



OPEN Nonlinear association between body roundness index and metabolic dysfunction associated steatotic liver disease in nondiabetic Japanese adults

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The global rise in obesity and diabetes has been paralleled by a rising incidence of metabolic dysfunction-associated steatotic liver disease (MASLD). Although previous studies have explored the association between body roundness index (BRI) and MASLD, the specific relationship in non-diabetic Japanese adults requires further investigation. This study analyzed data from 15,299 participants enrolled in the NAGALA cohort (2004–2015) to explore the association between BRI and MASLD through multivariable logistic regression, stratified analysis, and restricted cubic spline modeling. The prevalence of MASLD was 14.46%, with 13.73% occurring in non-obese individuals (BMI < 30). After adjusting for all confounding factors, BRI demonstrated a significant association with MASLD, yielding an adjusted odds ratio of 1.72 (95% CI 1.48–1.99). The restricted cubic spline model revealed a nonlinear relationship, with an inflection point at 3.06. Stratified analyses revealed stronger associations in individuals with lower BMI (≤ 24 kg/m²).

Keywords Body roundness index (BRI), Metabolic dysfunction associated steatotic liver disease (MASLD), Obesity, Non-diabetic Japanese, Nonlinear

Metabolic dysfunction-associated steatotic liver disease (MASLD) highlights the crucial role of metabolic dysfunction in the development and progression of the disease¹. Beyond indicating hepatic lesions, MASLD serves as a critical marker of systemic metabolic disturbances. Emerging evidence indicates that around 99% of non-alcoholic fatty liver disease (NAFLD) individuals also meet MASLD criteria, showing high concordance between the two definitions^{2,3}. Recently, there has been a dramatic increase in the incidence of MASLD, which has coincided with worldwide prevalence of obesity and diabetes⁴. MASLD is commonly recognized as the primary contributor to chronic liver disease globally, affecting approximately 38% of adults and between 7 and 14% of children^{5,6}.

The pathophysiology of MASLD encompasses various factors, including insulin signaling disruptions, irregular fatty acid metabolism, and the activation of inflammatory processes⁷. These factors collectively promote insulin resistance, obesity, and exacerbate metabolic dysfunction⁸. MASLD can worsen steatosis into non-alcoholic steatohepatitis, cirrhosis, and hepatocellular cancer⁹. A further point to consider is that MASLD is closely linked to metabolic syndrome and diabetes¹⁰. Thus, precise detection and effective intervention for populations at high risk of MASLD are key priorities in current research. Obesity, particularly visceral obesity, is strongly correlated with MASLD and is considered a key predictive factor for the disease^{11,12}. Among Asians, the prevalence was 23.5% for non-obese MASLD and 40.7% for obese MASLD¹³. Although BMI is extensively used to measure obesity, it does not completely capture the distribution of fat. To address this limitation, the body roundness index (BRI) was introduced by Thomas et al.¹⁴. Unlike BMI, which relies solely on weight and height, BRI uses waist circumference as a core metric, offering enhanced sensitivity to visceral fat accumulation¹⁵. BRI has been explored in relation to conditions including diabetes, cardiovascular diseases, metabolic syndrome^{15–18}.

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Due to the significant correlation between obesity and MASLD, BRI has emerged as a potential predictor of MASLD presence in the American population¹⁹.

However, the association between BRI and MASLD is still insufficiently explored, particularly in non-diabetic populations. This study aims to evaluate the association between BRI and MASLD in non-diabetic Japanese adults.

Methods

Data source and study population

This research utilized data from the NAGALA study, a longitudinal analysis focused on NAFLD in the Gifu Area. The original research began in 1994 at Murakami Memorial Hospital in Japan. This project conducts comprehensive medical evaluations, doing more than 8000 assessments each year. Around 60% of individuals undergo one to two examinations per year, enabling a thorough longitudinal analysis of health data.

The dataset for this research includes individuals who underwent several health assessments from 2004 to 2015. A total of 20,944 participants were initially identified, all of whom were free from diabetes at baseline. Data were sourced from the Dryad Digital Repository. The NAGALA project received ethical approval from the Clinical Research Ethics Committee of Murakami Memorial Hospital, and all participants provided informed consent for their data to be used in the research²⁰. To ensure the integrity of the analysis, several exclusion criteria were applied. Participants with pre-existing liver illnesses, including viral hepatitis, those with excessive alcohol intake, and persons on medication at baseline were excluded from the dataset. Furthermore, individuals diagnosed with diabetes were excluded. Subsequent to the application of these criteria, the final study cohort comprised 15,464 participants, encompassing 7034 women and 8430 men.

Participants without high-density lipoprotein cholesterol (HDL-C) data were eliminated from this study ($n = 11$). Furthermore, participants with extreme BRI values were excluded ($n = 154$). Extreme BRI values defined as $BRI < \text{mean} - 3 \times \text{SD}$ or $BRI > \text{mean} + 3 \times \text{SD}$. Finally, 15,299 participants were involved in the study (Fig. 1).

Data collection

This study retrieved various baseline data from the NAGALA database, encompassing fundamental demographic information and health markers of the individuals²⁰. Data collection encompassed age, gender, BMI, waist circumference (WC), blood pressure, HDL-C, liver enzymes, glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), and fasting plasma glucose (FPG). After fasting for at least 8 h, each participant had blood drawn for analysis, which was subsequently evaluated using an automatic biochemical analyzer. The lifestyle characteristics of participants were evaluated using standardized questionnaires that included smoking and alcohol consumption, exercise routines, and other relevant aspects. According to smoking habits, participants were classified into three categories: never, former, and current. Drinking status was characterized based on alcohol intake in the preceding month²¹. Exercise habits were characterized by participation in physical exercise a minimum of once per week. Specialists in gastroenterology diagnosed fatty liver according to findings of abdominal ultrasound examinations performed on patients²². Metabolic syndrome (MetS) is calculated based on the criteria set by the National Cholesterol Education Program²³. MASLD is defined in the 2020 International Expert Consensus Statement, which describes its diagnostic criteria as the presence of hepatic steatosis alongside metabolic abnormalities²⁴.

The BRI was computed as follows¹⁴:

$$BRI = 364.2 - 365.5 \sqrt{1 - \left(\frac{WC}{2\pi} \right)^2 \div (0.5 \text{height})^2}$$

Statistical analysis

Continuous data are typically presented as mean \pm standard deviation or median with interquartile range, while categorical data are generally reported as counts and proportions. Chi-square tests were utilized for the analysis of categorical data. In order to compare continuous variables between groups, we utilized analysis of variance (ANOVA) and Kruskal–Wallis tests. We estimated the variance inflation factor (VIF) in our multivariate models in order to manage the possibility of collinearity among the covariates. We excluded any covariates that had a VIF that was larger than 5 due to the fact that they were collinear (Supplementary Table S1). In addition to this, we carried out univariate logistic regression in order to investigate the potential impact that BRI may have on the occurrence of MASLD. Multivariable logistic regression analysis was conducted to evaluate associations with the dependent variable across three models. Model 1 adjusted for sex, age, BMI, exercise habits, smoking status, drinking status and SBP. Model 2 included HbA1c, ALT, AST, GGT, and FPG based on Model 1. Model 3 further adjusted for TG, TC, HDL-C and MetS.

To validate the robustness of our primary findings across different populations, we performed sensitivity analyses. These analyses were designed to assess the stability and consistency of the results by evaluating various scenarios and assumptions, thereby ensuring that our conclusions remain valid even when accounting for potential variations in the data. To minimize potential fat effects, sensitivity Analysis 1 excluded individuals whose BMI $> 24 \text{ kg/m}^2$. Sensitivity Analysis 2 excluded individuals aged > 50 years, while Sensitivity Analysis 3 excluded participants with MetS. To evaluate whether the association between BRI and MASLD remains significant after accounting for multiple comparisons, Bonferroni correction was applied. The dose–response relationship between BRI and MASLD was assessed using a restricted cubic spline (RCS) regression model with knots placed at the 25th, 50th, and 75th percentiles of the BRI distribution²⁵. A two-segment logistic regression approach was utilized to accurately identify the inflection point. Additionally, we performed stratified analyses based on demographic characteristics, exercise patterns, presence of fatty liver, and lifestyle behaviors like

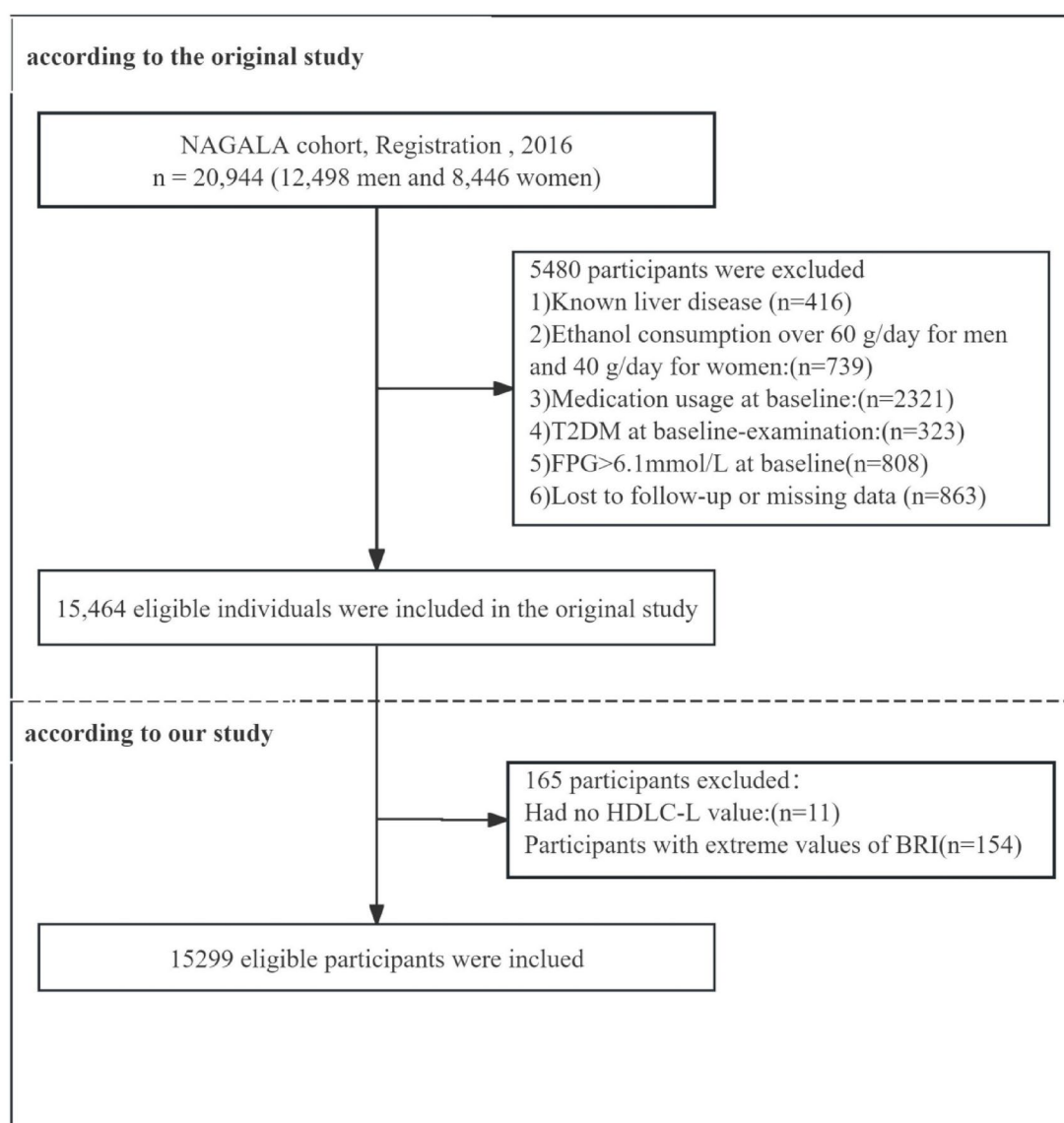


Fig. 1. Flowchart of the sample selection.

smoking and alcohol use, examining potential interactions among these factors. Data analyses were conducted utilizing Empower stats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA), with statistical significance defined as a *P* value of less than 0.05.

Results

Baseline characteristics

The study involved a total of 15,299 participants, where males represented 54.60% of the population. This cohort study revealed a prevalence of MASLD at 14.46%. The prevalence of MASLD in non-diabetic Japanese Adults (BMI < 30) was 13.73%. The study population was categorized into four quartile-based groups (Table 1). The analysis indicated that with the rise in BRI, there were notable increases in participants' age, BMI, WC, transaminases, TC, TG, HbA1c, FPG, and blood pressure, while HDL-C showed a marked decrease. Moreover, there was a considerable rise in the percentage of males in the elevated BRI categories, with the incidence of MASLD escalating markedly from 0.37% in Q1 to 39.69% in Q4. Exercise habits decreased as BRI increased, and there were observable trends in drinking and smoking statuses, although they were less pronounced than other variables. The findings demonstrate a strong link between elevated BRI and progression of MASLD, along with various aspects of metabolic syndrome and harmful lifestyle behaviors.

Association between BRI and MASLD

The univariate regression analysis, emphasizing notable correlations between all baseline variables and MASLD (Supplementary Table S2). Multivariable analysis demonstrated that the association between BRI and MASLD

Characteristic	Q1 (<2.09)	Q2 (2.09–2.63)	Q3 (2.63–3.23)	Q4 (≥ 3.23)	P value
Subjects, n	3825	3824	3825	3825	
Male, n (%)	1411 (36.89%)	2036 (53.24%)	2417 (63.19%)	2489 (65.07%)	<0.001
Age (years)	40.81 \pm 8.38	42.67 \pm 8.48	44.56 \pm 8.54	46.76 \pm 9.04	<0.001
BMI (kg/m ²)	19.02 \pm 1.53	21.02 \pm 1.52	22.68 \pm 1.70	25.35 \pm 2.45	<0.001
WC (cm)	66.28 \pm 4.49	73.34 \pm 4.18	78.90 \pm 4.30	86.33 \pm 5.74	<0.001
ALT (IU/L)	15.18 \pm 6.80	17.15 \pm 8.27	20.90 \pm 18.09	26.09 \pm 16.71	<0.001
AST (IU/L)	16.71 \pm 5.71	17.35 \pm 6.31	18.66 \pm 11.62	20.60 \pm 8.52	<0.001
GGT (IU/L)	14.41 \pm 11.20	18.11 \pm 15.27	21.98 \pm 20.19	26.33 \pm 21.24	<0.001
HDL-C (mmol/L)	1.66 \pm 0.39	1.53 \pm 0.39	1.39 \pm 0.38	1.28 \pm 0.34	<0.001
TC (mmol/L)	4.87 \pm 0.81	5.02 \pm 0.83	5.20 \pm 0.85	5.40 \pm 0.87	<0.001
TG (mmol/L)	0.60 \pm 0.33	0.78 \pm 0.51	1.01 \pm 0.69	1.24 \pm 0.80	<0.001
HbA1c (%)	5.10 \pm 0.30	5.14 \pm 0.31	5.18 \pm 0.32	5.26 \pm 0.33	<0.001
FPG (mmol/L)	4.99 \pm 0.39	5.11 \pm 0.39	5.22 \pm 0.40	5.31 \pm 0.39	<0.001
SBP (mmHg)	106.88 \pm 12.80	111.92 \pm 13.06	116.31 \pm 13.92	122.08 \pm 15.13	<0.001
DBP (mmHg)	66.40 \pm 8.82	69.63 \pm 9.36	72.95 \pm 10.05	76.88 \pm 10.47	<0.001
MetS, n (%)	6 (0.16%)	40 (1.05%)	137 (3.58%)	388 (10.14%)	<0.001
MASLD, n (%)	14 (0.37%)	127 (3.32%)	554 (14.48%)	1518 (39.69%)	<0.001
Habit of exercise, n (%)	689 (18.01%)	756 (19.77%)	676 (17.67%)	572 (14.95%)	<0.001
Drinking status, n (%)					<0.001
Non	3217 (84.10%)	2872 (75.10%)	2800 (73.20%)	2782 (72.73%)	
Light	335 (8.76%)	498 (13.02%)	458 (11.97%)	449 (11.74%)	
Moderate	218 (5.70%)	331 (8.66%)	386 (10.09%)	415 (10.85%)	
Heavy	55 (1.44%)	123 (3.22%)	181 (4.73%)	179 (4.68%)	
Smoking status, n (%)					<0.001
Never	2673 (69.88%)	2282 (59.68%)	2008 (52.50%)	1961 (51.27%)	
Past	451 (11.79%)	697 (18.23%)	877 (22.93%)	910 (23.79%)	
Current	701 (18.33%)	845 (22.10%)	940 (24.58%)	954 (24.94%)	

Table 1. Characteristics of the study population. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body mass index, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *HbA1c* glycated haemoglobin, *FPG* fasting plasma glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MetS* metabolic syndrome, *MASLD* metabolic dysfunction associated steatotic liver disease.

	OR (95% CI)		
	Model 1	Model 2	Model 3
BRI	2.16 (1.89, 2.47)	1.88 (1.63, 2.17)	1.72 (1.48, 1.99)
Q1	Ref	Ref	Ref
Q2	3.57 (2.04, 6.25)	3.10 (1.76, 5.46)	2.51 (1.42, 4.44)
Q3	8.29 (4.79, 14.34)	6.32 (3.63, 10.99)	4.46 (2.55, 7.79)
Q4	12.99 (7.38, 22.86)	9.19 (5.18, 16.30)	6.18 (3.46, 11.03)
P trend	<0.001	<0.001	<0.001

Table 2. Multivariable regression analyses for the association between BRI and MASLD. Model 1: sex, age, BMI, drinking status, smoking status, habit of exercise and SBP were adjusted. Model 2: sex, age, BMI, ALT, AST, GGT, habit of exercise, HbA1c, drinking status, smoking status, FPG and SBP were adjusted. Adjust 3: sex, age, BMI, ALT, AST, habit of exercise, GGT, HDL-C, TC, TG, MetS, HbA1c, drinking status, smoking status, FPG and SBP were adjusted.

remained robust even after controlling for confounding variables (Table 2). The model 1 revealed an OR of 2.16 (95% CI 1.89–2.47) for BRI. Following adjustment for covariates, the OR decreased to 1.88 (95% CI 1.63–2.17; Model 2) and then to 1.72 (95% CI 1.48–1.99; Model 3), affirming a strong and positive association between BRI and MASLD. Stratified analysis indicated that BMI significantly influences the association between BRI and MASLD (Fig. 2). The association was more pronounced in participants with a lower BMI (≤ 24 kg/m²). In this group, the relationship was notably stronger, with an OR of 3.16 (95% CI 2.60–3.84), compared to the BMI > 24 kg/m² group, which showed an OR of 2.21 (95% CI 1.92–2.56).

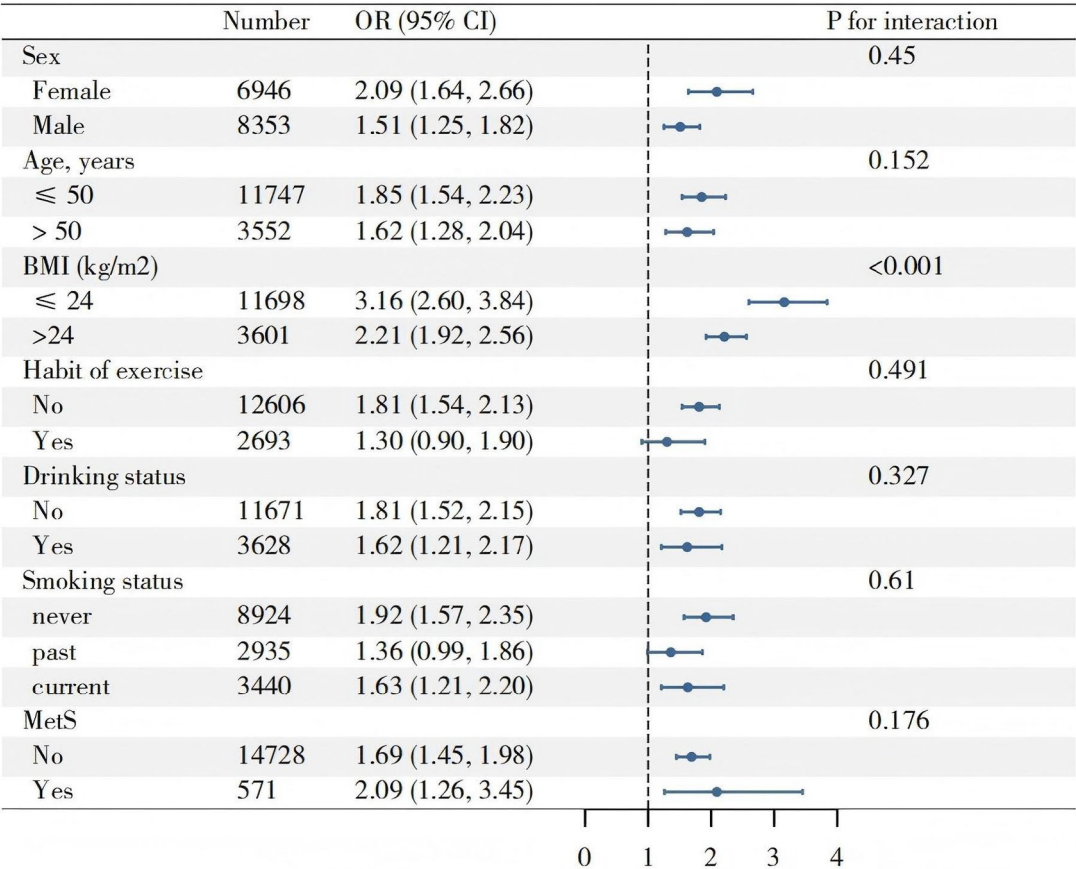


Fig. 2. Stratified analysis of associations between BRI and MASLD. Models adjusted for covariates as in Model 3.

	OR (95% CI)		
	Sensitivity-1	Sensitivity-2	Sensitivity-3
BRI	3.16 (2.60, 3.84)	1.85 (1.54, 2.23)	1.69 (1.45, 1.98)
Q1	Ref	Ref	Ref
Q2	3.67 (2.07, 6.51)	2.22 (1.22, 4.04)	2.33 (1.32, 4.14)
Q3	8.31 (4.76, 14.51)	3.81 (2.12, 6.87)	4.10 (2.34, 7.18)
Q4	12.78 (7.13, 22.89)	5.65 (3.05, 10.49)	5.75 (3.21, 10.32)

Table 3. Sensitivity analysis: the association between BRI and MASLD in different populations. (1) Sensitivity-1: Participants with BMI > 24 kg/m² at baseline were excluded (n = 11,698). (2) sensitivity-2: Participants diagnosed with age > 50 years at baseline were excluded (n = 11,747). (3) sensitivity-3: Participants diagnosed with MetS at baseline were excluded (n = 14,728). Sensitivity-1 was adjusted for sex, age, ALT, AST, habit of exercise, GGT, HDL-C, TC, TG, MetS, HbA1c, drinking status, smoking status, FPG and SBP. Sensitivity-3 was adjusted for sex, BMI, ALT, AST, habit of exercise, GGT, HDL-C, TC, TG, MetS, HbA1c, drinking status, smoking status, FPG and SBP. Sensitivity-3 was adjusted for sex, age, BMI, ALT, AST, habit of exercise, GGT, HDL-C, TC, TG, HbA1c, drinking status, smoking status, FPG and SBP.

Sensitivity analysis

Three sensitivity analyses were conducted to assess the robustness of the main results and assess the potential influence of specific subgroups (Table 3). Sensitivity analysis 1 excluded participants with a BMI exceeding 24 kg/m² to address the potential confounding effect of adiposity. Individuals aged > 50 years and those with MetS were excluded separately in sensitivity analysis 2 and sensitivity analysis 3. After including the extreme BRI values in the analysis, we performed a multivariable Cox regression analysis to verify the stability and consistency of the results, which demonstrated that the primary findings remained robust (Supplementary Table S3). Finally, after applying Bonferroni correction to account for multiple comparisons, the association between BRI and MASLD remained statistically significant across all subgroup analyses and sensitivity analyses ($P_{\text{adjusted}} < 0.05$).

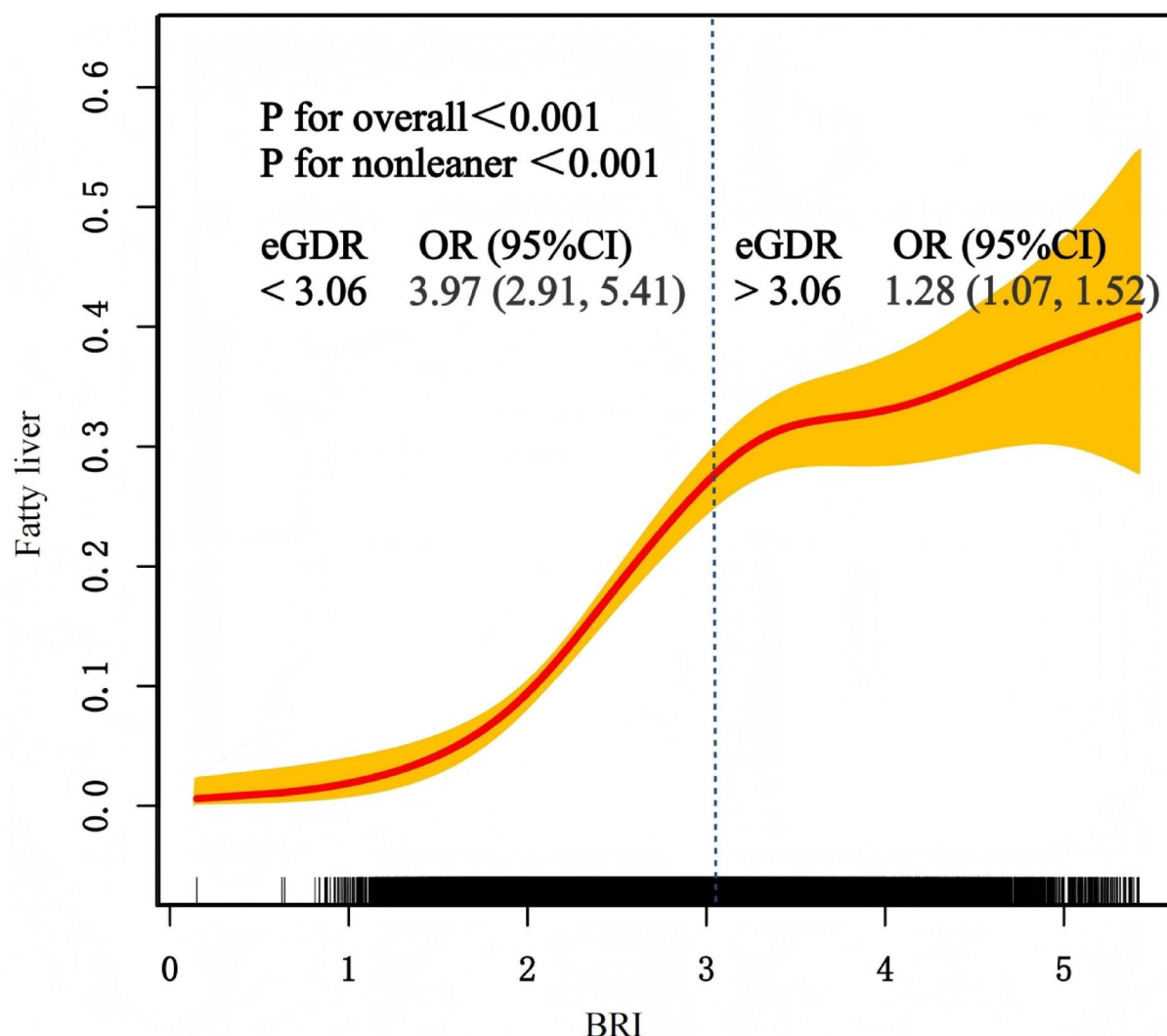


Fig. 3. Restricted cubic spline analysis of BRI for estimating the risk of MASLD.

Nonlinearity relationship between BRI and MASLD

The analysis using a restricted cubic spline regression model revealed a significant nonlinear relationship between BRI and MASLD (Fig. 3). Threshold effect analysis determined that BRI = 3.06 serves as the critical inflection point in this relationship. When BRI values dropped below 3.06, the OR reached as high as 3.97 (95% CI 2.91–5.41). However, when BRI values exceeded this threshold, the OR decreased to 1.28 (95% CI 1.07–1.52).

Discussion

This study examined the association between BRI and MASLD in non-diabetic Japanese adults using the NAGALA data, and identified three main findings. Firstly, an overall MASLD prevalence of 14.46% was observed, with a prevalence of 13.37% among the non-obese non-diabetic population (BMI < 30). Secondly, BRI showed a positive association with MASLD in non-diabetic Japanese adults, and the point of inflection was found to be 3.06. Thirdly, stratified analysis demonstrated that this association was stronger in individuals with a lower BMI.

The prevalence of MASLD varies significantly across different populations, with global rates reaching approximately 25% and specific rates of 23% in Germany²⁶. The overall prevalence in Asia stands at 29.62%, with notable variation: Indonesia shows the highest prevalence at 51.04%, while Japan is the lowest at 22.28%²⁷. In East Asia, the prevalence is around 29.7%, ranging from 25.95 to 33.76%, despite lower rates of overweight and obesity compared to Western countries⁵. A study of 831 faculty and staff at Gifu University undergoing annual occupational health examinations reported a MASLD prevalence of approximately 26% in the total group and 13% among those classified as non-obese (BMI < 25 kg/m²)²⁸. This disparity indicates that Asian populations may have an elevated risk of MASLD, potentially influenced by genetic factors and dietary habits that contribute to the onset and progression of the disease^{29,30}. This study investigates the prevalence of MASLD in a non-diabetic population, identifying a notable prevalence rate of 14.46%. These findings highlight the urgent need to address MASLD in non-diabetic individuals and underscore the importance of further research targeting this specific population.

Recent studies on BRI and MASLD have highlighted both commonalities and differences across various countries. In a large community-based study involving 4872 participants in northern Iran, BRI showed a strong association with ultrasound-defined MASLD (OR 5.484 in men and OR 3.482 in women)³¹. In the United States, BRI was identified as a more effective predictor of MASLD than BMI³². Moreover, there is a nonlinear relationship between BRI and MASLD³³. These findings highlight the importance of managing BRI levels to reduce MASLD incidence. Research from Taiwan and China also confirms a positive association between BRI and the severity and progression of MASLD³⁴. This study further observed a nonlinear association within the non-diabetic Japanese population. Specifically, the risk of MASLD prevalence escalated rapidly with increasing BRI below 3.06, but the increase moderated when BRI exceeded 3.06. The nonlinear association between BRI and MASLD demonstrates a critical inflection point at BRI = 3.06, suggesting differential contributions of visceral fat to MASLD risk³⁵. Below this threshold, the sharp increase in OR highlights the pivotal role of visceral fat in driving hepatic metabolic dysfunction. Beyond this inflection point, the plateau effect observed may reflect a state of metabolic saturation, where further visceral fat accumulation has a diminished impact on MASLD risk. Potential mechanisms underlying this phenomenon include genetic predispositions, systemic inflammation, or adaptive changes in hepatic lipid metabolism^{36,37}. Unlike previous studies, our findings reveal that the association between BRI and MASLD varies significantly depending on body fat.

Body fat accumulation is a major pathophysiological factor in MASLD³⁸. While obesity accelerates liver fibrosis in MASLD patients^{39,40}, MASLD typically coincides with the disease, non-obese MASLD is also prevalent, with global rates around 12.1% and higher in countries like Austria, Mexico, and Sweden⁴¹. In East Asia, this prevalence ranges from approximately 7.2–27%⁴². Our cohort study revealed a 14.46% prevalence of MASLD, with 13.37% among non-obese individuals (BMI < 30). Additionally, there are notable racial differences in BMI and its correlation with MASLD; Asians have an elevated MASLD risk at lower BMI levels⁴³. The Stratified analysis indicated that the relationship between BRI and MASLD was significantly stronger in participants with lower BMI compared to those with higher BMI. MI-based predictive indices, including the Fatty Liver Index and Hepatic Steatosis Index, are effective tools for detecting MASLD^{44,45}. Genetic polymorphisms, such as in the PNPLA3 gene, influence MASLD progression across racial groups, indicating excessive visceral fat despite normal BMI⁴⁶. Recent research highlights Golgi membrane protein 73 as a contributing factor, inhibiting lipid export from the liver and elevating disease risk, particularly in non-obese MASLD⁴⁷. BMI is an established risk factor for MASLD; Interestingly, this research indicated that individuals with a BMI below 24 exhibited a stronger association between BRI and MASLD. This finding suggests that BRI may be particularly informative in East Asian populations, who are more susceptible to genetic and weight-related factors³³.

Additionally, MASLD differs from NAFLD by focusing on metabolic dysfunction as the central pathological driver⁴⁸. MetS contributes to varying degrees of impact on cardiovascular outcomes in individuals with MASLD⁴⁹. Fortunately, this research found that MetS did not affect the association between BRI and MASLD. Moreover, the results of sensitivity analyses further support our conclusions.

Limitations

This study represents the first comprehensive cohort investigation of the relationship between BRI and MASLD in a non-diabetic Japanese population. Nevertheless, it is crucial to acknowledge the various constraints inherent in the design of our study. Firstly, although we thoroughly gathered potential confounding variables, we overlooked important factors like dietary patterns, stress, and genetic makeup that may influence the development of MASLD. Secondly, the diagnosis of MASLD was based on ultrasonography, which cannot determine disease progression and may underestimate its prevalence. Thirdly, this study excluded individuals with diabetes and included a limited percentage of elderly participants, which may affect the generalizability of the findings to broader populations. Fourthly, the small number of individuals with obesity in the sample limits its representativeness, making it challenging to determine whether the index provides added value over established indicators of body fat or offers clinical relevance and additional predictive utility. Finally, this study did not include FLI and HSI indices, and future research with larger cohorts is needed to validate the comparative efficacy of BRI against these indices. Future research should incorporate more objective measurement methods to enhance the reliability and validity of conclusions.

Conclusion

This study established a significant nonlinear relationship between BRI and MASLD in a non-diabetic Japanese adult population, with a particularly strong association observed in individuals with lower BMI. Considering the limitations inherent to the study population, future research should aim to increase the sample size and incorporate multicenter cohorts representing diverse ethnicities and geographic regions to further validate the utility of BRI in predicting MASLD across a wider demographic.

Data availability

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

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Author contributions

C.H. and Z.C.G. contributed to the concept and design of the study and drafted the manuscript. Z.X.H. analyzed the data and reviewed the manuscript. J.F.X. oversaw the project's progress, contributed to the discussion and reviewed the manuscript. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The NAGALA study was approved by the Clinical Research Ethics Committee of Murakami Memorial Hospital. All participants provided written informed consent prior to data collection. The Dryad Data Repository terms allow secondary analysis of de-identified data without additional ethical review.

Additional information

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