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The nonlinear connection between relative fat mass and non-alcoholic fatty liver disease in the Japanese population: an analysis based on data from a cross-sectional study

Changchun Cao[1†], Meiling Huang[2†], Yong Han[3†], Xiaohua Zhang[1*], Haofei Hu[4*] and Yulong Wang[2*]

Abstract

Background Relative fat mass (RFM) is a newly developed, sex-specific anthropometric formula designed to estimate total body fat percentage. However, research investigating the correlation between RFM and the risk of non-alcoholic fatty liver disease (NAFLD) remains limited. This study evaluates the association between RFM and the risk of NAFLD within the Japanese population.

Methods This study including 14,250 Japanese adults who underwent physical examinations at Murakami Memorial Hospital between 2004 and 2015. We employed binary logistic regression to elucidate the direct relationship between RFM levels and the incidence of NAFLD. Additionally, a generalized additive model (GAM) coupled with smooth curve fitting techniques was utilized to map the non-linear association.

Results The cohort had an average age of 43.53 ± 8.89 years, with a male majority of 52.00%. NAFLD was identified in 17.59% of the participants. After adjusting for confounding factors, a significant positive correlation between RFM and NAFLD risk was observed (OR: 1.15, 95%CI: 1.10–1.21, P < 0.0001 for females; OR: 1.15, 95%CI: 1.10–1.19, P < 0.0001 for males). Additionally, a non-linear relationship between RFM and the incidence of NAFLD was detected in both genders. The RFM threshold was identified as 34.95 for women and 23.40 for men. RFM was positively associated with the risk of NAFLD when RFM was below the respective threshold (OR: 1.29, 95%CI: 1.19–1.40, P < 0.0001 for females; OR: 1.23, 95%CI: 1.17–1.29, P < 0.0001 for males), whereas no significant association was found when RFM was above the threshold (OR: 1.05, 95%CI: 0.98–1.12, P = 0.1829 for females; OR: 1.01, 95%CI: 0.95–1.08, P = 0.7392 for males).

Conclusion Our findings suggest a positive, nonlinear relationship between RFM and the risk of NAFLD, with a saturation effect. These results imply that maintaining RFM at a lower level may be advantageous in mitigating the risk of NAFLD.

Keywords Relative fat mass, Non-alcoholic fatty liver disease, Nonlinearity

†Changchun Cao, Meiling Huang, and Yong Han, have contributed equally to this work.

*Correspondence:
Xiaohua Zhang
21386658@qq.com
Haofei Hu
huhaofei0319@126.com
Yulong Wang
ylwang668@163.com
Full list of author information is available at the end of the article

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of hepatic conditions, ranging from simple steatosis (fat accumulation) to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation and fibrosis. This condition has the potential to progress to cirrhosis and hepatocellular carcinoma [1]. The escalating prevalence of NAFLD, currently affecting approximately one-fourth of the adult population worldwide, is potentially linked to the rising incidence of obesity and metabolic syndrome [2, 3]. It has been reported that decreased muscle mass combined with excessive visceral adipose tissue are significantly correlated with the risk of NAFLD [4]. However, it has not been explored among populations with metabolic dysfunction-associated fatty liver disease (MAFLD) subtypes [4]. Visceral fat area and skeletal muscle mass ratio (VSR) is positively associated with the prevalence of MASLD in this Chinese population, with a notably higher risk for men as VSR increases compared to women [5].

Over recent decades, changes in dietary habits and lifestyles have contributed to obesity becoming a major health issue, affecting over two billion individuals worldwide [6]. Traditional metrics for assessing obesity, such as body mass index (BMI), are widely utilized in epidemiological studies; however, they possess notable limitations. BMI does not differentiate between fat and lean mass and fails to consider fat distribution, which is crucial for evaluating metabolic risk. Relative fat mass (RFM), an innovative anthropometric index, provides an improved method for estimating body fat percentage by incorporating height and waist circumference measurements. RFM emerged as the most accurate and user-friendly measure in a comprehensive analysis of 365 anthropometric metrics [7]. Furthermore, numerous studies suggest that RFM is strongly associated with dyslipidemia, heart failure, all-cause mortality, metabolic syndrome, diabetes, and cardiovascular disease [8–11]. Despite these findings, the relationship between RFM and NAFLD remains contentious [12–14]. In a cross-sectional study conducted in China, RFM was significantly associated with the prevalence of NAFLD [12]. Conversely, two other cross-sectional studies with smaller sample sizes found no association between RFM and NAFLD risk and severity of NAFLD [13, 14]. Given these conflicting observations, the present study aims to elucidate the association between RFM levels and the risk of NAFLD onset within a cohort, utilizing a comprehensive public database from Japan.

Methods

Study design and data source

This study leveraged open-source data from the NAGALA (NAFLD in Gifu Area, Longitudinal Analysis) database as part of a secondary analysis of a medical examination program. The facility conducting these programs, established in 1994, performs over 8,000 medical examinations annually, with 60% of participants attending one to two exams per year. Due to the high frequency of repeated examinations, the original study cohort included all participants who underwent multiple examinations between 2004 and 2015. Researchers can freely access the original study data via the Dryad Digital Repository (https://datadryad.org/). The dataset (DOI: https://doi.org/10.5061/dryad.8q0p192) contains baseline data for 15,464 participants [15]. This dataset was subject to further analytical procedures in accordance with the terms and conditions outlined in Dryad's data usage policy.

Study participants

In the original investigation, all participants provided written informed consent, and the study received approval from the Clinical Research Ethics Committee of Murakami Memorial Hospital [15]. Furthermore, ethical approval for the present study was granted by the Ethics Committee of Shenzhen Dapeng New District Nan'ao People's Hospital (approval number: 2022082201). This research adhered strictly to the ethical guidelines established by the Declaration of Helsinki, ensuring that all methods described in the Declarations section were implemented in accordance with relevant standards and regulations.

The initial cohort comprised 20,944 Japanese participants who had undergone health screenings and attended at least two evaluations between 2004 and 2015. Following the application of exclusion criteria, the final analysis included 14,250 subjects, as illustrated in Fig. 1. Exclusions were based on several criteria: (1) ethanol intake $\geq$ 30 g/day for males or $\geq$ 20 g/day for females (n = 1,952); (2) diagnosis of liver diseases other than fatty liver (n = 416); (3) current medication use (n = 2,321); (4) incomplete dataset for required variables (n = 863); (5) diagnosed diabetes or fasting plasma glucose (FPG) levels $\geq$ 6.1 mmol/L (n = 1,131); and (6) study attrition for undisclosed reasons (n = 10).

Covariates

The selection of covariates for this study was guided by clinical insights and findings from prior research [11, 12, 16–19]. The covariates included: gender, age, gamma-glutamyl transferase (GGT), glycosylated hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), FPG, systolic blood pressure

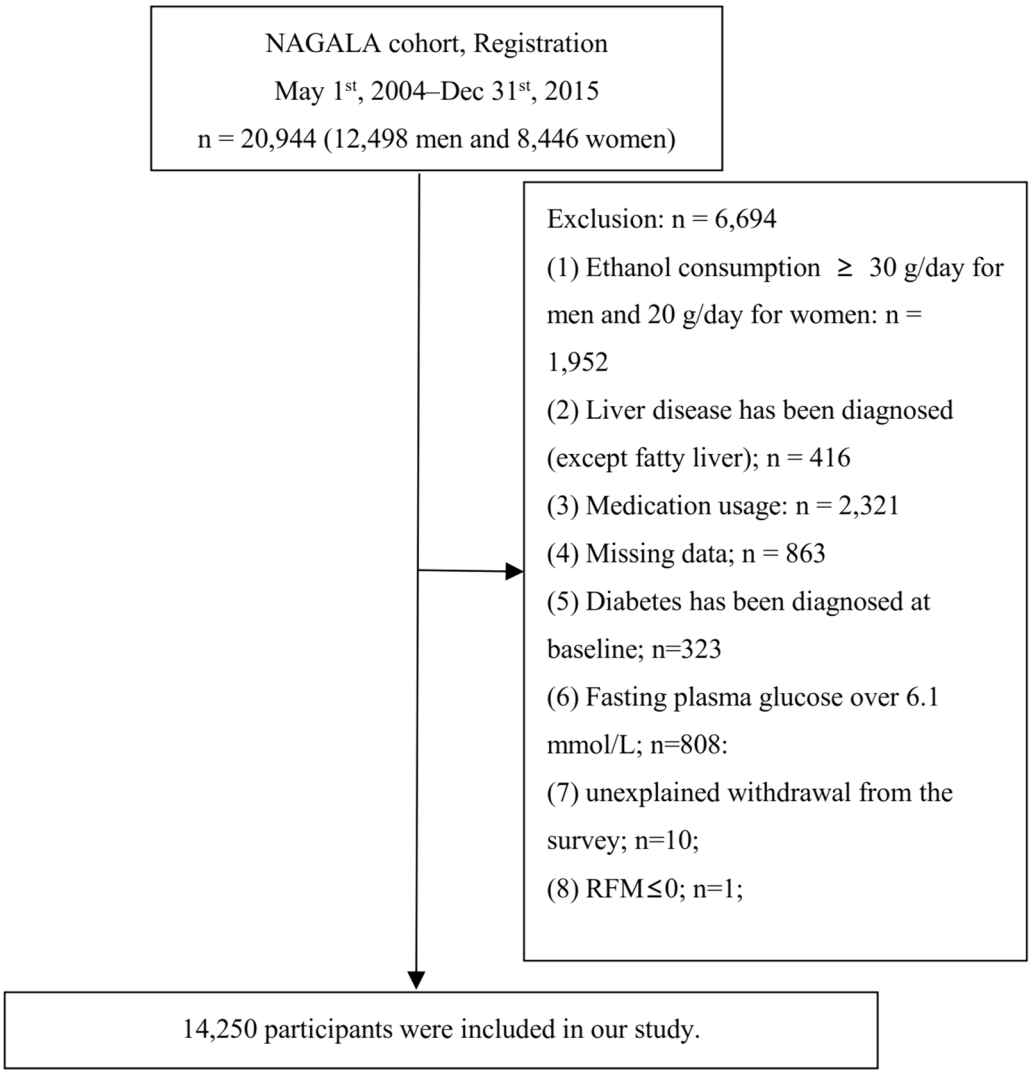

Fig. 1 Study population

(SBP), diastolic blood pressure (DBP), body mass index (BMI), smoking status, alcohol intake, and exercise habits. Data regarding each participant's lifestyle and medical history were systematically collected using a structured self-reported questionnaire. Anthropometric measurements, including weight, height, and blood pressure, were conducted with precision by trained personnel. Additionally, laboratory data acquisition, encompassing liver enzymes, blood glucose, and lipids, was performed uniformly and under stringent conditions by the original study's research team.

Relative fat mass

The formulas employed to calculate the RFM are tailored to gender, accounting for physiological differences in fat distribution. For males, RFM is calculated as: RFM = 64-[20 × height/waist circumference] for males, and RFM = 76-[20 × height/waist circumference] for females [7].

Diagnosis of incident NAFLD

Diagnostic procedures for NAFLD included liver ultrasonography, with stringent exclusion of subjects who had a history of excessive alcohol consumption or other known etiologies of liver pathology [20]. These ultrasonographic evaluations were performed by skilled technicians, while gastroenterology experts provided the definitive diagnoses. The diagnostic assessment was based on a comprehensive examination of

ultrasonographic parameters, including hepatic echogenicity, echogenic contrast between hepatic and renal tissues, visualization of vascular structures, and the degree of ultrasonic wave attenuation. Notably, this diagnostic process was conducted independently of any ancillary participant data [20], thereby minimizing potential bias in the assessment.

Statistical analysis

All statistical analyses were performed using EmpowerStats. Participants' characteristics were categorized by NAFLD status. Continuous variables with skewed and normal distributions were presented as median (quartile) and mean ± standard deviation, respectively. Group differences were employed One-Way Analysis of Variance (ANOVA) for normally distributed variables, the Chi-square ($\chi 2$) test for categorical variables, and the Kruskal–Wallis H test for skewed variables.

Our investigation examined the association between RFM levels and the development of NAFLD using logistic regression models. This analytical approach encompassed three models: Model 1, unadjusted for any variables; Model 2, adjusted for smoking status, DBP, age, alcoholic intake, SBP, BMI, and exercise habits; and Model 3, which further adjusted for HDL-C, ALT, HbA1c, TG, AST, TC, FPG and GGT. Odds ratios (OR) and 95% confidence intervals (CI) were calculated and reported throughout the analysis.

Sensitivity analyses were conducted to substantiate the robustness of our findings. These analyses were further extended to exclude individuals with a BMI ≥ 25 kg/m^2 or those aged ≥ 60 years, thereby examining the relationship between RFM levels and NAFLD risk within these specific subgroups. Additionally, E-values were computed to account for potential unmeasured confounding factors that might influence the association between RFM levels and NAFLD risk [21].

In light of concerns regarding the potential inadequacy of binary logistic regression models to capture non-linear associations, our investigation also explored the possible non-linearity between RFM levels and NAFLD risk using the Generalized Additive Model (GAM) complemented by smooth curve fitting methodologies. Upon the identification of non-linearity, a recursive algorithm was employed to determine the inflection point, after which a segmented logistic regression model was formulated to operate on either side of the inflection point. The selection of the most appropriate model was based on the minimization of the P-value from the logarithm of the likelihood ratio test. Statistical significance was determined based on a P-value threshold of less than 0.05 (two-tailed).

Results

This study analyzed data from 14,250 participants, comprising 11,743 individuals without NAFLD and 2,507 with NAFLD. The cohort had a mean age of 43.53 ± 8.89 years, with females constituting 48.00% of the sample. Table 1 presents the baseline characteristics, revealing statistically significant differences between the non-NAFLD and NAFLD groups across various metrics. The NAFLD group exhibited notably higher levels of blood pressure, BMI, RFM, WC, alcoholic intake, age, AST, ALT, GGT, TC, TG, FPG, and HbA1c. Furthermore, the NAFLD cohort had a higher proportion of males, and smokers. Conversely, the NAFLD group demonstrated reduced levels of HDL-C and a lower prevalence of exercise habits compared to the non-NAFLD group.

Table 1 The baseline characteristics of participants

Baseline characteristic	Non-NAFLD	NAFLD	P-value
Participants	11743	2507	
Gender			< 0.001
Female	6362 (54.18%)	478 (19.07%)	
Male	5381 (45.82%)	2029 (80.93%)	
Age(years)	43.27 ± 8.99	44.78 ± 8.33	< 0.001
Alcoholic intake (g/wk)	1.00 (0.00–36.00)	1.00 (0.00–36.00)	0.462
Smoking status			< 0.001
Never-smoker	7561 (64.39%)	1185 (47.27%)	
Ex-smoker	1920 (16.35%)	639 (25.49%)	
Current-smoker	2262 (19.26%)	683 (27.24%)	
Exercise habits			0.048
No	9650 (82.18%)	2130 (84.96%)	
Yes	2093 (17.82%)	377 (15.04%)	
SBP (mmHg)	111.91 ± 14.02	123.41 ± 14.83	< 0.001
DBP (mmHg)	69.69 ± 9.85	77.81 ± 10.19	< 0.001
BMI (kg/m^2)	21.33 ± 2.61	25.50 ± 3.13	< 0.001
WC (cm)	74.10 ± 7.92	85.98 ± 7.79	< 0.001
RFM	25.81 ± 6.92	26.94 ± 6.27	< 0.001
ALT (IU/L)	15 (12–20)	27 (20–39)	< 0.001
AST (IU/L)	17 (14–20)	20 (17–26)	< 0.001
GGT (IU/L)	14 (11–18)	23 (16–33)	< 0.001
HDL-C (mmol/L)	1.52 ± 0.40	1.18 ± 0.29	< 0.001
TG (mmol/L)	0.65 (0.45–0.95)	1.24 (0.87–1.80)	< 0.001
TC (mmol/L)	5.06 ± 0.85	5.44 ± 0.87	< 0.001
HbA1c (%)	5.15 ± 0.31	5.30 ± 0.33	< 0.001
FPG (mmol/L)	5.09 ± 0.40	5.39 ± 0.36	< 0.001

Values are n (%), mean ± SD, or median (quartile).

NAFLD: non-alcoholic fatty liver disease; SBP: systolic blood pressures; DBP: diastolic blood pressures; BMI: body mass index; RFM: relative fat mass; WC: waist circumference; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose

The results of the connection between RFM level and incident NAFLD

Table 2 meticulously presents the findings from a binary logistic regression analysis, elucidating the OR and 95%CI pertinent to the relationship between RFM levels and the incidence of NAFLD. In Model 1, which did not adjust for any confounders, a significant positive association was observed between RFM levels and NAFLD risk (OR: 1.02, 95%CI: 1.02–1.03). Model 2, which included adjustments for smoking status, DBP, age, alcoholic intake, SBP, BMI, and exercise habits, demonstrated a persistent correlation (OR: 1.22, 95%CI: 1.18–1.25). In Model 3, which further adjusted for HDL-C, ALT, HbA1c, TG, AST, TC, FPG, and GGT, in addition to the variables accounted for in Model 2, a positive relationship between RFM levels and NAFLD risk was revealed (OR: 1.15, 95%CI: 1.12–1.18). Notably, a positive correlation between RFM levels and the prevalence of NAFLD was observed in both men and women across different models.

Furthermore, the analysis revealed the effect of relative fat mass quartiles on NAFLD. Using the first quartile (Q1) of RFM as the reference point, the OR for the second quartile (Q2) was 1.71 (95%CI: 1.43–2.04), for the third quartile (Q3) was 1.61 (95%CI: 1.25–2.07), and for the fourth quartile (Q4) was 5.92 (95%CI: 3.40–10.30) (Table 2, Model 3).

Sensitive analysis

Table 3 presents the results of the sensitivity analyses. We conducted these analyses on participants with a BMI of less than 25 kg/m^2. Subsequent adjustments accounting for a variety of confounding factors revealed a persistently positive association between RFM levels and the risk of NAFLD (OR = 1.17, 95%CI: 1.13–1.22) (Table 3, Model 4). Similarly, further sensitivity analyses, which specifically excluded participants aged 60 years and above, demonstrated consistent results (OR = 1.16, 95%CI: 1.12–1.19) (Table 3, Model 5).

Additionally, we calculated an E-value to assess the robustness of our findings against unaccounted confounding factors. For NAFLD, the E-value was determined to be 1.35. This E-value, which surpasses the relative risk posed by potential unmeasured confounders, suggest that the influence of unidentified or unmeasured

Table 2 Relationship between RFM and incident NAFLD in different models

	Variable	Model 1 (OR, 95%CI, P)	Model 2 (OR, 95%CI, P)	Model 3 (OR, 95%CI, P)
All	RFM	1.02 (1.02, 1.03) < 0.0001	1.22 (1.18, 1.25) < 0.0001	1.15 (1.12, 1.18) < 0.0001
	RFM (quartile)			
	Q1	ref	ref	ref
	Q2	5.02 (4.35, 5.79) < 0.0001	2.27 (1.92, 2.67) < 0.0001	1.71 (1.43, 2.04) < 0.0001
	Q3	2.79 (2.40, 3.23) < 0.0001	2.41 (1.90, 3.05) < 0.0001	1.61 (1.25, 2.07) 0.0003
	Q4	1.98 (1.70, 2.31) < 0.0001	10.73 (6.26, 18.41) < 0.0001	5.92 (3.40, 10.30) < 0.0001
	P for trend	0.0021	< 0.0001	< 0.0001
Female	RFM	1.44 (1.40, 1.48) < 0.0001	1.18 (1.13, 1.24) < 0.0001	1.15 (1.10, 1.21) < 0.0001
	RFM (quartile)			
	Q1	ref	ref	ref
	Q2	4.03 (1.34, 12.07) 0.0128	2.34 (0.78, 7.03) 0.1302	2.26 (0.75, 6.81) 0.1486
	Q3	19.29 (7.04, 52.87) < 0.0001	6.43 (2.32, 17.80) 0.0003	5.24 (1.88, 14.61) 0.0015
	Q4	123.51 (46.01, 331.56) < 0.0001	12.15 (4.34, 33.98) < 0.0001	8.86 (3.14, 25.02) < 0.0001
	P for trend	< 0.0001	< 0.0001	< 0.0001
Male	RFM	1.44 (1.41, 1.47) < 0.0001	1.24 (1.20, 1.28) < 0.0001	1.15 (1.10, 1.19) < 0.0001
	RFM (quartile)			
	Q1	ref	ref	ref
	Q2	6.00 (4.42, 8.16) < 0.0001	3.33 (2.42, 4.58) < 0.0001	2.39 (1.71, 3.33) < 0.0001
	Q3	17.61 (13.12, 23.64) < 0.0001	5.93 (4.27, 8.23) < 0.0001	3.68 (2.61, 5.19) < 0.0001
	Q4	50.81 (37.90, 68.14) < 0.0001	8.07 (5.56, 11.70) < 0.0001	4.20 (2.83, 6.23) < 0.0001
	P for trend	< 0.0001	< 0.0001	< 0.0001

Model 1: we did not adjust for any covariants

Model 2: we adjusted for gender, age, BMI, alcoholic intake, smoking status, exercise habits, SBP, and DBP

Model 3: we adjusted for gender, age, BMI, alcoholic intake, smoking status, exercise habits, SBP, DBP, ALT, AST, GGT, HDL-C, TC, TG, HbA1c, and FPG

The models were not adjusted for gender variables in both male and female models

NAFLD: non-alcoholic fatty liver disease; OR: Odds ratios; CI: confidence interval; Ref: Reference; RFM: relative fat mass

Table 3 Relationship between RFM and NAFLD risk in different sensitivity analyses

Exposure	Model 4 (OR, 95%CI, P)	Model 5 (OR, 95%CI, P)
RFM	1.17 (1.13, 1.22) < 0.0001	1.16 (1.12, 1.19) < 0.0001
RFM (quartile)		
Q1	ref	ref
Q2	1.54 (1.26, 1.88) < 0.0001	1.74 (1.45, 2.08) < 0.0001
Q3	1.44 (0.96, 2.15) 0.0782	1.64 (1.26, 2.14) 0.0002
Q4	4.68 (2.42, 9.08) < 0.0001	6.48 (3.64, 11.56) < 0.0001
P for trend	< 0.0001	< 0.0001

Model 5 was sensitivity analysis after excluding those with BMI ≥ 25kg/m^2. We adjusted gender, age, BMI, alcoholic intake, smoking status, exercise habits, SBP, DBP, ALT, AST, GGT, HDL-C, TC, TG, HbA1c, and FPG

Model 6 was sensitivity analysis after excluding those with age ≥ 60 years. We adjusted agender, age, BMI, alcoholic intake, smoking status, exercise habits, SBP, DBP, ALT, AST, GGT, HDL-C, TC, TG, HbA1c, and FPG

NAFLD: non-alcoholic fatty liver disease; OR: Odds ratios; CI: Confidence interval: Ref: Reference

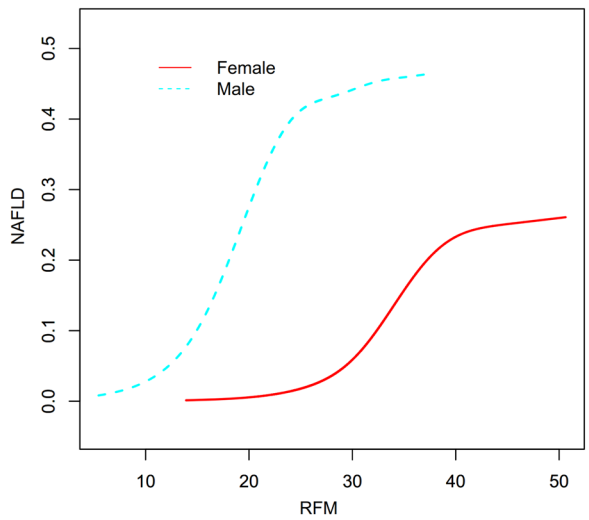

Fig. 2 The nonlinear relationship between the RFM and prevalence of NAFLD. A nonlinear relationship was detected after adjusting for age, alcoholic intake, smoking status, exercise habits, SBP, DBP, BMI, ALT, AST, GGT, TC, TG, HDL-C, HbA1c, and FPG

confounders on the association between RFM levels and NAFLD risk is minimal.

The analyses of the non-linear relationship

Figure 2 illustrates the nonlinear relationship between RFM and the risk of NAFLD in both male and female cohorts. A nonlinear correlation between RFM levels and NAFLD risk was observed after adjusting for confounding covariates (Table 4). To identify the threshold for RFM, a two-piecewise logistic regression model was applied, yielding thresholds of 34.95 for females and 23.40 for males (P for log-likelihood ratio test < 0.001). Below the thresholds, RFM was positively associated with NAFLD risk (OR: 1.29, 95% CI: 1.19–1.40, P < 0.0001 for females; OR: 1.23, 95% CI: 1.17–1.29, P < 0.0001 for males). Conversely, no significant association was found when RFM exceeded the respective thresholds (OR: 1.05, 95% CI: 0.98–1.12, P = 0.1821 for females; OR: 1.01, 95% CI: 0.95–1.08, P = 0.7424 for males).

Discussion

In this cross-sectional study, we observed a significant association between elevated RFM and incident NAFLD after adjusting for potential confounding factors. The analysis revealed a nonlinear relationship between RFM levels and NAFLD onset, which was gender-specific, with thresholds identified at 34.95 for females and 23.40 for males. Notably, below these gender-specific thresholds, a statistically significant positive relationship was observed between RFM levels and the incidence of NAFLD. However, the association between RFM levels and NAFLD risk did not achieve statistical significance above these thresholds.

The global prevalence of NAFLD has demonstrated a significant upward trend in recent decades, imposing substantial economic burdens on national healthcare systems [22, 23]. Obesity remains a primary risk factor in the etiology of NAFLD [24]. While BMI is widely employed as a diagnostic tool for obesity, it presents inherent limitations, notably its inability to distinguish between weight gain attributable to muscle mass versus adipose tissue [25]. Recently, the RFM has emerged as a novel metric for estimating body fat percentage, incorporating variables such as sex, waist WC, and height. RFM has exhibited superior accuracy in predicting body fat percentage compared to BMI, particularly across heterogeneous populations [7]. Although robust evidence exists correlating decreased RFM with elevated risks of metabolic syndrome, and cardiovascular disease [8, 9], the association between RFM and NAFLD risk remains contentious [12–14]. In a cross-sectional study involving 11,532 adult participants, adjustments were made for potential confounding variables including current alcohol consumption, age, educational attainment, HbA1c, low-density lipoprotein cholesterol, current smoking status, and hypertension (OR: 4.33, 95%CI: 3.79–4.93 for males; OR: 5.16, 95% CI: 4.62–5.77 for females). However, a cross-sectional studies involving 1,763 participants indicated that elevated RFM levels were not associated with the incidence of NAFLD (OR: 1.54, 95%CI: 0.89–2.69) [14]. In another cross-sectional study involving 744 patients, the findings indicated that RFM was not significantly associated with various aspects of NAFLD or indicators

Table 4 The result of the two-piecewise logistic regression model for NAFLD by gender

Incident NAFLD	All participants (OR, 95%CI, P)	Female (OR, 95%CI, P)	Male (OR, 95%CI, P)
Fitting model by standard logistic regression	1.15 (1.12, 1.18) < 0.0001	1.15 (1.10, 1.21) < 0.0001	1.15 (1.10, 1.19) < 0.0001
Fitting model by two-piecewise logistic regression			
The inflection point of RFM	19.24	34.95	23.40
≤ Inflection point	1.41 (1.25, 1.59) < 0.0001	1.29 (1.19, 1.40) < 0.0001	1.23 (1.17, 1.29) < 0.0001
> Inflection point	1.13 (1.09, 1.16) < 0.0001	1.05 (0.98, 1.12) 0.1821	1.01 (0.95, 1.08) 0.7424
P for log-likelihood ratio test	< 0.001	< 0.001	< 0.001

Note 1: In all participants, we adjusted gender, age, BMI, alcoholic intake, smoking status, exercise habits, SBP, DBP, ALT, AST, GGT, HDL-C, TC, TG, HbA1c, and FPG

Note 2: For female and male subgroups, we adjusted for age, BMI, alcoholic intake, smoking status, exercise habits, SBP, DBP, ALT, AST, GGT, HDL-C, TC, TG, HbA1c, and FPG

NAFLD: non-alcoholic fatty liver disease; OR: Odds ratios; CI: confidence; RFM: relative fat mass

of liver injury after adjusting for confounders [13]. This study reinforces the existing academic literature suggesting that elevated RFM levels are positively associated with an increased risk of NAFLD. Variations in study outcomes can be attributed to several factors, including the gender distribution of the study cohort, demographic characteristics, the range of RFM levels examined, and differences in the covariates adjusted for in the analyses. Additionally, it is crucial to acknowledge that results derived from linear regression analyses may be susceptible to distortions caused by non-linear relationships, potentially compromising the validity of established linear associations. Consequently, the disparate results reported in the literature may partly arise from the non-linear relationship between RFM levels and the prevalence of NAFLD.

The relationship between RFM, a metric that accounts for body fat percentage, and the development of NAFLD is not well understood. Elevated RFM, indicative of increased adiposity, leads to an enhanced release of free fatty acids from adipose tissue through lipolysis [26]. This surge in circulating free fatty acids overwhelms the liver's capacity for very-low-density lipoprotein secretion, resulting in hepatic lipid accumulation [26]. Concurrently, insulin resistance, often associated with increased adiposity, promotes de novo lipogenesis in the liver, further exacerbating lipid deposition [27, 28]. Adipose tissue releases pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, which can lead to hepatic inflammation [29]. Concurrently, adipose tissue is associated with oxidative stress due to an imbalance between reactive oxygen species production and antioxidant defenses [29]. This oxidative stress further damages hepatocytes, promote lipid peroxidation, and exacerbate NAFLD progression by worsening hepatic steatosis [29].

This study is pioneering in its examination of the non-linear association between RFM levels and the risk of NAFLD across genders. By accounting for various confounding variables, our analysis uncovered a nonlinear relationship for both males and females. Employing a two-piecewise logistic regression model, we discerned specific RFM inflection points: 34.95 for females and 23.40 for males. A one-unit increment in RFM below these inflection points was linked to a 29% increase in NAFLD risk for females and a 23% increase for males (OR: 1.29, 95%CI: 1.19–1.40, P < 0.0001 for females; OR: 1.23, 95%CI: 1.17–1.29, P < 0.0001 for males). However, above these inflection points, RFM levels did not exhibit a significant correlation with NAFLD risk in either gender (OR: 1.05, 95% CI: 0.98–1.12, P = 0.1821 for females; OR: 1.01, 95% CI: 0.95–1.08, P = 0.7424 for males). Recognizing this curvilinear relationship between RFM and NAFLD risk may enhance clinical recommendations and decision-making, thus improving preventive strategies for NAFLD.

This investigation offers several notable advantages. Firstly, it utilizes GAM in conjunction with smooth curve fitting techniques to explore the nonlinear relationship under study, thereby providing clinically relevant insights not previously addressed in the literature. Secondly, the use of stringent statistical methodologies has effectively minimized the impact of residual confounding variables. Thirdly, the robustness of our conclusions is reinforced through sensitivity analyses, which included transforming RFM and re-evaluating the RFM-NAFLD relationship after excluding participants with a BMI ≥ 25 kg/m^2 or those aged ≥ 60 years.

Nevertheless, this investigation has certain limitations. Firstly, it is confined to a Japanese cohort, thereby limiting the generalizability of our findings to other ethnic and geographical populations. Secondly, the cross-sectional design of the study impedes the establishment of a

direct causal relationship between RFM and NAFLD risk. Thirdly, unmeasured or uncontrolled confounding variables, such as high-fat diet or a family history of NAFLD, could potentially influence our results despite our efforts to account for known covariates. Fourthly, RFM has been shown to correlate strongly with body fat percentage in general populations; however, it may overestimate body fat percentage in individuals with higher muscle mass, such as athletes or those engaged in regular resistance training. This limitation could potentially affect the interpretation of our findings in subgroups with atypical body compositions. Future studies may benefit from incorporating additional body composition assessment methods, such as dual-energy X-ray absorptiometry or bioelectrical impedance analysis, to provide a more comprehensive evaluation of body fat distribution and its relationship with NAFLD risk across diverse populations.

Conclusion

Our study elucidated the nonlinear relationship and saturation effect between RFM and NAFLD risk, stratified by sex. Notably, a significant positive correlation with NAFLD risk emerges when RFM levels are below the threshold of 34.95 for females and 23.40 for males. These findings suggest that maintaining RFM at lower levels may be advantageous in mitigating the risk of NAFLD.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
MAFLD	Metabolic dysfunction-associated fatty liver disease
VSR	Visceral fat area and skeletal muscle mass ratio
HbA1c	Hemoglobin A1c
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyl transferase
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
TC	Total cholesterol
TG	Triglyceride
RFM	Relative fat mass
LDL-C	Low-density lipid cholesterol
GAM	Generalized additive models
OR	Odds ratios
CI	Confidence intervals
Ref	Reference

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Not applicable.

Author contributions

Changchun Cao, Meiling Huang, and Yong Han contributed to the concept and design of the study and drafted the manuscript. Xiaohua Zhang, Haofei Hu, and Yulong Wang analyzed the data and reviewed the manuscript. Changchun Cao, Meiling Huang, and Yong Han oversaw the project's progress, contributed to the discussion and reviewed the manuscript. Xiaohua Zhang, Haofei Hu, and Yulong Wang are the guarantors of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data can be downloaded from the 'DATADRYAD' database (www.Datadryad.org). Dryad Digital Repository. https://datadryad.org/stash/dataset/doi:10.5061%2Fdryad.8q0p192.

Declarations

Ethics approval and consent to participate

This study was conducted under the approval of the institutional review board of the Murakami Memorial Hospital and followed the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all patients. The original researchers encoded their identity information as non-traceable codes to ensure participants' privacy and data anonymization. In addition, the study has also been approved by the Ethics Committee of the Shenzhen Dapeng New District Nan'ao People's Hospital (2022082201).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Rehabilitation, Shenzhen Dapeng New District Nan'ao People's Hospital, No. 6, Renmin Road, Dapeng New District, Shenzhen 518000, Guangdong, China. [2]Department of Rehabilitation, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, No.3002, Sungang West Road, Futian District, Shenzhen 518000, Guangdong, China. [3]Department of Emergency, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen 518000, Guangdong, China. [4]Department of Nephrology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen 518000, Guangdong, China.

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