity (i.e., body mass index [BMI] ≥ 28 kg/m²) and abdominal obesity (i.e., waist circumference ≥ 85 cm in female or waist circumference ≥ 90 cm in male).
3. Participants with evidence of non-alcoholic fatty liver disease (NAFLD) by ultrasound, computed tomography or magnetic resonance imaging.

Participants who have any of the following conditions will be excluded:

1. Coronary heart disease, stroke, or peripheral arterial disease.
2. Diabetes, or taking oral glucose-lowering drugs
3. Severely uncontrolled hypertension
4. Excess alcohol consumption
5. Other causes of fatty liver disease
6. Thyroid disease, including hyperthyroidism or hypothyroidism
7. Heart failure
8. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times upper limit of normal, liver cirrhosis or hepatic insufficiency
9. Renal insufficiency, or estimated glomerular filtration rate (eGFR) < 60 ml/(min \times 1.73m²)
10. Weight loss surgery, or currently taking drugs for weight loss, or plans to undergo

weight loss surgery or drugs in the following 6 months after randomization

11. Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency
12. Intake of berberine or drug containing berberine 1 month prior to screening
13. Any adverse reaction to berberine
14. Severe constipation, diarrhea, and/or severe chronic intestinal diseases
15. Long-term or intermittent use of corticosteroids, immunosuppressants, antibiotics,
or other drugs that significantly affect inflammatory biomarkers
16. Pregnancy or breastfeeding status, or plans to be pregnant during the trial
17. Malignant tumors
18. Mental disorders, cognitive disorders, and/or other serious diseases
19. Participation in other trials 3 months prior to screening
20. Any other conditions that may hinder the compliance to the study intervention or
follow-up.

eMethods 3. The lifestyle intervention

All participants received standardized lifestyle counseling based on Chinese guidelines for obesity and MASLD management, including advice on smoking, alcohol consumption, diet, and physical activity. Personalized guidance was provided according to assessments.

Lifestyle	Questionnaire	Advice
Smoking	<p>The frequency of smoking habit</p> <p>What is your current smoking status?</p> <ul style="list-style-type: none">○ Smoke daily for more than one year○ Smoke daily for less than one year○ Smoke occasionally○ Quit smoking○ Never smoked	<p>If the answer was “smoke daily for more than one year,” “smoke daily for less than one year,” or “smoke occasionally,” the advice was as follow:</p> <p><i>Smoking is harmful to both your health and that of your family. According to the China Report on the Health Hazards of Smoking (2020), smoking damages lung structure, lung function, and the immune system of the respiratory tract, leading to various respiratory diseases. It is also closely associated with the occurrence of cancer, cardiovascular and cerebrovascular diseases, and diabetes, posing serious threats to life. Quitting smoking, however, benefits your health - the risk of the above diseases will decrease after cessation. A U.S. report on smoking cessation showed that 15 years after quitting, the excess risk of cardiovascular disease associated with smoking disappears. It is important to note that e-cigarettes also cause harm to the body, although long-term health effects remain unclear. You may ask friends or family to monitor your smoking habits and help you gradually reduce the frequency and amount of smoking. Consult a physician if necessary for smoking cessation assistance. Try to avoid using e-cigarettes as a means to quit smoking.</i></p>
Alcohol consumption	<p>The frequency of drinking habit</p>	<p>If the answer to Question 1 was “drink daily for more than one year,” “drink daily for less than one year,” or “drink occasionally,” the advice was as follow:</p>

	<p>What is your current drinking status?</p> <ul style="list-style-type: none"> ○ Drink weekly for more than one year ○ Drink weekly for less than one year ○ Drink occasionally ○ Quit drinking ○ Never drank 	<p><i>According to recent large-scale studies in China, alcohol consumption, regardless of amount, harms health and increases the risk of cardiovascular disease and mortality. Small amounts of alcohol do not prevent stroke. Excessive drinking (defined as daily alcohol intake exceeding 25 g for men or 15 g for women) can cause liver cirrhosis, cancer, and traffic accidents, and increases the risk of atrial fibrillation, myocardial infarction, and heart failure. It is also closely related to hypertension and cerebral hemorrhage, posing serious threats to life. You can consciously reduce the amount and frequency of alcohol consumption in daily life and minimize the presence of alcohol in your routine. Consult a physician if necessary for assistance in quitting alcohol.</i></p>
Diet	A three-day diet diary record (two weekdays and one weekend day)	<p>The three-day diet diary was recorded (two weekdays and one weekend day) using a mobile application. This application calculated the resting energy expenditure based on participant's height and updated body weight. A daily caloric intake of 500 kcal lower than the resting energy expenditure was recommended. The application provided feedback on whether the energy intake exceeded the recommendation and whether food intake should be reduced, according to the daily diet diary record. It automatically performed a nutritional analysis, quantifying the main macronutrients (protein, fat, carbohydrates) and micronutrients, and provided the corresponding recommended intake ranges. Upward and downward arrows, as well as checkmarks, indicated whether the intake was above or below the recommended range. The nutritional analysis also displayed the energy contribution of each meal and the recommended caloric intake per meal, the proportion of high-quality protein sources, whole-grain carbohydrate sources, and dark-colored vegetable sources, along with the</p>

		corresponding recommended proportions.
Physical activity	A 7-day international physical activity questionnaire (IPAQ)	<p>According to the classification criteria for the IPAQ, the participant was classified into three levels: low, moderate, high.</p> <p>If PHYSICAL ACTIVITY LEVEL was Low and sedentary time exceeded 4 hours, the advice was as follow:</p> <p><i>You need to increase your physical activity level. Your daily lack of moderate-to-vigorous physical activity, combined with prolonged sedentary time exceeding 4 hours, can negatively affect your current and future health. Ideally, you should reduce your daily sitting time to less than 4 hours and increase moderate-to-vigorous physical activity according to your health status. If it is difficult to reduce sitting time due to work or personal reasons, you should aim for 60-75 minutes of moderate-intensity activity, 30-35 minutes of vigorous-intensity activity, or 45-55 minutes of combined moderate-to-vigorous activity daily to offset the negative impact of prolonged sitting.</i></p> <p>If PHYSICAL ACTIVITY LEVEL was Low and sedentary time was less than 4 hours, the advice was as follows:</p> <p><i>You need to increase your physical activity level. Although your daily sitting time is low, under 4 hours, your moderate-to-vigorous physical activity remains insufficient, which can negatively impact your current and future health. Depending on your health status, you should aim for 60-75 minutes of moderate-intensity activity, 30-35 minutes of vigorous-intensity activity, or 45-55 minutes of combined moderate-to-vigorous activity daily.</i></p>

		<p>If PHYSICAL ACTIVITY LEVEL was Moderate and sedentary time exceeded 4 hours, the advice was as follows:</p> <p><i>It is recommended that you increase your physical activity level. You still need to increase moderate-to-vigorous physical activity, and your prolonged daily sitting time of over 4 hours can negatively affect your current and future health. Ideally, you should reduce your daily sitting time to under 4 hours and increase moderate-to-vigorous physical activity according to your health status. If reducing sitting time is difficult due to work or personal reasons, you should aim for 60-75 minutes of moderate-intensity activity, 30-35 minutes of vigorous-intensity activity, or 45-55 minutes of combined moderate-to-vigorous activity daily to offset the negative impact of prolonged sitting.</i></p> <p>If PHYSICAL ACTIVITY LEVEL was Moderate and sedentary time was less than 4 hours, the advice was as follows:</p> <p><i>It is recommended that you increase your physical activity level. Although your daily sitting time is low, under 4 hours, you still need to increase moderate-to-vigorous physical activity to promote your physical and mental health. Depending on your health status, you should aim for 60-75 minutes of moderate-intensity activity, 30-35 minutes of vigorous-intensity activity, or 45-55 minutes of combined moderate-to-vigorous activity daily.</i></p> <p>If PHYSICAL ACTIVITY LEVEL was High and sedentary time exceeded 4 hours, the advice was as follows:</p> <p><i>Your physical activity level is sufficient in both quality and quantity. The time you spend</i></p>
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		<p><i>in moderate-to-vigorous activity is nearly ideal-please continue! However, your prolonged daily sitting time of over 4 hours can negatively affect your current and future health. Ideally, you should reduce your daily sitting time to under 4 hours and increase moderate-to-vigorous physical activity according to your health status. If reducing sitting time is difficult due to work or personal reasons, you should aim for 60-75 minutes of moderate-intensity activity, 30-35 minutes of vigorous-intensity activity, or 45-55 minutes of combined moderate-to-vigorous activity daily to offset the negative impact of prolonged sitting.</i></p>
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eMethods 4. The study procedure

Table shows the procedures of each visits. At the screening visit, participants provided lifestyle information on smoking, alcohol use and physical activity via standardized questionnaires,¹ and received tailored lifestyle advice.^{2,3} All participants underwent physical examinations and a non-enhanced quantitative CT scan. Blood and urine samples were collected using centrally dispensed collection kits, processed and stored according to standardized specifications, and subsequently transported to the central laboratory for analysis at regular intervals. Run-in medication was dispensed. Before randomization, participants recorded a three-day diet (two weekdays and one weekend day) using a customized application and received personalized guidance targeting a daily reduction of 500 kcal intake. Before randomization, eligibility criteria were reassessed after which the study medication was initiated for eligible participants.

Thereafter, participants attended follow-up visits at 2, 4, and 6 months. At each follow-up visit, investigators dispensed the study medication and collected information on treatment adherence, concomitant medications and adverse events. Participants underwent standardized physical examinations. At 2 months, serum alanine aminotransferase (ALT) and creatinine levels were monitored at local sites. At 6 months, lifestyle assessments, a non-enhanced quantitative CT scan, and blood and urine samples collection were repeated. Central laboratory tests included glycated hemoglobin A1c (HbA1c), lipid indicators, uric acid and hs-CRP. Local laboratory tests included fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPG), serum ALT, and creatinine.

Table. Schedule and Procedures for Study Clinic Visits

	First screening visit	Second screening visit	Randomization visit	2-month follow-up visit	4-month follow-up visit	6-month follow-up visit
Informed consent	X					
Inclusion / exclusion criteria	X	X	X			
Basic information						
Sociodemographic characteristics		X				
Medical history and medication	X	X	X			
NAFLD diagnostic report	X					
Lifestyle behavior		X	X			X
Physical examination	X	X		X	X	X
Local Liver and kidney function test	X			X		X
Local OGTT	X					X
Local blood routine test	X					X
Central blood sample collection	X					X
Central urine sample collection	X					X
Central stool sample collection		X				X
Genetic analyses		X				X
CT scan		X				X
Echocardiography		X				X
Medication adherence			X	X	X	X
Adverse event			X	X	X	X

Abbreviations: NAFLD: non-alcoholic fatty liver disease; OGTT: stands for Oral

Glucose Tolerance Test.

eMethods 5. The measurement of adipose tissue

Parameter of non-enhanced quantitative CT scanning

Non-enhanced quantitative CT scanning was performed on the same scanners (Philips, GE, or Neusoft) at each hospital at baseline and 6 months. The scanners were calibrated with a dedicated phantom each month. The CT scan acquired spiral scan data (120 kV, automatic tube current modulation, 1.00 / 1.25 mm slice thickness, 50 cm scanning field of view) from the thoracic inlet to the pubic symphysis in the supine position. The images were reconstructed to 5-mm-thick and 1-mm-thick slices with 40 cm display field of view by the adaptive iterative dose reduction three-dimensional (AIDR3D) algorithm. Then, all de-identified imaging data were submitted to the imaging core laboratory for blind independent central review by specialized radiologists, with results documented accordingly.

The methodology of adipose tissue

The methodology of visceral adipose tissue (VAT)^{4,5} and liver fat content⁶⁻⁸ measurement has been described previously. Briefly, the VAT for a given slice was first segmented and mapped based on the CT measurement threshold of -190 to -30 Hounsfield units, and the outer contour of abdominal wall was outlined by the software automatically. The segmentation and outlining process could be manually modified by the user as needed. VAT area (cm²) was measured by the Tissue Composition Module of the Mindways Quantitative CT workstation with a PRO Bone Mineral Densitometry System (version 5.1, 2022 Mindways, Austin, TX, USA). In this study, the VAT area at the level of L2/L3 intervertebral space was pre-specified for

analysis, since VAT at this level showed the strongest correlation with the total VAT volume in Chinese population.⁵

The liver fat content (%) was measured directly in regions of interest (ROIs) drawn on the liver parenchyma based on the Hounsfield units and data from the calibration phantom. The radiologist placed 3 ROIs with an area of 300 mm² in the peripheral area of the left lobe, the right anterior lobe, and the right posterior lobe. The average of the 3 ROIs was used for the final quantitative CT measurement of liver fat content. Quantitative CT measurement of liver fat content has shown good correlation and accuracy with proton density fat fraction measured with chemical shift encoded MRI in Chinese population.⁸

eMethods 6. The definition of safety outcomes

Serious adverse events (SAEs) were defined as any unexpected medical events at any drug dose resulting in death, life-threatening condition, hospitalization or its prolongation, disability affecting work, congenital anomalies, or other medically significant events.

Non-serious adverse events of interest included the following adverse events which did not meet the criteria of SAEs:

- a) liver function impairment: ALT exceeding 5 times of the upper limit of normal (ULN) or more.
- b) renal function impairment: a 50% increase in creatinine or more from baseline, or estimated glomerular filtration rate (eGFR) less than 60ml / (min \times 1.73m²) calculated by CKD-EPI formula.⁹
- c) constipation
- d) other gastrointestinal reactions
- e) hypoglycemia: blood glucose less than 3.9 mmol/L.

eTable 1. Participants excluded in the per-protocol set stratified by outcomes

Outcomes	Placebo	Berberine hydrochloride
Excluded from the per-protocol set of liver fat content	31	37
Treatment non-adherence	23	28
Incomplete outcome data	9	10
Outcome measured beyond planned window	6	3
Excluded from the per-protocol set of VAT area	25	29
Treatment non-adherence	23	28
Incomplete outcome data	3	2
Outcome measured beyond planned window	6	3

Participants meeting any one of the 3 criteria were excluded from the per-protocol set. Treatment non-adherence was defined as having treatments adherence <80% across 2, 4, or 6 months of follow-up. Incomplete outcome data was defined as no corresponding outcome data either at baseline or at 6 months. Outcome data measured beyond planned window was defined as completing the 2nd outcome measurements after 8 months post-randomization.

Abbreviations: VAT: visceral adipose tissue

eTable 2. Baseline characteristics in the per-protocol set of liver fat content

Variable	Overall (N = 269)	Placebo (n = 137)	Berberine hydrochloride (n = 132)
Age, mean (SD), y	41.4 (10.5)	40.9 (10.4)	42.0 (10.7)
Sex, No. (%)			
Male	180 (66.9)	90 (65.7)	90 (68.2)
Female	89 (33.1)	47 (34.3)	42 (31.8)
Employment, No. (%)			
Unemployed	15 (5.6)	9 (6.6)	6 (4.6)
Employed	254 (94.4)	128 (93.4)	126 (95.5)
Education level, No. (%)			
≤ High school	57 (21.2)	34 (24.8)	23 (17.4)
≥ College	212 (78.8)	103 (75.2)	109 (82.6)
Smoking, No. (%)			
Never	179 (66.5)	92 (67.2)	87 (65.9)
Former	7 (2.6)	4 (2.9)	3 (2.3)
Current	83 (30.9)	41 (29.9)	42 (31.8)
Alcohol consumption, No. (%)			
Never	125 (46.5)	62 (45.3)	63 (47.7)
Former	8 (3.0)	5 (3.7)	3 (2.3)
Current	136 (50.6)	70 (51.1)	66 (50.0)

Variable	Overall (N = 269)	Placebo (n = 137)	Berberine
			hydrochloride (n = 132)
Physical activity, median (IQR), MET min/wk	1386 (693, 2772)	1386 (678, 2772)	1386 (693, 2772)
Waist circumference, mean (SD), cm	104.2 (10.1)	104.6 (9.8)	103.8 (10.4)
Body mass index, mean (SD)	31.9 (3.4)	31.9 (3.4)	31.8 (3.4)
^a			
Systolic blood pressure, mean (SD), mmHg	132.8 (13.2)	131.7 (12.8)	134.0 (13.6)
Diastolic blood pressure, mean (SD), mmHg	87.0 (9.4)	86.3 (8.9)	87.7 (9.9)
eGFR, mean (SD), mL/(min*1.73m ²)	117.67 (10.83)	117.47 (9.98)	117.88 (11.68)
ALT, mean (SD), U/L	34.7 (23.5)	35.8 (25.8)	33.5 (21.0)
AST, mean (SD), U/L	24.7 (11.8)	25.6 (13.2)	23.8 (10.2)
Liver function, No. (%) ^b			
Normal	184 (68.4)	96 (70.1)	88 (66.7)
Abnormal	85 (31.6)	41 (29.9)	44 (33.3)
FPG, mean (SD), mg/dL	94.86 (10.44)	95.04 (10.44)	94.86 (10.62)
2hPG, mean (SD), mg/dL	129.24 (33.30)	127.98 (33.48)	130.50 (33.30)
HbA1c, mean (SD), %	5.68 (0.45)	5.70 (0.43)	5.67 (0.46)

Variable	Overall (N = 269)	Placebo (n = 137)	Berberine hydrochloride (n = 132)
Prediabetic status, No. (%) ^c			
No	170 (63.2)	90 (65.7)	80 (60.6)
Yes	99 (36.8)	47 (34.3)	52 (39.4)
LDL-C, mean (SD), mg/dL	115.44 (32.43)	117.03 (31.66)	113.51 (33.21)
TG, mean (SD), mg/dL	197.35 (136.28)	190.27 (130.97)	204.42 (141.59)
Serum uric acid, mean (SD), mg/dL	6.92 (1.72)	6.94 (1.68)	6.89 (1.76)
hs-CRP, mean (SD), mg/dL	0.23 (0.36)	0.24 (0.37)	0.21 (0.34)
Liver fat content, mean (SD), %	17.7 (7.5)	18.1 (7.5)	17.3 (7.5)
Antihypertensive medication, No. (%)			
No	234 (87.0)	118 (86.1)	116 (87.9)
Yes	35 (13.0)	19 (13.9)	16 (12.1)
Lipid-lowering medication, No. (%)			
No	262 (97.4)	134 (97.8)	128 (97.0)
Yes	7 (2.6)	3 (2.2)	4 (3.0)

a Body mass index calculated as weight in kilograms divided by height in meters squared.

b Abnormal liver function was defined as ALT or AST exceeding 2 times the upper limit of normal.

c Prediabetic status was defined as FPG between 109.8 and 126.0 mg/dL, inclusive, or 2hPG between 140.4 and 199.8 mg/dL, inclusive.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; MET: metabolic equivalent; SD: standard deviation; TG: triglyceride; 2hPG: 2-hour postprandial plasma glucose.

SI conversion factors: To convert ALT and AST to $\mu\text{kat/L}$, multiply by 0.0167; hs-CRP to mg/L, by 10; LDL-C and TG to mmol/L, by 0.0259 and 0.0113, respectively; FPG and 2hPG to mmol/L, by 0.0555; HbA1c to proportion of total hemoglobin, by 0.01; and uric acid to mmol/L, by 0.0595.

eTable 3. Baseline characteristics in the per-protocol set of VAT area

Variable	Overall (N = 283)	Placebo (n = 143)	Berberine hydrochloride (n = 140)
Age, mean (SD), y	41.6 (10.5)	41.2 (10.3)	42.0 (10.7)
Sex, No. (%)			
Male	188 (66.4)	94 (65.7)	94 (67.1)
Female	95 (33.6)	49 (34.3)	46 (32.9)
Employment, No. (%)			
Unemployed	15 (5.3)	9 (6.3)	6 (4.3)
Employed	268 (94.7)	134 (93.7)	134 (95.7)
Education level, No. (%)			
≤ High school	62 (21.9)	37 (25.9)	25 (17.9)
≥ College	221 (78.1)	106 (74.1)	115 (82.1)
Smoking, No. (%)			
Never	187 (66.1)	94 (65.7)	93 (66.4)
Former	8 (2.8)	4 (2.8)	4 (2.9)
Current	88 (31.1)	45 (31.5)	43 (30.7)
Alcohol consumption, No. (%)			
Never	131 (46.3)	64 (44.8)	67 (47.9)
Former	8 (2.8)	5 (3.5)	3 (2.1)
Current	144 (50.9)	74 (51.8)	70 (50.0)

Variable	Overall (N = 283)	Placebo (n = 143)	Berberine
			hydrochloride (n = 140)
Physical activity, median (IQR), MET min/wk	1386 (693, 2772)	1386 (678, 2772)	1386 (693, 2772)
Waist circumference, mean (SD), cm	104.3 (10.1)	104.5 (9.9)	104.0 (10.4)
Body mass index, mean (SD)	31.8 (3.3)	31.9 (3.3)	31.8 (3.4)
^a			
Systolic blood pressure, mean (SD), mmHg	132.5 (13.3)	131.6 (12.9)	133.5 (13.7)
Diastolic blood pressure, mean (SD), mmHg	86.9 (9.5)	86.4 (9.0)	87.4 (10.0)
eGFR, mean (SD), mL/(min*1.73m ²)	117.61 (10.81)	117.46 (9.83)	117.77 (11.77)
ALT, mean (SD), U/L	34.2 (23.3)	35.4 (25.5)	32.9 (20.8)
AST, mean (SD), U/L	24.7 (11.8)	25.6 (13.2)	23.8 (10.1)
Liver function, No. (%) ^b			
Normal	194 (68.6)	101 (70.6)	93 (66.4)
Abnormal	89 (31.5)	42 (29.4)	47 (33.6)
FPG, mean (SD), mg/dL	95.04 (10.44)	95.04 (10.26)	94.86 (10.62)
2hPG, mean (SD), mg/dL	129.60 (32.94)	128.52 (33.30)	130.50 (32.76)
HbA1c, mean (SD), %	5.69 (0.45)	5.70 (0.44)	5.67 (0.46)

Variable	Overall (N = 283)	Placebo (n = 143)	Berberine
			hydrochloride (n = 140)
Prediabetic status, No. (%) ^c			
No	176 (62.2)	92 (64.3)	84 (60.0)
Yes	107 (37.8)	51 (35.7)	56 (40.0)
LDL-C, mean (SD), mg/dL	115.44 (32.05)	117.37 (31.27)	113.51 (32.82)
TG, mean (SD), mg/dL	195.58 (133.63)	188.50 (129.20)	203.54 (138.94)
Serum uric acid, mean (SD), mg/dL	6.90 (1.74)	6.90 (1.68)	6.90 (1.80)
hs-CRP, mean (SD), mg/dL	0.22 (0.35)	0.24 (0.37)	0.21 (0.33)
VAT area, mean (SD), cm ²	252.5 (73.5)	248.3 (68.4)	256.7 (78.4)
Antihypertensive medication, No. (%)			
No	248 (87.6)	124 (86.7)	124 (88.6)
Yes	35 (12.4)	19 (13.3)	16 (11.4)
Lipid-lowering medication, No. (%)			
No	276 (97.5)	140 (97.9)	136 (97.1)
Yes	7 (2.5)	3 (2.1)	4 (2.9)

^a Body mass index calculated as weight in kilograms divided by height in meters squared.

b Abnormal liver function was defined as ALT or AST exceeding 2 times the upper limit of normal.

c Prediabetic status was defined as FPG between 109.8 and 126.0 mg/dL, inclusive, or 2hPG between 140.4 and 199.8 mg/dL, inclusive.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; MET: metabolic equivalent; SD: standard deviation; TG: triglyceride; VAT: visceral adipose tissue; 2hPG: 2-hour postprandial plasma glucose.

SI conversion factors: To convert ALT and AST to $\mu\text{kat/L}$, multiply by 0.0167; hs-CRP to mg/L, by 10; LDL-C and TG to mmol/L, by 0.0259 and 0.0113, respectively; FPG and 2hPG to mmol/L, by 0.0555; HbA1c to proportion of total hemoglobin, by 0.01; and uric acid to mmol/L, by 0.0595.

eTable 4. Sensitivity analyses and post-hoc analyses of primary outcomes

Outcomes	Difference of changes between groups (97.5% CI)	p-value
Absolute change in liver fat content, %		
Adjust for age, sex, prediabetes, abnormal liver function, and use of lipid-lowering medications	0.90 (-0.37, 2.16)	0.11
Consider site as random effect	0.81 (-0.46, 2.07)	0.15
Full analysis set without imputation ^a	0.90 (-0.21, 2.01)	0.11
Relative change in VAT area, %		
Adjust for age, sex, prediabetes, abnormal liver function, and use of lipid-lowering medications	1.39% (-2.39, 5.17)	0.41
Consider site as random effect	1.38% (-2.43, 5.18)	0.42
Full analysis set without imputation ^a	1.45% (-1.83, 4.73)	0.38

Abbreviations: VAT: visceral adipose tissue.

^a These analyses were post-hoc.

eTable 5. Comparison of primary outcomes in the per-protocol set

Outcomes	Placebo			Berberine hydrochloride			Difference of changes between groups (97.5% CI)	p-value
	Before, mean (SD)	6 months, mean (SD)	Change, mean (SD)	Before, mean (SD)	6 months, mean (SD)	Change, mean (SD)		
Liver fat content, %	18.1 (7.5)	16.8 (7.0)	-1.4 (5.0)	17.3 (7.5)	16.9 (6.9)	-0.4 (5.4)	0.71 (-0.58, 1.99)	0.22
VAT area, cm ² ^a	248.3 (68.4)	240.7 (71.7)	-2.4% (13.9)	251.0 (79.7)	240.7 (71.7)	-1.8% (13.2)	0.85% (-2.75, 4.46)	0.60

a Data are means (SD). Value for change and difference is mean percentage.

Abbreviations: CI: confidence interval; SD: standard deviation; VAT: visceral adipose tissue.

eTable 6. Comparison of biomarkers of metabolism, inflammation and liver function in the full analysis set

Outcomes	Placebo N=168			Berberine hydrochloride N = 169			Difference of changes between groups (95% CI)	p-value
	Baseline, mean (SD)	6 months, mean (SD)	Change, mean (SD)	Baseline, mean (SD)	6 months, mean (SD)	Change, mean (SD)		
Metabolism								
HbA1c, %	5.71 (0.44)	5.78 (0.52)	0.06 (0.36)	5.68 (0.45)	5.70 (0.49)	0.02 (0.33)	-0.05 (-0.12, 0.02)	0.17
FPG, mg/dL	95.04 (11.16)	94.86 (15.48)	-0.36 (12.60)	94.32 (10.44)	95.22 (15.48)	0.72 (13.68)	1.08 (-1.80, 3.78)	0.48
2hPG, mg/dL	129.24 (33.84)	127.44 (39.42)	-1.62 (41.22)	129.78 (32.94)	126.00 (37.44)	-3.96 (40.50)	-1.80 (-9.54, 5.94)	0.65
HOMA-IR	4.13 (2.55)	4.33 (3.53)	0.20 (3.13)	4.05 (2.58)	4.06 (2.72)	0.00 (2.65)	-0.22 (-0.81, 0.37)	0.46
HOMA-β ^a	5.18 (0.51)	5.25 (0.69)	0.05 (0.65)	5.24 (0.74)	5.23 (0.77)	-0.00 (0.67)	-0.03 (-0.17, 0.10)	0.61
HOMA-IS	0.32 (0.16)	0.34 (0.21)	0.02 (0.18)	0.34 (0.19)	0.35 (0.20)	0.01 (0.19)	-0.01 (-0.04, 0.03)	0.75

TG, mg/dL	189.38		-22.12	203.54	183.19	-18.58		
	(131.86)	168.14 (90.27)	(108.85)	(135.40)	(130.09)	(122.57)	9.73 (-9.73, 30.09)	0.32
TC, mg/dL	186.10 (36.68)	167.95 (37.45)	-17.76 (33.98)	183.78 (39.77)	161.78 (40.15)	-21.99 (37.83)	-5.02 (-11.97, 1.93)	0.15
LDL-C, mg/dL	117.76 (31.27)	100.39 (30.50)	-17.37 (26.64)	113.13 (31.66)	90.35 (32.05)	-23.17 (32.05)	-7.72 (-13.13, -1.93)	0.008
HDL-C, mg/dL	41.70 (10.04)	34.75 (8.49)	-6.57 (7.34)	41.70 (10.81)	34.75 (10.81)	-6.95 (9.27)	-0.39 (-1.93, 1.16)	0.58
Lipoprotein(a), mg/dL	15.65 (20.23)	14.45 (18.52)	-0.77 (5.19)	16.19 (20.87)	15.19 (20.12)	-1.08 (6.72)	-0.21 (-1.46, 1.03)	0.74
ApoA1, mg/dL	141.40 (24.13)	129.35 (24.17)	-11.64 (23.97)	143.84 (26.05)	130.33 (28.43)	-13.62 (27.00)	-0.60 (-5.53, 4.33)	0.81
ApoB, mg/dL	80.27 (16.65)	67.61 (16.24)	-12.51 (15.17)	78.92 (18.52)	63.50 (16.63)	-15.28 (16.63)	-3.42 (-6.33, -0.51)	0.02
Serum uric acid, mg/dL	6.94 (1.69)	5.82 (1.53)	-1.11 (1.31)	6.94 (1.80)	5.86 (1.75)	-1.06 (1.46)	0.04 (-0.22, 0.31)	0.75
Systolic blood pressure, mmHg	131.96 (13.11)	131.42 (13.64)	-0.75 (10.06)	132.78 (13.34)	131.35 (13.75)	-1.56 (11.44)	-0.59 (-2.77, 1.59)	0.59

Diastolic blood								
pressure, mmHg	86.59 (9.15)	86.13 (9.71)	-0.51 (8.49)	87.29 (9.66)	85.76 (9.79)	-1.54 (7.63)	-0.81 (-2.43, 0.81)	0.32
Inflammation								
hs-CRP, mg/dL	0.24 (0.34)	0.29 (0.46)	0.05 (0.43)	0.22 (0.35)	0.20 (0.20)	-0.004 (0.27)	-0.07 (-0.14, -0.004)	0.04
Liver function								
FIB-4	0.77 (0.42)	0.73 (0.49)	-0.03 (0.31)	0.81 (0.40)	0.77 (0.44)	-0.04 (0.34)	-0.00 (-0.07, 0.07)	0.97
NFS	-2.10 (1.37)	-1.73 (1.35)	0.38 (1.01)	-1.88 (1.22)	-1.64 (1.24)	0.24 (0.98)	-0.08 (-0.28, 0.13)	0.46
ALT, U/L	35.4 (25.4)	25.3 (18.3)	-10.1 (19.9)	32.1 (20.1)	26.0 (17.6)	-6.1 (15.5)	2.39 (-0.59, 5.36)	0.12
AST, U/L	25.6 (13.1)	19.5 (10.6)	-6.2 (11.6)	24.0 (9.9)	20.3 (12.5)	-3.7 (12.2)	1.60 (-0.61, 3.81)	0.16
γ-GGT, U/L	42.4 (27.5)	37.8 (27.6)	-4.4 (20.3)	51.4 (67.0)	41.4 (50.3)	-7.4 (33.3)	-1.16 (-6.46, 4.14)	0.67

a The value of HOMA-β was log-transformed.

Abbreviations: ALT: alanine aminotransferase; ApoA1: apolipoprotein A1; ApoB: apolipoprotein B; AST: aspartate aminotransferase; CI: confidence interval; FIB-4: the Fibrosis-4 index; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment-insulin resistance; HOMA-IS: homeostatic model assessment-insulin sensitivity; HOMA-

β : homeostatic model assessment- β cell function; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; NFS: non-alcoholic fatty liver disease fibrosis score; SD: standard deviation; TC: total cholesterol; TG: triglyceride; γ -GGT: gamma-glutamyl transferase; 2hPG: 2-hour postprandial plasma glucose.

SI conversion factors: To convert ALT and AST to $\mu\text{kat/L}$, multiply by 0.0167; hs-CRP to mg/L , by 10; LDL-C and TG to mmol/L , by 0.0259 and 0.0113, respectively; FPG and 2hPG to mmol/L , by 0.0555; HbA1c to proportion of total hemoglobin, by 0.01; and uric acid to mmol/L , by 0.0595.

eTable 7. Subgroup analysis for primary and other outcomes stratified by baseline high sensitivity C-reactive protein in the full analysis set

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
hs-CRP, mg/dL	< 0.2	111	0.08 (0.27)	118	0.06 (0.12)	-0.02 (-0.08, 0.03)	0.03
	0.2-0.3	20	0.02 (0.16)	24	0.03 (0.27)	0.007 (-0.13, 0.14)	
	> 0.3	34	-0.03 (0.80)	25	-0.32 (0.50)	-0.29 (-0.65, 0.08)	
TG, mg/dL	< 0.2	111	-27.43 (122.12)	118	-18.58 (127.43)	11.50 (-14.16, 37.17)	0.82
	0.2-0.3	20	-24.78 (54.87)	24	-62.83 (82.30)	-7.96 (-41.59, 24.78)	
	> 0.3	34	-4.42 (86.73)	25	26.55 (124.78)	28.32 (-23.01, 78.76)	
TC, mg/dL	< 0.2	111	-17.37 (31.27)	118	-17.76 (37.83)	-0.77 (-9.27, 7.33)	0.04
	0.2-0.3	20	-36.68 (40.54)	24	-38.99 (36.68)	-8.11 (-25.48, 9.27)	
	> 0.3	34	-8.88 (36.29)	25	-25.10 (35.52)	-18.53 (-35.52, -1.16)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
LDL-C, mg/dL	< 0.2	111	-16.22 (25.48)	118	-19.31 (32.82)	-3.86 (-10.81, 3.09)	0.01
	0.2-0.3	20	-34.75 (30.12)	24	-32.05 (27.80)	-5.79 (-18.15, 6.95)	
	> 0.3	34	-10.04 (25.87)	25	-31.66 (29.34)	-23.55 (-36.68, -10.04)	
HDL-C, mg/dL	< 0.2	111	-6.56 (7.72)	118	-6.56 (9.65)	0.39 (-1.93, 2.32)	0.25
	0.2-0.3	20	-8.49 (7.72)	24	-10.04 (7.72)	-2.70 (-6.56, 1.16)	
	> 0.3	34	-5.79 (6.17)	25	-7.33 (7.33)	-1.54 (-4.63, 1.54)	
Lipoprotein (a), mg/dL	< 0.2	111	-0.96 (4.72)	118	-0.77 (7.15)	0.35 (-1.19, 1.89)	0.19
	0.2-0.3	20	0.19 (5.81)	24	-1.32 (5.41)	-1.63 (-4.97, 1.70)	
	> 0.3	34	-0.73 (6.30)	25	-2.31 (5.78)	-1.63 (-4.51, 1.25)	
ApoA1, mg/dL	< 0.2	111	-12.04 (23.47)	118	-11.22 (28.22)	1.84 (-4.20, 7.87)	0.11
	0.2-0.3	20	-20.25 (24.27)	24	-23.00 (24.62)	-3.94 (-17.42, 9.53)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
ApoB, mg/dL	> 0.3	34	-5.29 (24.32)	25	-15.92 (21.42)	-8.08 (-19.74, 3.58)	0.009
	< 0.2	111	-12.44 (13.95)	118	-13.04 (16.15)	-1.36 (-4.79, 2.08)	
	0.2-0.3	20	-19.55 (19.80)	24	-19.58 (18.44)	-1.28 (-8.52, 5.96)	
	> 0.3	34	-8.59 (14.94)	25	-21.68 (15.15)	-12.20 (-19.28, -5.12)	
Liver fat content, %	< 0.2	113	-1.2 (4.7)	119	-0.0 (5.5)	0.99 (-0.26, 2.25)	0.85
	0.2-0.3	20	-1.2 (6.6)	24	0.1 (7.1)	1.01 (-2.33, 4.36)	
	> 0.3	35	-0.8 (5.5)	26	0.7 (8.2)	0.54 (-2.39, 3.48)	
VAT area, cm ² ^a	< 0.2	113	-2.6% (13.4)	119	-0.5% (17.0)	1.93% (-2.01, 5.87)	0.36
	0.2-0.3	20	-4.7% (15.4)	24	1.5% (9.2)	6.48% (-1.10, 14.07)	
	> 0.3	35	1.5% (16.5)	26	-3.1% (20.2)	-3.61% (-12.95, 5.74)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
Weight, kg	< 0.2	110	-2.3 (3.9)	117	-1.7 (3.6)	0.66 (-0.31, 1.63)	0.02
	0.2-0.3	20	-1.8 (2.5)	24	-2.1 (2.8)	-0.38 (-2.01, 1.24)	
	> 0.3	34	-0.5 (2.9)	25	-2.2 (5.0)	-1.79 (-3.89, 0.30)	
Body mass index	< 0.2	110	-0.8 (1.3)	117	-0.6 (1.3)	0.20 (-0.14, 0.53)	0.04
	0.2-0.3	20	-0.6 (1.0)	24	-0.7 (1.0)	-0.09 (-0.67, 0.50)	
	> 0.3	34	-0.2 (1.0)	25	-0.7 (1.7)	-0.54 (-1.27, 0.19)	
Waist circumference, cm	< 0.2	110	-3.6 (6.1)	117	-2.8 (4.8)	0.74 (-0.65, 2.13)	0.02
	0.2-0.3	20	-3.3 (5.2)	24	-2.6 (6.1)	0.50 (-2.75, 3.74)	
	> 0.3	34	0.0 (4.9)	25	-2.7 (6.2)	-2.90 (-5.83, 0.02)	
Waist-height ratio	< 0.2	110	-0.02 (0.04)	117	-0.02 (0.03)	0.00 (-0.00, 0.01)	0.02
	0.2-0.3	20	-0.02 (0.03)	24	-0.02 (0.04)	0.00 (-0.02, 0.02)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
HbA1c, %	> 0.3	34	0.00 (0.03)	25	-0.02 (0.04)	-0.02 (-0.04, 0.00)	0.62
	< 0.2	110	0.06 (0.29)	118	0.01 (0.24)	-0.07 (-0.13, -0.00)	
	0.2-0.3	20	-0.03 (0.31)	24	0.18 (0.49)	0.21 (-0.05, 0.47)	
FPG, mg/dL	> 0.3	34	0.12 (0.54)	25	-0.08 (0.44)	-0.20 (-0.46, 0.07)	0.36
	< 0.2	110	-0.18 (11.16)	118	-0.02 (12.42)	-0.18 (-3.06, 2.88)	
	0.2-0.3	20	-2.16 (14.04)	24	4.14 (16.92)	4.68 (-4.86, 14.22)	
2hPG, mg/dL	> 0.3	34	0.04 (16.02)	25	1.62 (15.12)	1.44 (-7.02, 9.72)	0.61
	< 0.2	109	-2.16 (40.50)	117	-5.94 (37.98)	-4.50 (-13.32, 4.32)	
	0.2-0.3	20	-5.58 (41.22)	24	11.52 (43.74)	17.64 (-7.74, 43.02)	
HOMA-IR	> 0.3	34	2.16 (44.28)	25	-9.72 (46.80)	-4.86 (-25.74, 15.84)	0.15
	< 0.2	111	-0.01 (2.01)	118	0.07 (2.14)	0.05 (-0.46, 0.57)	
	0.2-0.3	20	0.16 (2.16)	24	-0.45 (4.19)	0.28 (-1.39, 1.94)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
HOMA- β ^b	> 0.3	34	0.91 (5.64)	25	0.12 (3.01)	-1.14 (-3.57, 1.30)	0.11
	< 0.2	109	0.02 (0.60)	118	0.06 (0.59)	0.05 (-0.10, 0.20)	
	0.2-0.3	20	0.19 (0.68)	24	-0.35 (0.93)	-0.11 (-0.50, 0.27)	
HOMA-IS	> 0.3	33	0.10 (0.77)	25	0.06 (0.65)	-0.17 (-0.55, 0.20)	0.43
	< 0.2	111	0.03 (0.19)	118	0.01 (0.19)	-0.02 (-0.07, 0.03)	
	0.2-0.3	20	-0.00 (0.18)	24	0.05 (0.15)	0.04 (-0.06, 0.14)	
Serum uric acid, mg/dL	> 0.3	34	0.00 (0.13)	25	-0.01 (0.20)	0.01 (-0.07, 0.09)	0.78
	< 0.2	111	-0.97 (1.30)	118	-0.97 (1.41)	0.05 (-0.27, 0.37)	
	0.2-0.3	20	-1.53 (1.25)	24	-1.52 (1.07)	0.08 (-0.57, 0.74)	
Systolic blood pressure, mmHg	> 0.3	34	-1.32 (1.33)	25	-1.09 (1.92)	-0.11 (-0.83, 0.62)	0.42
	< 0.2	110	-0.44 (9.20)	117	-2.07 (9.93)	-1.23 (-3.56, 1.10)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
	0.2-0.3	20	-4.00 (10.36)	24	-2.40 (12.25)	2.25 (-4.54, 9.03)	
	> 0.3	34	0.16 (12.29)	25	1.63 (16.34)	0.76 (-6.13, 7.65)	
Diastolic blood pressure, mmHg	< 0.2	110	-0.09 (7.55)	117	-1.66 (7.24)	-1.29 (-3.03, 0.46)	0.41
	0.2-0.3	20	-2.25 (7.93)	24	-3.15 (8.12)	-0.10 (-5.14, 4.93)	
	> 0.3	34	-0.86 (11.38)	25	0.59 (8.73)	0.37 (-4.90, 5.65)	
ALT, U/L	< 0.2	111	-9.7 (19.2)	118	-5.4 (15.4)	2.60 (-0.75, 5.95)	0.59
	0.2-0.3	20	-11.7 (17.0)	24	-8.7 (17.6)	5.20 (-3.76, 14.16)	
	> 0.3	34	-10.4 (24.0)	25	-6.8 (13.7)	-0.44 (-9.48, 8.61)	
AST, U/L	< 0.2	111	-5.7 (8.9)	118	-3.8 (9.7)	1.28 (-0.45, 3.02)	0.83
	0.2-0.3	20	-6.9 (7.4)	24	-2.8 (22.3)	3.85 (-6.97, 14.66)	
	> 0.3	34	-7.4 (19.4)	25	-3.8 (9.6)	-1.11 (-8.25, 6.03)	

Outcomes	hs-CRP subgroups, mg/dL	Placebo		Berberine hydrochloride		Difference of changes between groups (95% CI)	p for interaction
		No. of participants	Change, mean (SD)	No. of participants	Change, mean (SD)		
γ -GGT, U/L	< 0.2	111	-3.9 (18.5)	118	-7.3 (37.4)	-1.56 (-8.09, 4.98)	0.70
	0.2-0.3	20	-7.9 (21.3)	24	-5.6 (26.2)	2.99 (-11.17, 17.15)	
	> 0.3	34	-3.9 (25.5)	25	-9.8 (13.4)	-3.55 (-14.21, 7.10)	

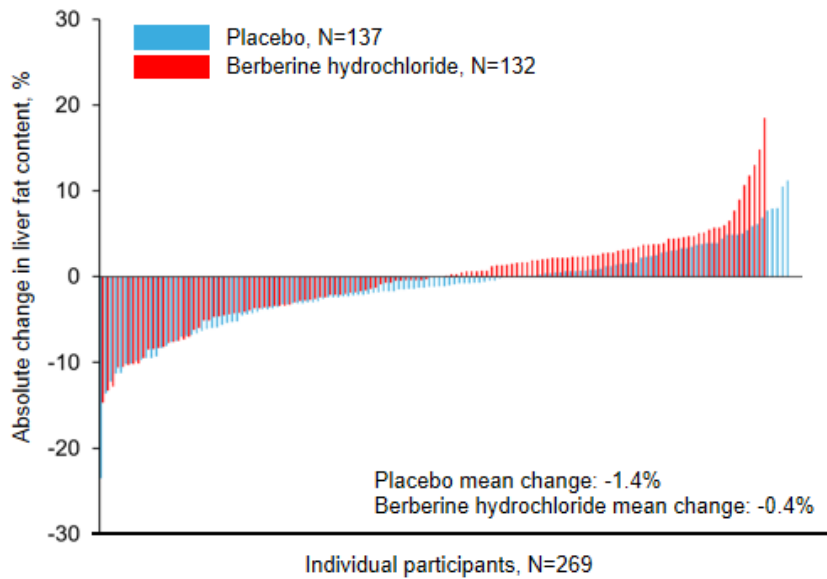
a Value for change and difference is mean percentage.

b The value of HOMA- β was log-transformed.

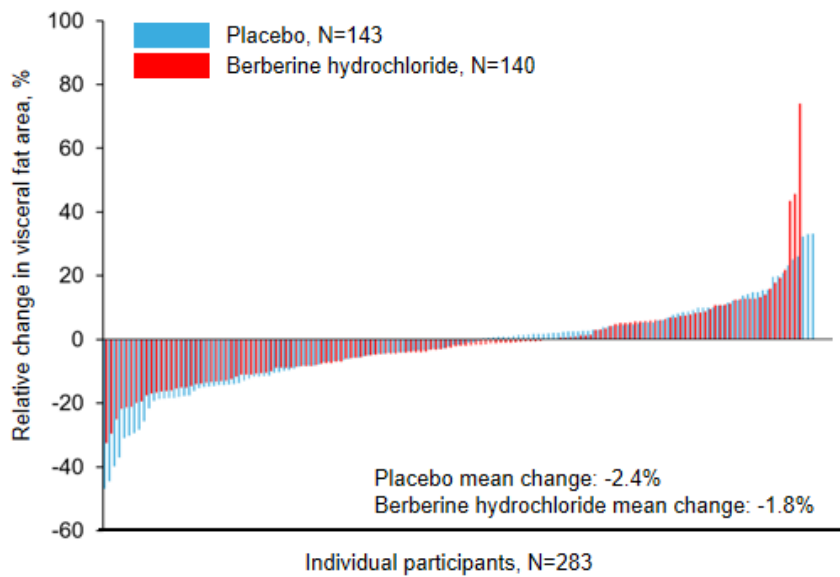
Abbreviations: ALT: alanine aminotransferase; ApoA1: apolipoprotein A1; ApoB: apolipoprotein B; AST: aspartate aminotransferase; CI: confidence interval; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment-insulin resistance; HOMA- β : homeostatic model assessment- β cell function; HOMA-IS: homeostatic model assessment-insulin sensitivity; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation; TC: total cholesterol; TG: triglyceride; VAT: visceral adipose tissue; γ -GGT: gamma-glutamyl transferase; 2hPG: 2-hour postprandial plasma glucose.

SI conversion factors: To convert ALT and AST to $\mu\text{kat/L}$, multiply by 0.0167; hs-CRP to mg/L , by 10; LDL-C and TG to mmol/L , by 0.0259 and 0.0113, respectively; FPG and 2hPG to mmol/L , by 0.0555; HbA1c to proportion of total hemoglobin, by 0.01; and uric acid to mmol/L , by 0.0595.

(A) Absolute change in liver fat content



(B) Relative change in VAT area



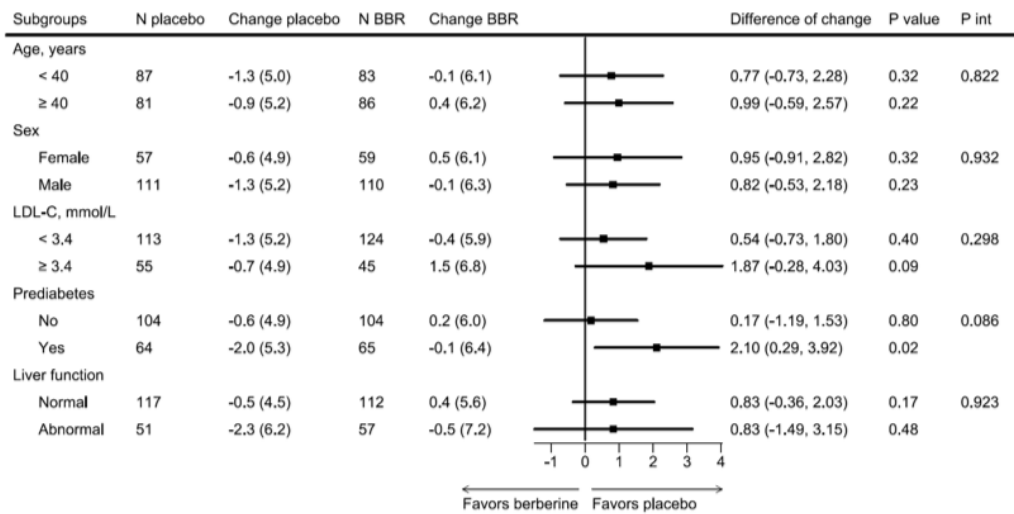
eFigure 1. Participant-level changes in primary outcomes in the per-protocol set

(A) Absolute change in liver fat content; (B) Relative change in VAT area.

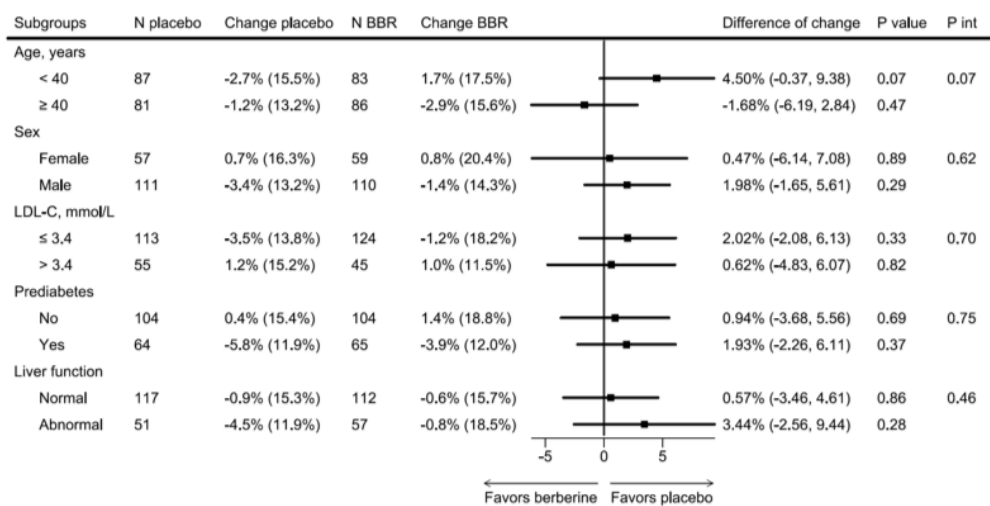
Individual, participant-level changes in primary outcomes are shown in this waterfall plot. Participants assigned to berberine hydrochloride are in red and those assigned to placebo are in blue.

Abbreviations: VAT: visceral adipose tissue.

(A) Absolute change in liver fat content



(B) Relative change in VAT area



eFigure 2. Effect of berberine hydrochloride on primary outcomes by subgroups

(A) Absolute change in liver fat content; (B) Relative change in VAT area. Differences are plotted as squares; the horizontal lines represent 95% confidence intervals. The overall difference is represented by a diamond.

Abbreviations: BBR: berberine; LDL-C: low-density lipoprotein cholesterol; VAT: visceral adipose tissue.

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