

# Increased Serum Adipsin Correlates with MAFLD and Metabolic Risk Abnormalities

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**Purpose:** A panel of international experts proposed a new definition of fatty liver in 2020, namely metabolic dysfunction-associated fatty liver disease (MAFLD). As an adipokine, adipsin is closely related to metabolic-related diseases. In this study, we aimed to evaluate the relationship among MAFLD, serum adipsin, and metabolic risk abnormalities.

**Methods:** Our study was a cross-sectional study based on the first follow-up of the Guangzhou Nutrition and Health Study (GNHS). A total of 908 patients with hepatic steatosis were involved in our study. Detailed data of patients were collected based upon questionnaire information, physical examination, and blood biochemical test.

**Results:** Among the 908 patients, 789 patients were diagnosed with MAFLD. The levels of serum adipsin in the MAFLD group and non-MAFLD group were (3543.00 (3187.94–3972.50) ng/mL) and (3095.33 (2778.71–3354.77) ng/mL) ( $P < 0.001$ ), respectively. After adjusting for potential confounders, adipsin levels were found to be associated with MAFLD. The OR was 3.46 (95% CI: 1.57–7.64) for adipsin when comparing subjects in the highest tertile with those in the lowest tertile. With the increase in the number of metabolic risk abnormalities, both the levels of serum adipsin and the proportion of moderate to severe fatty liver increased (all  $p$ -trend  $< 0.001$ ).

**Conclusion:** Increased serum adipsin correlates with MAFLD. Both adipsin levels as well as fatty liver severity increase with higher numbers of metabolic risk abnormalities.

**Keywords:** metabolic dysfunction-associated fatty liver disease, adipsin, metabolic risk abnormalities, hepatic steatosis

## Introduction

Traditionally, nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis ( $\geq 5\%$ ) with the absence of significant alcohol consumption and the lack of other secondary causes of liver fat accumulation.<sup>1</sup> At present, an increasing number of studies have shown that NAFLD is related to metabolism.<sup>2,3</sup> The metabolic risk factors behind NAFLD-related pathological progressions should not be ignored. In 2020, a panel of international experts proposed a new term “metabolic dysfunction-associated fatty liver disease” (MAFLD) to replace NAFLD as the definition of fatty liver disease.<sup>4</sup> The diagnostic criteria of MAFLD are based on the presence of both hepatic steatosis as well as one of the following three conditions, namely overweight/obesity, type 2 diabetes mellitus or metabolic dysregulation.<sup>4</sup> A meta-analysis showed that the global prevalence of MAFLD affects 38.77% (95% CI: 32.94–44.95%) of the population.<sup>5</sup> This significantly exceeds the previous estimation of the global prevalence of NAFLD.<sup>6–8</sup> Additionally, MAFLD has been found to be positively associated with increased risks of all-cause mortality in the United States,<sup>9</sup> and MAFLD increases mortality risk independent of excessive alcohol consumption.<sup>10</sup>

Adipokines are polypeptides produced by adipose tissue and can significantly influence the progression of NAFLD by regulating hepatic fat accumulation, insulin resistance and fibrosis.<sup>11,12</sup> Adipsin was the first adipokine described which is equivalent to complement factor D and is expressed at high levels in adipocytes.<sup>13,14</sup> It plays an important role in glucose and lipid metabolism, energy balance and maintenance of islet  $\beta$ -cell function.<sup>15–17</sup> In our previous study, we found that

increased circulating levels of adipon were positively associated with the risk of NAFLD.<sup>18</sup> As an adipokine, adipon is closely related to metabolic-related diseases. To date, there has been no studies exploring the relationship between adipon and MAFLD. In this study, we investigated the levels of serum adipon in both the MAFLD group and the non-MAFLD group and compared the differences among different MAFLD subgroups. In addition, we aimed to evaluate the association between serum adipon levels and MAFLD. Since MAFLD emphasizes the role of metabolism, we will also explore the changes in serum adipon levels and the severity of fatty liver as the number of metabolic risk abnormalities increases.

## Methods

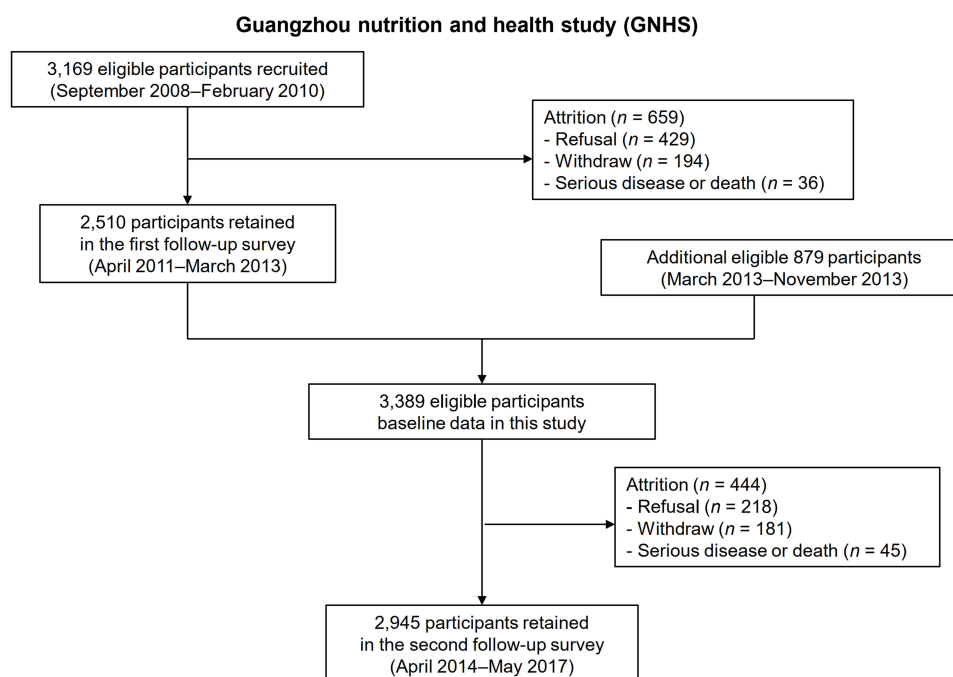
### Study Design and Participants

The Guangzhou Nutrition and Health Study (GNHS) is a community-based prospective cohort study in China focusing on evaluating the risk factors of chronic diseases. The details of GNHS can be found in a previous article.<sup>19</sup> Participants in this cohort and the time of enrollment are shown in Figure 1. Our study was a cross-sectional study based on the first follow-up of GNHS. Among the 2510 participants who completed the follow-up, 908 patients were diagnosed with hepatic steatosis by ultrasound and were selected as the subjects of our study. The specific grouping characteristics of the research subjects are shown in Figure 2.

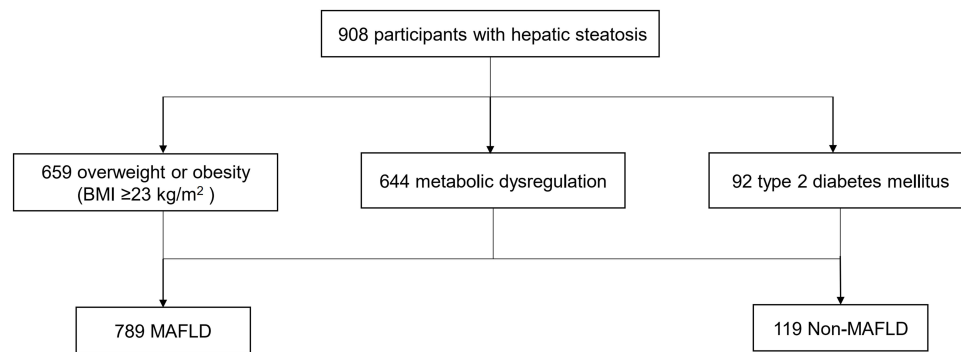
The GNHS was registered on ClinicalTrials.gov (registration number NCT03179657) and approved by the Ethics Committee of the School of Public Health at Sun Yat-sen University (approval number ZDGWYL2009-3), which meets the guidelines in the Declaration of Helsinki. Written informed consent was obtained from all participants.

### Clinical and Laboratory Data Collection

Participants were interviewed face-to-face by trained investigators using standardized questionnaires covering demographic sociological characteristics, economic status, behavior, and lifestyle. Height, weight, waist circumference, hip circumference and neck circumference were measured twice and averaged. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m<sup>2</sup>). Blood pressure was measured twice and averaged on the left arm of participants using an automated sphygmomanometer (HEM 7011; OMRON Corp., Osaka, Japan). The metabolic



**Figure 1** Flow chart of participants and enrollment time in Guangzhou Nutrition and Health Study.



**Figure 2** Specific grouping characteristics of the participants in this study.

equivalent intensity was calculated to estimate daily physical activity levels of participants using a 24-h physical activity questionnaire.<sup>20</sup> The fat mass of the trunk region was tested using dual-energy X-ray absorptiometry scans (Discovery W; Hologic Inc., Waltham, MA, USA). All venous blood samples of participants were obtained after overnight fasting. The serum was separated into several aliquots and stored at  $-80^{\circ}\text{C}$  within 2 h. The baseline biochemical measurements were determined by a Hitachi 7600–010 automated analyzer (Hitachi, Tokyo, Japan) and included fasting glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb), uric acid (UA), and insulin. The homeostasis model assessment of insulin resistance (HOMA-IR) was defined as  $[\text{fasting glucose (mmol/L)} \times \text{insulin } (\mu\text{U/mL})]/22.5$ . Adipsin levels were measured by quantitative sandwich enzyme immunoassay using kits obtained from R&D Systems (DFD00, Minneapolis, MN, USA) with a Spark 10M Multimode Reader Platform (Tecan Trading AG, Männedorf, Switzerland).

## Diagnosis of Hepatic Steatosis

Abdominal ultrasound was performed using a Doppler sonographer with a 3.5 MHz probe (Sonoscape SSI-5500, Shenzhen, China) by an experienced physician who was unaware of participant information. Presence of fatty liver disease and the degree of steatosis were evaluated according to the criteria used by Graif<sup>21</sup> (ranging from absent, mild or moderate to severe), and reported in our previous article.<sup>22</sup>

## Working Definitions

The diagnostic criteria of MAFLD are based on the presence of both hepatic steatosis and one of the following three conditions, namely overweight/obesity, type 2 diabetes mellitus (T2DM) or metabolic dysregulation (MD). Metabolic dysregulation is defined by the presence of at least two metabolic risk abnormalities: (1) waist circumference  $\geq 90/80$  cm in Asian men and women; (2) blood pressure  $\geq 130/85$  mmHg or specific drug treatment; (3) plasma triglycerides  $\geq 1.70$  mmol/L or specific drug treatment; (4) plasma HDL-cholesterol  $< 1.0$  mmol/L for men and  $< 1.3$  mmol/L for women or specific drug treatment; (5) prediabetes [fasting glucose levels 5.6 to 6.9 mmol/L]; (6) homeostasis model assessment of insulin resistance score  $\geq 2.5$ ; and (7) plasma high-sensitivity C-reactive protein level  $> 2$  mg/L.<sup>4</sup> In patients diagnosed with MAFLD, we defined the severity of MAFLD based on the degree of hepatic steatosis.

Metabolic syndrome (MetS) is diagnosed by meeting at least three of the following criteria:<sup>23</sup> (1) waist circumference  $\geq 90/80$  cm in Asian men and women; (2) triglycerides  $\geq 1.7$  mmol/L; (3) high-density lipoprotein cholesterol  $< 1.0$  mmol/L for men and  $< 1.3$  mmol/L for women; (4) systolic blood pressure  $\geq 130$  mmHg and/or diastolic blood pressure  $\geq 85$  mmHg; and (5) fasting plasma glucose  $\geq 5.6$  mmol/L.

Hypertension is diagnosed by the following conditions: systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg or having a history of hypertension or using antihypertensive drugs. T2DM is defined as fasting glucose  $\geq 7.0$  mmol/L or having a history of T2DM or taking antidiabetic medications. The diagnostic criteria for dyslipidemia are as

follows: TC  $\geq 6.2$  mmol/L or TG  $\geq 2.3$  mmol/L or HDL-cholesterol  $< 1.0$  mmol/L or LDL-cholesterol  $\geq 4.1$  mmol/L.<sup>24</sup> In addition, people under lipid-lowering therapy can also be considered to have dyslipidemia.

In this study, smoking was defined as smoking at least one cigarette a day for at least six months, and alcohol drinking was defined as drinking once a week for at least six months.

## Statistical Analysis

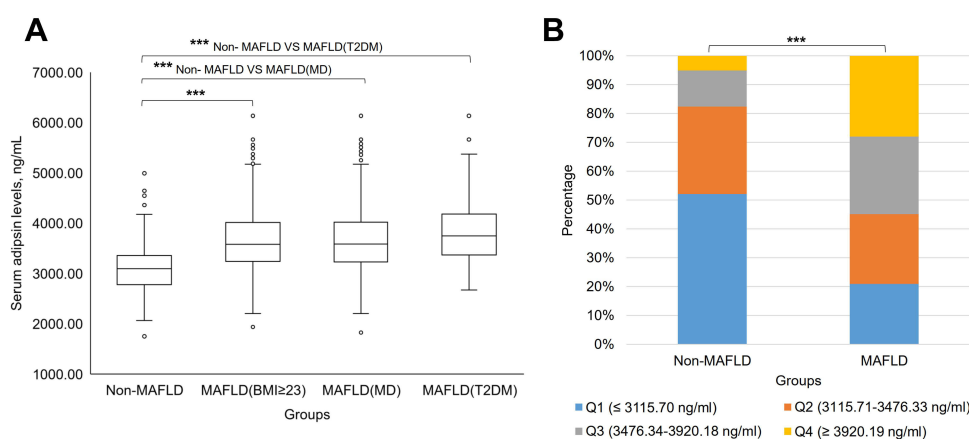
The continuous variables were expressed as means  $\pm$  standard deviation or median (interquartile range) according to whether the data were normally distributed. Categorical variables are presented as frequency (percentage). Independent samples *t*-test, Mann–Whitney *U*-test and Pearson Chi-Square test were used to compare between two groups. One-way ANOVA, Kruskal–Wallis test, and Pearson Chi-Square test were used to compare among multiple groups. The trend tests were conducted by Jonckheere–Terpstra, linear contrast in one-way ANOVA and linear-by-linear association chi square test. Binary logistic regression models were used to examine the associations of serum adipsin levels with MAFLD. The lowest tertile of serum adipsin levels served as the reference group. Age, gender, education, smoking, drinking, physical activities, hypertension, dyslipidemia, TG, HDL-C, UA, HOMA-IR, and AST/ALT were adjusted in binary logistic regression models. The correlations of serum adipsin levels with other variables were tested by Spearman correlation analysis.

Data on education levels were missing for 11 participants and were filled in by the mode value. Data on trunk fat and percentage of trunk fat were missing for 5 participants and were filled in by the median value. Statistical analysis was performed using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). A *p* value  $< 0.05$  (two-sided) was considered to be statistically significant.

## Results

### Comparison Between the MAFLD and Non-MAFLD Groups

As shown in Figure 3A, serum adipsin levels were higher in the MAFLD group (regardless of the participants were diagnosed with MAFLD based on having overweight/obesity, T2DM or MD) than in the non-MAFLD group (all  $P < 0.001$ ). Serum adipsin levels in the MAFLD group (3543.00 (3187.94–3972.50) ng/mL) were higher than those in the non-MAFLD group (3095.33 (2778.71–3354.77) ng/mL) ( $P < 0.001$ ). Under univariate comparisons between groups, age, BMI, WC, HC, NC, WHR, trunk fat, trunk fat percentage, SBP, DBP, TG, fasting glucose, insulin, HOMA-IR, ALT, and UA levels were found to be higher in the MAFLD group than those in the non-MAFLD group. Compared with the non-MAFLD group, the MAFLD group had higher proportion of T2DM, hypertension, dyslipidemia and MetS. In addition, MAFLD subjects had lower levels of HDL-C and AST/ALT than non-MAFLD subjects. There were no significant differences in gender, education, smoking, drinking, physical activity levels as well as levels of TC, LDL-C, AST, ALP, and albumin between the two groups (Table 1). The differences in the distribution of adipsin quartile levels



**Figure 3** (A) Comparison of the non-MAFLD group and MAFLD groups diagnosed by different criteria. (B) Distribution of adipsin quartile levels between the MAFLD and non-MAFLD groups. \*\*\* $p < 0.001$ .

**Table 1** Clinical Characteristics of Subjects in Non-MAFLD and MAFLD Groups

Variables	Non-MAFLD (n=119)	MAFLD (n=789)	P value
Age, years <sup>b</sup>	58.92 (55.50–62.92)	60.17 (56.75–64.00)	0.020*
Male, n (%) <sup>c</sup>	34 (28.57)	252 (31.94)	0.461
Educational level, n (%) <sup>c</sup>			
No formal education or primary school	5 (4.20)	46 (5.83)	0.453
Middle school	20 (16.81)	174 (22.05)	
High school or technical secondary school	61 (51.26)	380 (48.16)	
College or university	33 (27.73)	189 (23.95)	
Smoking, n (%) <sup>c</sup>	8 (6.72)	67 (8.49)	0.513
Drinking, n (%) <sup>c</sup>	11 (9.24)	62 (7.86)	0.604
Physical activity, MET/day <sup>b</sup>	23.68 (20.20–28.55)	23.10 (19.74–27.53)	0.151
BMI, kg/m <sup>2b</sup>	21.57 (20.40–22.24)	25.12 (23.57–27.07)	<0.001***
Adipsin, ng/ml <sup>b</sup>	3095.33 (2778.71–3354.77)	3543.00 (3187.94–3972.50)	<0.001***
WC, cm <sup>b</sup>	78.15 (74.30–80.80)	88.75 (84.30–93.80)	<0.001***
HC, cm <sup>b</sup>	89.65 (87.15–91.90)	95.00 (91.73–98.63)	<0.001***
NC, cm <sup>b</sup>	31.70 (30.70–33.95)	34.15 (32.50–36.55)	<0.001***
WHR <sup>a</sup>	0.87±0.06	0.94±0.06	<0.001***
Trunk fat, kg <sup>b</sup>	8.10 (6.88–9.12)	11.23 (9.76–13.02)	<0.001***
Trunk fat percentage, % <sup>b</sup>	32.44 (27.17–35.16)	36.80 (32.07–40.52)	<0.001***
SBP, mmHg <sup>b</sup>	114.50 (107.00–123.50)	127.50 (117.00–140.00)	<0.001***
DBP, mmHg <sup>b</sup>	70.50 (64.00–75.00)	78.00 (71.00–85.00)	<0.001***
TC, mmol/L <sup>a</sup>	5.58±1.01	5.51±0.99	0.494
TG, mmol/L <sup>b</sup>	1.03 (0.81–1.25)	1.51 (1.05–2.09)	<0.001***
LDL-C, mmol/L <sup>a</sup>	3.64±0.92	3.64±0.91	0.987
HDL-C, mmol/L <sup>b</sup>	1.52 (1.34–1.91)	1.24 (1.02–1.47)	<0.001***
Fasting glucose, mmol/L <sup>b</sup>	4.49 (4.19–4.81)	4.80 (4.40–5.35)	<0.001***
Insulin, μU/mL <sup>b</sup>	6.38 (4.38–7.90)	10.24 (7.58–14.43)	<0.001***
HOMA-IR <sup>b</sup>	1.24 (0.88–1.57)	2.26 (1.59–3.22)	<0.001***
ALT, U/L <sup>b</sup>	13.00 (10.00–19.00)	17.00 (13.00–22.50)	<0.001***
AST, U/L <sup>b</sup>	19.00 (15.00–21.00)	18.00 (16.00–22.00)	0.432
AST/ALT <sup>b</sup>	1.31 (1.11–1.56)	1.08 (0.88–1.31)	<0.001***
ALP, U/L <sup>b</sup>	69.35 (55.59–81.54)	71.59 (60.03–84.30)	0.099
Albumin, g/L <sup>b</sup>	45.60 (41.70–48.30)	45.60 (42.30–47.90)	0.946
UA, μmol/L <sup>b</sup>	311.31 (277.96–346.97)	348.90 (299.74–404.73)	<0.001***
T2DM, n (%) <sup>c</sup>	0	92 (11.66)	<0.001***
Hypertension, n (%) <sup>c</sup>	21 (17.65)	383 (48.54)	<0.001***
Dyslipidemia, n (%) <sup>c</sup>	62 (52.10)	563 (71.36)	<0.001***
MetS, n (%) <sup>c</sup>	0	315 (39.92)	<0.001***

**Note:** \* $P < 0.05$ ; \*\*\* $P < 0.001$ . <sup>a</sup>Independent samples *t*-test, <sup>b</sup>Mann–Whitney *U*-test; <sup>c</sup>Pearson Chi-Square test.

**Abbreviations:** BMI, body mass index; WC, waist circumference; HC, hip circumference; NC, neck circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; UA, uric acid; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome.

between the two groups are shown in [Figure 3B](#), with adipsin levels in Q3 and above accounting for more than 50% in the MAFLD group and less than 20% in the non-MAFLD group ( $P < 0.001$ ).

## Association Between Serum Adipsin Levels and MAFLD

The ORs and 95% CI for the association of MAFLD with serum adipsin levels are shown in [Table 2](#). In model 1, the OR (95% CI) of MAFLD was 10.76 (5.27–21.94;  $p$ -trend  $< 0.001$ ) for adipsin in the highest tertile compared with that in the lowest tertile. After adjusting for age, gender, education, smoking, drinking, physical activity, hypertension, and dyslipidemia in model 2, we found that the OR (95% CI) of MAFLD was 7.90 (3.81–16.38;  $p$ -trend  $< 0.001$ ) when

**Table 2** Association Between Serum Adipsin Levels and MAFLD

	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Adipsin (ng/mL, median [range])						
Tertile 1 (2976.82 [<3237.85])	Reference		Reference		Reference	
Tertile 2 (3476.33 [3237.85–3748.62])	2.54 (1.64–3.94)	<0.001***	2.08 (1.32–3.27)	0.002**	1.36 (0.81–2.27)	0.248
Tertile 3 (4113.90 [>3748.62])	10.76 (5.27–21.94)	<0.001***	7.90 (3.81–16.38)	<0.001***	3.46 (1.57–7.64)	0.002**
P for trend	<0.001***		<0.001***		0.002**	

**Notes:** \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . Binary logistic regression models: model 1: crude model; model 2: adjusted for age, gender, education, smoking, drinking, physical activity, hypertension, dyslipidemia; model 3: adjusted for variables in model 2 plus TG, HDL-C, UA, HOMA-IR, AST/ALT.

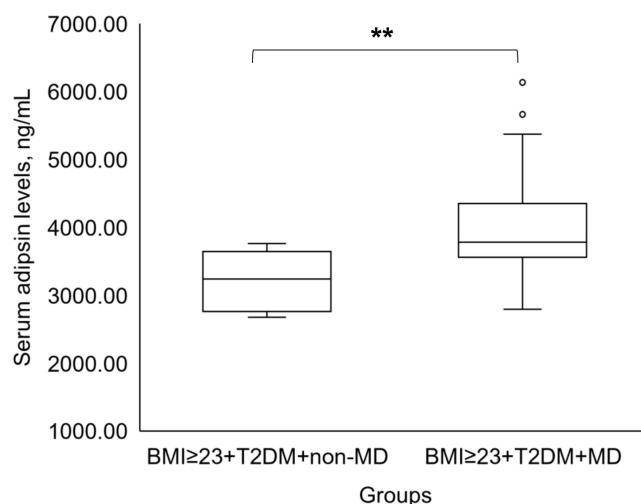
comparing adipsin levels in the highest tertile with that in the lowest tertile. Based on model 2, after further adjusting TG, HDL-C, UA, HOMA-IR, and AST/ALT, we found that the OR (95% CI) of MAFLD was 3.46 (1.57–7.64;  $p$ -trend = 0.002) when comparing adipsin levels in the highest tertile with that in the lowest tertile.

## Relationship Among Metabolic Risk Abnormalities, Severity of Fatty Liver and Serum Adipsin Levels

As shown in Figure 4, in the MAFLD group, the group with MD had higher adipsin levels than those without MD ( $P < 0.05$ ). Furthermore, we found that with the increase in the number of metabolic risk abnormalities, adipsin levels and the proportion of moderate to severe fatty liver in participants increased, all  $p$ -trend  $< 0.001$  (Figure 5). The levels of serum adipsin in the mild-MAFLD, moderate-MAFLD and severe-MAFLD groups were (3487.93 (3141.16–3920.39) ng/mL), (3631.98 (3293.55–3972.50) ng/mL) and (4150.88 (3238.88–4524.72) ng/mL) respectively,  $p$ -trend  $< 0.001$  (Figure 6).

## Correlation of Adipsin with Other Parameters in the MAFLD and Non-MAFLD Groups

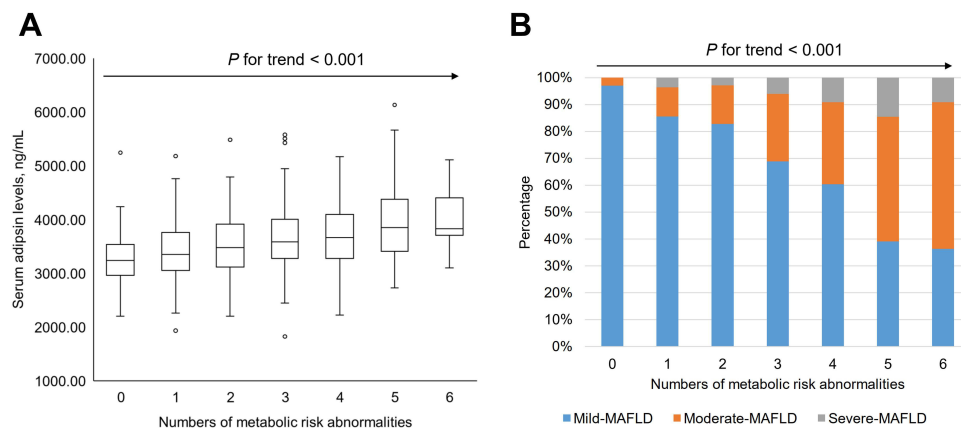
In the MAFLD group, the level of adipsin was positively correlated with BMI, WC, HC, NC, WHR, trunk fat, SBP, DBP, TG, insulin, HOMA-IR, and UA, and was inversely correlated with HDL-C, AST/ALT, and albumin. In the non-MAFLD group, adipsin was positively correlated with BMI, WC, WHR, trunk fat, insulin, and HOMA-IR, and was inversely correlated with HDL-C (Table 3).



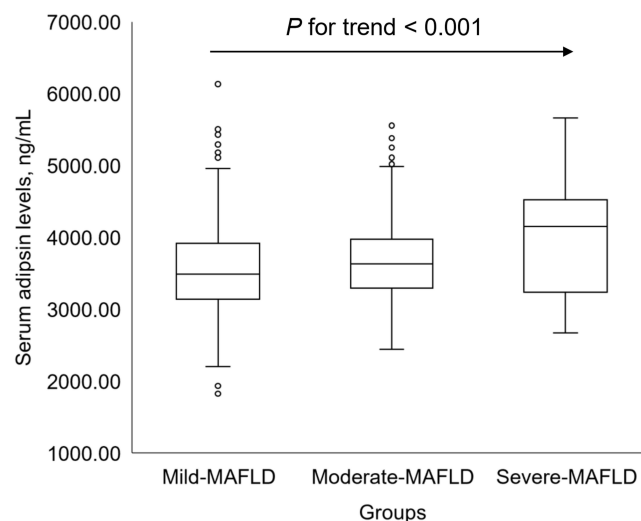
**Figure 4** Serum adipsin levels in MAFLD patients with or without metabolic dysregulation. \*\* $P < 0.01$ .

**Abbreviation:** MD, metabolic dysregulation.





**Figure 5 (A)** Relationship between the number of metabolic risk abnormalities and serum adipsin levels. The trend test was conducted by Jonckheere-Terpstra. **(B)** Relationship between the number of metabolic risk abnormalities and the severity of MAFLD. The trend test was conducted by linear-by-linear association chi square test.



**Figure 6** Differences in serum adipsin levels among MAFLD with different severity. The trend test was conducted by Jonckheere-Terpstra.

## Subgroup Analysis of the Clinical and Laboratory Characteristics Based on Severity of Fatty Liver in the MAFLD Group

In the subgroup analysis of clinical characteristics of patients with MAFLD based on the severity of fatty liver (Table 4), parameters including BMI, WC, HC, NC, WHR, trunk fat, trunk fat percentage, TG, HDL-C, fasting glucose, insulin, HOMA-IR, ALT, AST/ALT, and the proportion of T2DM, hypertension, dyslipidemia, and MetS were not completely consistent across groups (all  $P < 0.05$ ). A further trend test found that the more severe the fatty liver, BMI, WC, HC, NC, WHR, trunk fat, trunk fat percentage, SBP, TG, fasting glucose, insulin, HOMA-IR, ALT, AST, and albumin levels were higher, as well as the proportion of T2DM, hypertension, dyslipidemia and MetS (all  $P$  trend  $< 0.05$ ). There were similarities found in age, gender, education, smoking, drinking, physical activity levels as well as levels of DBP, TC, LDL-C, ALP, and UA among the three groups (all  $P$  and  $P$  trend  $> 0.05$ ).

## Discussion

Through cross-sectional analysis of 908 subjects, we found that the MAFLD group had higher adipsin levels than that in the non-MAFLD group. After adjusting for multiple variables, adipsin levels were associated with MAFLD. To our knowledge, we are the first to describe the relationship among the metabolic risk abnormalities, serum adipsin levels and

**Table 3** Spearman Correlation of Adipsin with Some Factors in MAFLD and Non-MAFLD Groups

	MAFLD		Non-MAFLD	
	r	P value	r	P value
Adipsin, ng/mL				
BMI, kg/m <sup>2</sup>	0.293	<0.001***	0.251	0.006**
Physical activities, MET/day	-0.067	0.058	0.020	0.826
WC, cm	0.258	<0.001***	0.235	0.010*
HC, cm	0.191	<0.001***	0.127	0.168
NC, cm	0.214	<0.001***	0.174	0.059
WHR	0.171	<0.001***	0.203	0.027*
Trunk fat, kg	0.227	<0.001***	0.195	0.033*
SBP, mmHg	0.127	<0.001***	0.076	0.414
DBP, mmHg	0.149	<0.001***	-0.019	0.836
TC, mmol/L	-0.044	0.215	-0.076	0.412
TG, mmol/L	0.150	<0.001***	0.117	0.204
LDL-C, mmol/L	-0.040	0.265	0.043	0.640
HDL-C, mmol/L	-0.180	<0.001***	-0.214	0.020*
Fasting glucose, mmol/L	0.089	0.013*	0.050	0.592
Insulin, $\mu$ U/mL	0.217	<0.001***	0.265	0.004**
HOMA-IR	0.226	<0.001***	0.266	0.003**
ALT, U/L	0.086	0.015*	0.051	0.584
AST, U/L	0.038	0.288	-0.027	0.773
AST/ALT	-0.116	0.001**	-0.106	0.251
ALP, U/L	0.026	0.465	0.057	0.542

Note: \*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001.

**Abbreviations:** BMI, body mass index; WC, waist circumference; HC, hip circumference; NC, neck circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

MAFLD. We found that with the increase in the number of metabolic risk abnormalities, the levels of adipsin and the proportion of moderate to severe fatty liver increased.

Interestingly, we found no differences in LDL-C and TC levels between the MAFLD and non-MAFLD groups as well as among the MAFLD subgroups. In recent studies, no differences in TC and LDL-C levels were found between MAFLD and control groups or among different subgroups of MAFLD.<sup>25–28</sup> Similar results have been found in NAFLD related studies. Serum TC and LDL-C concentrations did not differ between NAFLD and control groups.<sup>29</sup> There were no significant differences in TC and LDL-C levels between mild and severe NAFLD fibrosis groups.<sup>30</sup> There was also no statistically significant correlation between adipsin levels and LDL-C or TC levels. This result was consistent to the outcomes reported in Qiu et al<sup>18</sup> as well as other previous studies. Nonetheless, one study reported that when there was the presence of dyslipidemia in patients with metabolic syndrome, total cholesterol and low-density lipoprotein cholesterol levels did not increase significantly in accordance.<sup>31</sup> Thus, future long-term follow-up observations and experimental studies are necessary to confirm above phenomenon.

Another notable finding of this study is that with the increase in the number of metabolic risk abnormalities, serum adipsin levels of participants gradually increased, and the proportion of moderate to severe fatty liver in participants also increased, this suggests that serum adipsin levels may be related to metabolic complications. Although the relationships between adipsin and metabolic components have not been clearly demonstrated till now, there have been some related studies reported. Serum adipsin levels were strongly associated with visceral adipose and glucolipid metabolism.<sup>32</sup> In addition, literature has suggested that adipsin may be a novel early biomarker of T2DM<sup>33</sup> and that circulating adipsin



**Table 4** Subgroup Analysis of Clinical Characteristics of Patients with MAFLD Based on Severity of Fatty Liver

Variables	Mild-MAFLD (n=571)	Moderate-MAFLD (n=173)	Severe-MAFLD (n=45)	P value	P trend
Age, years <sup>ad</sup>	60.33 (56.83–64.08)	59.58 (56.88–64.46)	58.33 (55.54–63.21)	0.426	0.684
Male, n (%) <sup>cf</sup>	191 (33.45)	51 (29.48)	10 (22.22)	0.219	0.087
Educational level, n (%) <sup>cf</sup>					
No formal education or primary school	34 (5.95)	10 (5.78)	2 (4.44)	0.133	0.961
Middle school	115 (20.14)	47 (27.17)	12 (26.67)		
High school or technical secondary school	293 (51.31)	70 (40.46)	17 (37.78)		
College or university	129 (22.59)	46 (26.59)	14 (31.11)		
Smoking, n (%) <sup>cf</sup>	50 (8.76)	14 (8.09)	3 (6.67)	0.869	0.608
Drinking, n (%) <sup>cf</sup>	46 (8.06)	15 (8.67)	1 (2.22)	0.339	0.403
Physical activities, MET/day <sup>ad</sup>	23.18 (19.85–27.33)	23.00 (19.63–27.81)	22.70 (19.53–27.73)	0.994	0.939
BMI, kg/m <sup>2ad</sup>	24.80 (23.39–26.41)	26.33 (24.45–28.02)	26.77 (25.21–29.59)	<0.001***	<0.001***
Adipsin, ng/ml <sup>ad</sup>	3487.93 (3141.16–3920.39)	3631.98 (3293.55–3972.50)	4150.88 (3238.88–4524.72)	<0.001***	<0.001***
WC, cm <sup>ad</sup>	87.80 (83.50–92.80)	90.70 (86.43–94.75)	94.10 (87.63–100.55)	<0.001***	<0.001***
HC, cm <sup>ad</sup>	94.35 (91.35–97.70)	97.00 (92.85–100.65)	97.30 (93.73–100.23)	<0.001***	<0.001***
NC, cm <sup>ad</sup>	34.00 (32.25–36.35)	34.75 (33.23–37.50)	35.25 (33.28–36.40)	<0.001***	<0.001***
WHR <sup>be</sup>	0.93±0.06	0.94±0.05	0.96±0.05	0.003**	0.001**
Trunk fat, kg <sup>ad</sup>	10.76 (9.50–12.28)	12.35 (10.92–14.07)	12.77 (11.16–15.06)	<0.001***	<0.001***
Trunk fat percentage, % <sup>ad</sup>	36.19 (30.96–39.56)	39.21 (33.86–42.24)	38.05 (35.99–40.93)	<0.001***	<0.001***
SBP, mmHg <sup>ad</sup>	126.50 (116.50–139.50)	130.00 (119.00–141.75)	133.50 (117.50–146.00)	0.059	0.018*
DBP, mmHg <sup>ad</sup>	77.50 (70.50–85.00)	78.50 (71.75–86.00)	78.00 (71.50–84.25)	0.467	0.299
TC, mmol/L <sup>be</sup>	5.49±1.02	5.56±0.91	5.56±0.90	0.669	0.400
TG, mmol/L <sup>ad</sup>	1.36 (0.97–1.96)	1.77 (1.30–2.34)	1.73 (1.32–2.17)	<0.001***	<0.001***
LDL-C, mmol/L <sup>be</sup>	3.63±0.92	3.65±0.89	3.78±0.91	0.581	0.370
HDL-C, mmol/L <sup>ad</sup>	1.26 (1.06–1.52)	1.16 (0.96–1.41)	1.15 (0.96–1.40)	<0.001***	<0.001***
Fasting glucose, mmol/L <sup>ad</sup>	4.73(4.38–5.20)	4.94 (4.60–5.51)	5.36 (4.84–6.79)	<0.001***	<0.001***
Insulin, μU/mL <sup>ad</sup>	9.41 (6.93–12.62)	13.73(9.76–17.52)	13.86(9.99–19.08)	<0.001***	<0.001***
HOMA-IR <sup>ad</sup>	2.04 (1.44–2.84)	2.93 (2.15–3.96)	3.35 (2.19–5.53)	<0.001***	<0.001***
ALT, U/L <sup>ad</sup>	16.00 (12.00–21.00)	19.00 (14.00–26.50)	22.00 (16.50–32.00)	<0.001***	<0.001***
AST, U/L <sup>ad</sup>	18.00 (16.00–21.00)	19.00 (15.00–23.00)	20.00 (16.00–24.50)	0.053	0.017*

(Continued)

**Table 4** (Continued).

Variables	Mild-MAFLD (n=571)	Moderate-MAFLD (n=173)	Severe-MAFLD (n=45)	P value	P trend
AST/ALT <sup>ad</sup>	1.13 (0.93–1.33)	1.00 (0.80–1.18)	0.84 (0.77–1.00)	<0.001***	<0.001***
ALP, U/L <sup>ad</sup>	71.59 (59.60–84.12)	70.95 (61.03–85.01)	72.62 (61.81–85.69)	0.831	0.549
Albumin, g/L <sup>ad</sup>	45.30 (41.90–47.70)	46.20 (42.80–48.15)	44.70 (42.85–48.65)	0.118	0.047*
UA, μmol/L <sup>ad</sup>	345.58 (296.12–408.34)	352.54 (307.91–402.44)	363.33 (311.97–412.83)	0.182	0.077
T2DM, n (%) <sup>cf</sup>	55 (9.63)	24 (13.87)	13 (28.89)	<0.001***	<0.001***
Hypertension, n (%) <sup>cf</sup>	258 (45.18)	95 (54.91)	30 (66.67)	0.004**	0.001**
Dyslipidemia, n (%) <sup>cf</sup>	390 (68.30)	139 (80.35)	34 (75.56)	0.007**	0.009**
MetS, n (%) <sup>cf</sup>	191 (33.45)	97 (56.07)	27 (60.00)	<0.001***	<0.001***

**Notes:** \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001. *P* value: <sup>a</sup>Kruskal–Wallis test, <sup>b</sup>One-Way ANOVA, and <sup>c</sup>Pearson Chi-Square test; *P* trend: <sup>d</sup>Jonckheere–Terpstra, <sup>e</sup>Linear contrast in one-way ANOVA and <sup>f</sup>Linear-by-linear association chi square test.

**Abbreviations:** BMI, body mass index; WC, waist circumference; HC, hip circumference; NC, neck circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; UA, uric acid; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome.

levels might act as potential predictors for the presence and development of metabolic syndrome.<sup>34</sup> A cross-sectional study suggested that higher concentrations of adipokines, including adipon, are related to higher waist circumference in cardiometabolic disorder patients.<sup>35</sup> In postmenopausal women, metabolic syndrome was mainly associated with abdominal obesity and dyslipidemia, and also found to be associated with higher levels of insulin and adipon.<sup>36</sup> Serum adipon levels have been reported to be correlated with serum lipids, insulin resistance and waist obesity.<sup>37</sup> However, it has also been reported that serum adipon had no association with insulin resistance in obese children.<sup>38</sup> A positive correlation between adipon and HOMA-IR was observed in our study. We found that the more severe the MAFLD in patients, the higher the adipon levels. This suggests that serum adipon levels can be used as a potential biomarker for predicting the severity of fatty liver disease in patients with MAFLD among the Chinese population. Nonetheless, each of the metabolic risk factor listed in the new definition that are used to identify metabolic dysregulation has a different phenotype. Therefore, the mechanisms of the relationships between adipon and specific metabolic risk factors are needed to be explored in-depth in the future.

In the literature, contradictory outcomes have been found between animals and humans with respect to the relationship of adipon and the metabolic conditions, for example, lower adipon levels have been found to be associated with overweight/obesity in animals,<sup>39</sup> while increased adipon levels were in population studies of metabolic diseases, especially in obese patients.<sup>36,40</sup> Azizi et al<sup>41</sup> found that no changes in serum adipon levels after an 8-week aerobic exercise training intervention in obese women with type 2 diabetes. Another interventional study reported that obese patients had adipon levels comparable to controls before and after diet intervention.<sup>42</sup> Additionally, patients with T2DM had significantly higher serum adipon concentrations than those with normal blood glucose.<sup>43</sup> Zhou et al<sup>44</sup> reported that serum adipon levels were lower in patients with T2DM and impaired glucose tolerance. The levels of adipon were selectively decreased in T2DM patients with  $\beta$  cell failure.<sup>15</sup> Systemic levels of adipon may be initially high because of a compensatory mechanism in the early stages of metabolic syndrome and diabetes, but then decline with adipose dysfunction.<sup>15</sup> As such, future longitudinal studies of adipon levels at various stages from prediabetes to advanced diabetes are warranted, including population studies and molecular mechanisms. The lack of adipon expression in the adipose tissue of obese mice could be due to the absence of a positive regulatory factor or due to the presence of an inhibitory factor.<sup>45</sup> Differences in adipon levels among human studies may be attributed to race, study design, measurement methods, and other potential confounders. In summary, adipon levels have been found to be low in animal models of metabolic-related diseases, whereas in population studies of metabolic-related diseases, contradictory outcomes have been reported in which both increased and decreased adipon levels among patients have been found.

The heterogeneity of NAFLD in terms of its major metabolic drivers is an important barrier to the discovery of effective therapies of the disease. Using “positive” characteristics to diagnose MAFLD can better stratify the risks of patients, which in turn helps to take targeted prevention and treatment measures to improve clinical outcomes. Above diagnostic criteria of MAFLD may have advantages over NAFLD diagnostic conditions. For instance, a study using the NHANES III database showed that the MAFLD diagnostic criteria were more effective than NAFLD diagnostic criteria for identifying patients with fatty liver disease at high risk of disease progression.<sup>46</sup> The MAFLD definition specifically incorporates recognized cardiovascular risk factors, so the future clinical impact of MAFLD on cardiovascular disease should also be concerned.<sup>47</sup>

To date, the high prevalence of MAFLD worldwide has attracted increasing attention, and various metabolic risk factors all have a non-negligible impact on MAFLD. At the same time, precision medicine has always been advocated, and risk stratification of diseases and targeted prevention and treatment measures are also necessary. This study sought to analyze the relationship among adipon, MAFLD and specific metabolic risk factors in a future prospective study design, which could provide more robust evidence for the inconsistent findings of adipon and metabolic-related diseases among different populations as well as between humans and animals.

Nevertheless, there were several limitations in our study. First, this was a cross-sectional study that cannot make causal inferences, but it can still provide clues for subsequent analytical or experimental studies. Second, hepatic steatosis and its severity were diagnosed by ultrasonography, which is less sensitive than liver biopsy. Third, due to the lack of data on plasma high-sensitivity C-reactive protein levels, their effect on MAFLD could not be investigated. Finally, the controls in this study were patients with simple hepatic steatosis, instead of healthy patients.

## Conclusion

Our study found that participants in the MAFLD groups (regardless of the participants were diagnosed with MAFLD based on having overweight/obesity, T2DM or MD) had higher levels of adipsin than ones in the non-MAFLD group and that serum adipsin levels were positively associated with MAFLD. On top of that, in the MAFLD group, as the number of metabolic risk abnormalities increased, the levels of serum adipsin and the proportion of moderate to severe fatty liver disease were increased.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

The GNHS was registered on ClinicalTrials.gov (registration number NCT03179657) and approved by the Ethics Committee of the School of Public Health at Sun Yat-sen University (approval number ZDGWYL2009-3), which meets the guidelines in the Declaration of Helsinki. Written informed consent was obtained from all participants.

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## Disclosure

The authors declare that there are no conflicts of interest in this work.

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