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Cardiac metabolic index as a predictor of new-onset diabetes in non-alcoholic fatty liver disease patients: a longitudinal cohort analysis

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Abstract

Objective The purpose of this investigation is to assess the clinical risk linked to the onset of diabetes in individuals with non-alcoholic fatty liver disease (NAFLD) through the utilization of the cardiac metabolic index (CMI), which is derived from triglycerides, high-density lipoprotein, height, and waist circumference. Research focusing on the application of CMI for evaluating diabetes risk among NAFLD patients remains scarce, and an exploration of the association between CMI and the emergence of diabetes within this demographic has not been conducted. This investigation aims to illuminate this connection, thereby providing novel insights into the prevention of diabetes progression in individuals with NAFLD.

Methods Data were procured from a cross-sectional study involving 15,435 participants conducted by the Japanese government, resulting in a final cohort of 2,503 adults aged 18 and above who met the eligibility criteria for evaluation. The CMI is determined using the formula: TG (mmol/L) / HDL-C (mmol/L) * WHtR. CMI values were categorized into quartiles (Q1 to Q4) based on their scores, arranged from low to high. The investigation utilized logistic regression models, restricted cubic spline analysis, and subgroup analyses, with adjustments made for continuous models to elucidate the association between CMI and diabetes development among individuals with NAFLD, as well as the non-linear relationship between CMI and this outcome.

Results The investigation comprised 2,503 subjects with an average age of 44.79 ± 8.33 years, of whom 204 were diagnosed with new-onset diabetes (8.15%). Multivariate logistic regression analysis indicated that within the CMI

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quartile groupings, individuals with NAFLD in the uppermost quartile (Q4) exhibited the greatest likelihood of new-onset diabetes relative to those in the lowest quartile (Q1) (odds ratio, OR = 3.239, 95% confidence interval [CI]: 1.993–5.264, $P < 0.001$). Additionally, escalating CMI values corresponded to an increasing probability of new-onset diabetes in NAFLD subjects (OR = 1.705, 95% CI: 1.362–2.133, $P < 0.001$). Restricted cubic spline analysis demonstrated a non-linear connection between CMI and new-onset diabetes in NAFLD patients (P overall < 0.001, P non-linear = 0.035), with a risk inflection point identified at a CMI of 0.5554. Subgroup analysis revealed no significant interactions between gender, age, physical activity, alcohol consumption, or smoking status and the likelihood of new-onset diabetes in this patient population (P for interaction > 0.05).

Conclusion Findings from this study indicate a notable positive non-linear connection between elevated CMI scores and the probability of new-onset diabetes in individuals afflicted with NAFLD.

Clinical trial number Not applicable.

Keywords Cardiac metabolic index (CMI), Longitudinal study, Non-alcoholic fatty liver disease (NAFLD), New-onset diabetes, Risk assessment

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder that has experienced an upward trend in clinical prevalence in conjunction with economic advancement and enhanced living conditions, thereby emerging as a significant public health concern impacting human health [1]. NAFLD is acknowledged as one of the principal pathogenic contributors to chronic liver diseases, with evidence suggesting that it constitutes approximately 25% of chronic liver disease occurrences [2]. Non-alcoholic steatohepatitis (NASH) represents a serious clinical manifestation that develops from NAFLD [3, 4]. Investigations reveal that around 20–25% of NAFLD cases may progress to varying degrees of NASH [5], which can culminate in liver fibrosis, cirrhosis, and even liver cancer [2]. Projections indicate that by 2030, NAFLD cases will account for 33.5% of the global population, while NASH cases are expected to comprise 9.02% [6], presenting a considerable potential threat to human health. Additionally, NAFLD is not solely a metabolic disorder; it has the capacity to provoke multi-system diseases and is recognized as an independent risk factor for numerous chronic systemic ailments [7, 8]. Consequently, the prevention and management of NAFLD hold critical clinical importance for the advancement of human health.

Diabetes mellitus (DM) is a systemic and chronic condition that has emerged as the third most significant threat to human health, trailing only cardiovascular diseases and cancers [9]. Data from research indicate that in 2021, approximately 540 million individuals aged 20 and older worldwide were affected by diabetes, with projections suggesting that this figure may escalate to 780 million by 2045 [10]. The prevalence of NAFLD among obese and diabetic populations surpasses 80%, with studies indicating a strong correlation between NAFLD and diabetes, as both conditions are known to influence and aggravate one another [11]. The underlying mechanism is characterized by NAFLD contributing to heightened insulin resistance, which progresses to diabetes, while diabetes additionally facilitates the onset and clinical advancement of NAFLD [12].

Current investigations have conducted preliminary analyses on the interrelations among diabetes, lipid metabolism, and body indices, establishing positive correlations between the risk of diabetes and factors including body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), the total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C), and the triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-C), although the clinical predictive significance of these indices remains constrained [13]. The cardiac metabolic index (CMI), introduced by Wakabayashi et al. in 2015 [14], has been tentatively associated with diabetes within the general population [15]. Nevertheless, the relationship between CMI and new-onset diabetes in NAFLD patients has yet to be explored. Consequently, this study intends to examine the link between CMI and the emergence of new-onset diabetes in individuals with NAFLD, seeking to provide novel perspectives and direction for preventing and treating related disorders.

Methodologies

Data source

This investigation is predicated on a secondary statistical analysis of data obtained from the DRYAD database (https://datadryad.org/stash), specifically a dataset co ntributed by Okamura et al. in 2019 [16]. The dataset is derived from a long-term longitudinal investigation that included 15,464 residents in Japan, with follow-up conducted over a five-year period. The cohort consists of 8,430 men and 7,034 women, thereby providing a balanced demographic structure (link: https://datadryad.org/stash/dataset/ doi: https://doi.org/10.5061/dryad.8q0p192#citations). Publicly shared by the authors, the data set permits researchers to utilize it for non-commercial

scientific inquiries and the dissemination of findings, contingent upon proper citation. It encompasses 21 baseline demographic and clinical indicators, including fatty liver status, smoking behaviors, hemoglobin A1c (HbA1c), BMI, alcohol consumption, physical activity, new-onset diabetes, age, and gender.

Study participants and study design

The data utilized for this analysis is derived from the dataset published by Okamura in 2019 [16], which was developed from a health screening initiative commenced by Murakami Memorial Hospital in Japan in 1994. This program was designed to identify independent risk factors associated with chronic diseases, resulting in data extraction covering the years from 2004 to 2015, encompassing a total of 15,464 samples. The research investigates the link between CMI and diabetes development among NAFLD subjects, following the inclusion and exclusion criteria outlined below. Inclusion Criteria: (1) Adults aged 18 years and above; (2) Diagnosed with fatty liver; (3) Participation in follow-up without any loss to follow-up. Exclusion Criteria: (1) Individuals under the age of 18; (2) Patients diagnosed with alcoholic fatty liver disease, various hepatitis types, or other liver disorders (excluding NAFLD) during initial screening; (3) Alcohol consumption exceeding 60 g per day for men or 40 g per day for women; (4) Absence of core baseline data or clinical indicators (including height, weight, exercise habits, alcohol intake, WC, and abdominal ultrasound results); (5) Individuals exhibiting diagnosed with diabetes during the initial screening; (6) Individuals lack follow-up data. Based on these criteria, 2741 participants were identified from the original dataset of 15,464 samples published by Okamura [16]. Of these, 235 patients were excluded because their alcohol consumption exceeded 60 g per day for men and 40 g per day for women. Furthermore, three patients with NAFLD were excluded due to the absence of critical data, such as WC measurements. Consequently, the final analysis comprised 2,503 non-alcoholic fatty liver patients who fulfilled the study criteria. The process of patient selection is depicted in Fig. 1. The original dataset and associated study received ethical approval from the ethics committee of Murakami Memorial Hospital, and all participants provided written informed consent prior to enrollment [16]. Given that this investigation constitutes a secondary analysis of publicly accessible data from Okamura [16], it was exempt from further ethical review.

Data collection and measurements

This investigation is conducted as a secondary statistical analysis of data sourced from publicly available databases, with all information extracted from the dataset published by Okamura [16]. The dataset encompasses demographic characteristics, physical examination data, and results from blood tests. Smoking status is classified into three categories: non-smokers, occasional smokers, and regular smokers. Alcohol consumption is classified into three frequency categories: none, low, and moderate; individuals identified as heavy drinkers in the original study were excluded according to the previously outlined alcohol consumption criteria [16, 17]. Exercise habits are defined by participants' engagement in any form of exercise more than once per week [18]. Based on abdominal ultrasound findings and established clinical diagnostic criteria for fatty liver, participants are categorized as either having or not having fatty liver [19]. The original study supplies data regarding participants' BMI, WC, and weight, with height being calculated using the BMI formula. The CMI is determined using the formula: TG (mmol/L) / HDL-C (mmol/L) * WHtR. CMI quartiles are computed and classified into Q1 to Q4.

Statistical analysis

Statistical analyses for the present investigation were executed utilizing SPSS 22.0 and R 4.3.2 software. Continuous variables were articulated as means and standard deviations if they followed a normal distribution; otherwise, they were reported as medians (P50) along with interquartile ranges (P25, P75). Categorical variables were represented as frequencies and percentages. Chi-square tests were employed to compare categorical variables between groups. For continuous variables, ANOVA was utilized when the data were normally distributed, whereas Mann-Whitney tests were utilized for non-normally distributed data. Logistic regression analyses were conducted to evaluate the link between CMI and the risk of new-onset diabetes in NAFLD patients, with results expressed as odds ratios (OR) and 95% confidence intervals (95% CI). Both unadjusted and adjusted models for confounding variables were implemented to confirm the stability of the model. Model 1 adjusted for sex and age; Model 2 included exercise habits; Model 3 accounted for GGT, AST, TC, FPG, SBP, DBP, height, and ethanol consumption. Confounding factors were selected based on two principles: (1) previous relevant studies were consulted to identify essential confounders [20–23]; (2) confounders that, when included in the model, resulted in an OR change exceeding 10% compared to the original model were selected [24, 25]. Restricted cubic spline analysis was employed to explore the linear association between CMI and the incidence of diabetes among NAFLD patients. Subgroup analyses were executed utilizing stratified logistic regression models for variables such as gender, age, exercise, alcohol consumption, and smoking. Continuous variables were converted into categorical variables according to clinically significant cut points, with age divided into two groups (< 60 years and

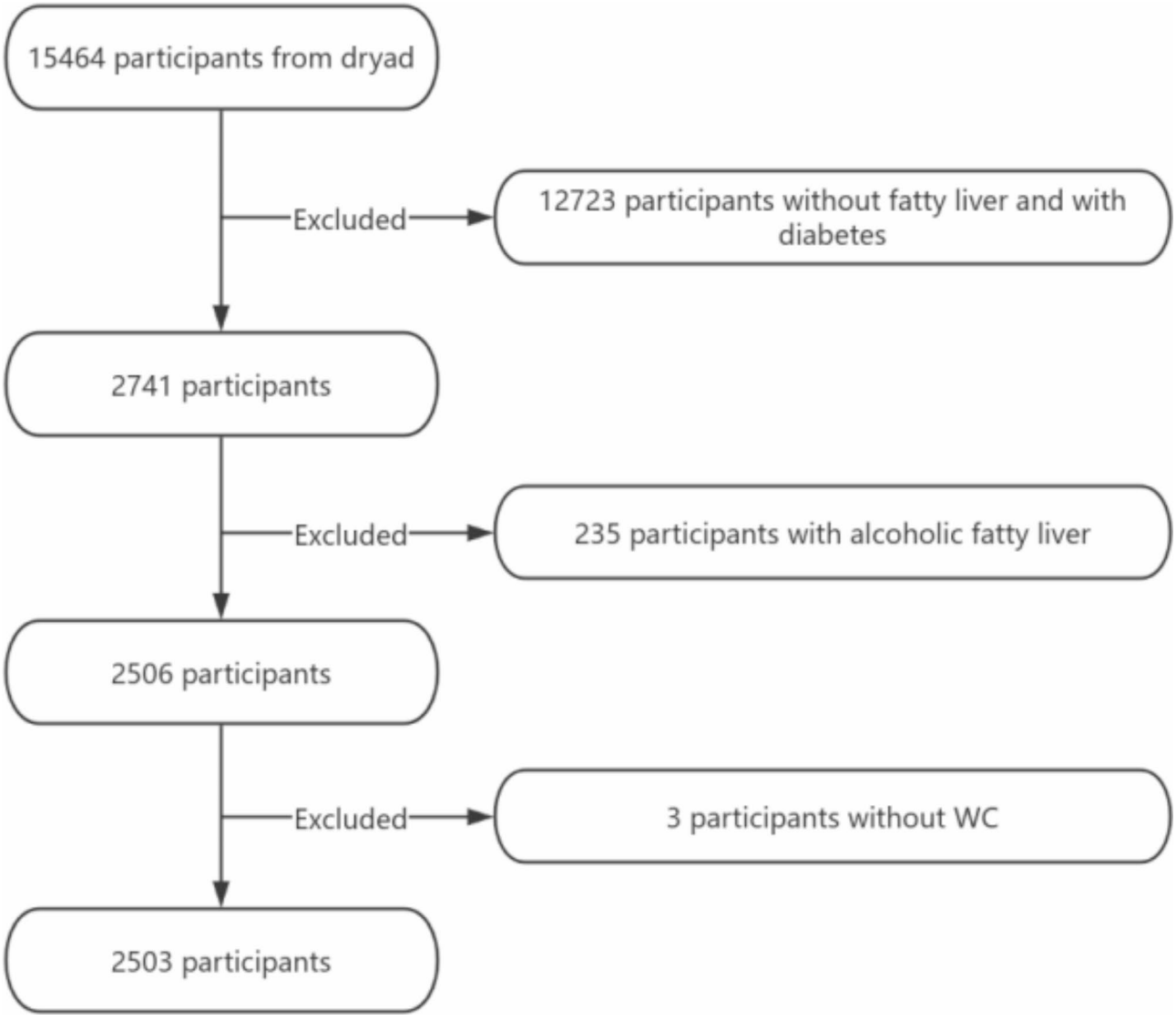

Fig. 1 Diagram of participant enrollment process

≥ 60 years). Interaction analyses were conducted to assess potential interactions within the model [26]. Receiver operating characteristic curves and area under the curve were utilized to evaluate the clinical predictive power of CMI concerning the onset of diabetes in NAFLD patients. A p-value of < 0.05 was deemed statistically significant across all analyses.

Results

Baseline characteristics

In this investigation, the 2,503 patients with non-alcoholic fatty liver who satisfied the specified criteria were separated into four groups according to their CMI, employing quartiles for the analysis of baseline data. The participants had a mean age of 44.79 ± 8.33 years, comprising 2,025 men (80.9%) and 478 women (19.1%). Statistical comparisons between groups indicated significant differences in various parameters, including gender, exercise habits, smoking status, incidence of new-onset DM, BMI, WC, ALT, AST, weight, GGT, HDL-C, total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), height, systolic blood pressure (SBP), diastolic blood pressure (DBP), and ethanol consumption ($P < 0.05$). Among these parameters, BMI, WC, ALT, AST, weight, GGT, TC, TG, height, SBP, DBP, and ethanol consumption exhibited a progressive increase from Q1 to Q4, whereas HDL-C demonstrated a gradual decline across the quartiles, with all comparisons attaining statistical significance. Comprehensive results are depicted in Table 1.

Multivariate logistic regression analysis

This investigation utilized multivariate logistic regression analysis to assess the link between CMI and the

Table 1 Baseline characteristics of patients included according to CMI quartile

Variable	Q1(<0.344)	Q2(0.344 ~ 0.556)	Q3(0.556 ~ 0.877)	Q4(>0.877)	*P*
Gender					<0.001
Female(478)	204(42%)	132(28%)	87(18%)	55(12%)	
Male(2025)	422(21%)	494(24%)	539(27%)	570(28%)	
Exercise					0.044
No(2126)	520(24%)	518(24%)	544(26%)	544(26%)	
Yes(377)	106(28%)	108(29%)	82(22%)	81(21%)	
Alcohol					0.165
Never(2085)	539(26%)	520(25%)	514(25%)	512(24%)	
Light(285)	65(23%)	65(23%)	79(28%)	76(26%)	
Moderate(133)	22(16%)	41(31%)	33(25%)	37(28%)	
Smoking					<0.001
Never(1183)	368(31%)	313(27%)	265(22%)	237(20%)	
Past(637)	148(23%)	166(26%)	178(28%)	145(23%)	
Heavy(683)	110(16%)	147(21%)	183(27%)	243(36%)	
New Diabetes Mellitus					<0.001
No(2299)	599(26%)	583(25%)	576(25%)	541(23%)	
Yes(204)	27(13%)	43(21%)	50(25%)	84(41%)	
Age	44.00[38.00,51.00]	49.00[39.00,51.00]	44.00[38.00,51.00]	43.00[38.00,50.00]	0.136
BMI	24.00[22.27,25.85]	24.79[23.12,26.75]	25.54[23.89,27.84]	26.02[24.25,28.32]	<0.001
WC	82.00[77.00,87.00]	84.90[80.30,90.00]	86.50[82.00,91.00]	87.80[83.50,94.00]	<0.001
ALT	23.00[17.00,31.00]	26.00[19.00,37.00]	29.00[21.00,40.00]	32.00[24.00,46.00]	<0.001
AST	19.00[15.00,23.00]	20.00[16.00,25.00]	21.00[17.00,26.00]	22.00[18.00,28.00]	<0.001
Weight	67.10[60.00,73.60]	70.20[63.90,77.10]	73.55[66.50,80.30]	74.70[68.60,82.90]	<0.001
GGT	18.00[14.00,25.00]	22.00[16.00,30.00]	24.00[18.00,34.00]	28.00[21.00,40.00]	<0.001
HDL-C	1.42[1.26,1.62]	1.19[1.07,1.34]	1.10[0.98,1.22]	0.93[0.84,1.05]	<0.001
TC	5.20[4.55,5.74]	5.38[4.84,5.84]	5.51[4.91,6.15]	5.64[5.09,6.18]	<0.001
TG	0.69[0.55,0.82]	1.05[0.91,1.21]	1.46[1.29,1.65]	2.27[1.91,2.85]	<0.001
HbA1c%	5.30[5.10,5.50]	5.30[5.10,5.50]	5.30[5.10,5.50]	5.35[5.10,5.50]	0.875
FPG	5.33[5.11,5.61]	5.38[5.16,5.66]	5.38[5.16,5.66]	5.50[5.22,5.72]	<0.001
Height	167.20[159.60,172.90]	168.75[162.80,173.20]	168.90[164.00,173.50]	170.20[165.60,174.40]	<0.001
SBP	119.50[110.00,128.50]	121.25[112.50,131.00]	124.00[115.50,134.00]	124.50[115.50,134.00]	<0.001
DBP	75.00[68.50,81.00]	76.50[70.50,83.50]	78.50[72.50,85.50]	79.00[72.00,86.00]	<0.001
Ethanol consumption	1.00[0.00,22.00]	1.00[0.00,36.00]	1.00[0.00,54.00]	4.20[1.00,54.00]	<0.001

Group variables were expressed by frequency and percentage, Quantitative variables are represented using quartiles

WC: Waist circumference; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma glutamyl transferase; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride; HbA1c%: Hemoglobin A1c; FPG: Fasting plasma glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CMI: Cardiometabolic Index

risk of developing new-onset diabetes among patients diagnosed with NAFLD. Findings from the unadjusted model revealed a positive correlation between CMI and the clinical risk of new diabetes in this patient population (OR = 1.876, 95% CI: 1.526–2.306). When Q1 was designated as the reference group, the risk of new diabetes was observed to escalate by 1.636 times (OR = 1.636, 95% CI: 0.998–2.683) for Q2, by 1.926 times (OR = 1.926, 95% CI: 1.189–3.118) for Q3, and by 3.445 times (OR = 3.445, 95% CI: 2.199–5.396) for Q4. The adjusted models, which included Model 1 (adjusted for sex and age), Model 2 (Model 1 + exercise habits), and Model 3 (Model 2 + GGT, AST, TC, FPG, SBP, DBP, height, and ethanol consumption), the marked positive connection between CMI and the clinical risk of new diabetes was maintained. Treating CMI as a continuous variable and adjusting for all relevant confounders indicated that each 1-unit increase in CMI was linked to a 1.705-fold higher likelihood of new-onset diabetes in patients with NAFLD. Comprehensive results are depicted in Table 2.

Restrictive cubic spline analysis and threshold effect analysis

This investigation undertook a comprehensive analysis of the link between CMI and the onset of diabetes in individuals with NAFLD, employing restrictive cubic spline analysis. Upon adjusting for all relevant confounders, a non-linear positive connection was identified between CMI and the risk of developing new diabetes (P overall < 0.001, P non-linear = 0.035). The threshold value of CMI for the clinical risk of new-onset diabetes was established at 0.5554. Notably, when CMI surpasses this

Table 2 Logistic regression analysis results for the association between the CMI and new diabetes mellitus from non-alcohol fatty liver disease

Vairable	Unadjusted Model		Model 1		Model 2		Model 3	
CMI	1.876(1.526 ~ 2.306)	<0.001	1.923(1.560 ~ 2.371)	<0.001	1.913(1.551 ~ 2.359)	<0.001	1.705(1.362 ~ 2.133)	<0.001
Q1	Ref		Ref		Ref		Ref	
Q2	1.636(0.998 ~ 2.683)	0.051	1.693(1.029 ~ 2.785)	0.038	1.694(1.029 ~ 2.787)	0.038	1.678(1.005 ~ 2.803)	0.048
Q3	1.926(1.189 ~ 3.118)	0.008	2.062(1.264 ~ 3.365)	0.004	2.029(1.234 ~ 3.313)	0.005	1.890(1.137 ~ 3.141)	0.014
Q4	3.445(2.199 ~ 5.396)	<0.001	3.774(2.378 ~ 5.991)	<0.001	3.714(2.338 ~ 5.899)	<0.001	3,239(1.993 ~ 5.264)	<0.001
P for trend	3.141(2.151 ~ 4.586)	<0.001	3.399(2.304 ~ 5.016)	<0.001	3.343(2.264 ~ 4.936)	<0.001	2.877(1.905 ~ 4.345)	<0.001

Model 1:adjust Sex and Age; Model 2: Model 1 + Habit of exercise ; Model 3: Model 2 + GGT, AST, TC, FPG, SBP, DBP, Height, Ethanol consumption

threshold, the risk of new diabetes increases progressively with rising CMI values, as illustrated in Fig. 2. The analysis indicated that for CMI > 0.5554, each incremental unit increase in CMI corresponded to a 50.5% rise in the risk of new-onset diabetes among individuals with NAFLD (OR = 1.505, 95% CI: 1.155–1.962). Comprehensive results are depicted in Table 3.

Subgroup analyses

This investigation employed subgroup and interaction analyses to examine the link between CMI and the onset of diabetes in patients with NAFLD across various subgroups. The findings from the interaction analysis revealed that the correlation between CMI and new-onset diabetes did not display statistical significance across the different subgroups. Notably, factors including gender (Female/Male), age (< 60/≥60), exercise (No/Yes), alcohol consumption (Light/Moderate/Never), and smoking status (Heavy/Never/Past) did not markedly affect the relationship between CMI and new diabetes in patients with non-alcoholic fatty liver (all interaction $P > 0.05$). Additionally, the association between CMI and new diabetes was consistent across all subgroups, indicating a high degree of stability and reliability. Comprehensive results are depicted in Fig. 3.

Discussion

This longitudinal study, encompassing 2,503 participants, represents a significant advancement in exploring the association between CMI and the onset of diabetes in individuals with NAFLD. The results indicate a statistically significant non-linear positive correlation between CMI and the occurrence of new diabetes cases within this population. Notably, this association persists even when CMI is examined as a categorical variable, thereby enhancing the robustness of the conclusions drawn. This research offers essential insights into the complex role of CMI in the pathogenesis of diabetes in the context of NAFLD, supplying valuable information regarding the implications of lipid metabolism in this clinical setting.

The connection between lipid metabolism and the onset of diabetes, along with the advancement of NAFLD, has garnered significant interest in recent years. CMI, a clinical marker derived from lipid profiles, is increasingly acknowledged for its association with metabolic disorders, including diabetes and stroke. Numerous investigations have recorded associations between heightened CMI levels and the emergence of metabolic diseases [27, 28]. NAFLD is marked by excessive lipid accumulation in the liver, frequently accompanied by mitochondrial dysfunction [29, 30], which has been correlated with notable disturbances in lipid metabolism [31, 32]. This condition not only exacerbates hepatic fat accumulation but also serves a vital function in the onset of insulin resistance, a fundamental element in the pathophysiology of diabetes. Diabetes is defined by increased blood glucose levels, primarily resulting from diminished insulin sensitivity and a progressive decline in β-cell function [33]. Studies indicate that disruptions in lipid metabolism can trigger β-cell dysfunction, emphasizing lipid metabolism irregularities as essential factors in the onset of diabetes [34]. Moreover, the literature suggests that abnormal lipid metabolism can initiate chronic inflammatory responses [35]. These inflammatory processes can interfere with insulin signaling pathways, thereby fostering insulin resistance [36]. In individuals with simple NAFLD, the ongoing metabolic inflammation associated with lipid dysregulation may progressively undermine insulin signaling, ultimately leading to the development of diabetes [31, 32].

CMI, derived from the formula: [TG(mmol/L)/HDL – C(mmol/L)]∗WHtR, has been evidenced to possess a positive correlation with the WHtR, which serves as an effective indicator of abdominal obesity [26]. Both abdominal obesity and disorders of lipid metabolism are known to considerably exacerbate insulin resistance, indicating that CMI could act as a novel biomarker for evaluating the risk of diabetes onset and progression [26–37]. Current research has demonstrated significant associations between CMI and various health conditions, including cardiovascular disease and renal disease [27, 38–40]. Preliminary evidence further suggests a potential connection between CMI, diabetes, and NAFLD [37, 41]. Despite the well-documented link between NAFLD and diabetes, the precise relationship between CMI and the onset of new diabetes cases in individuals

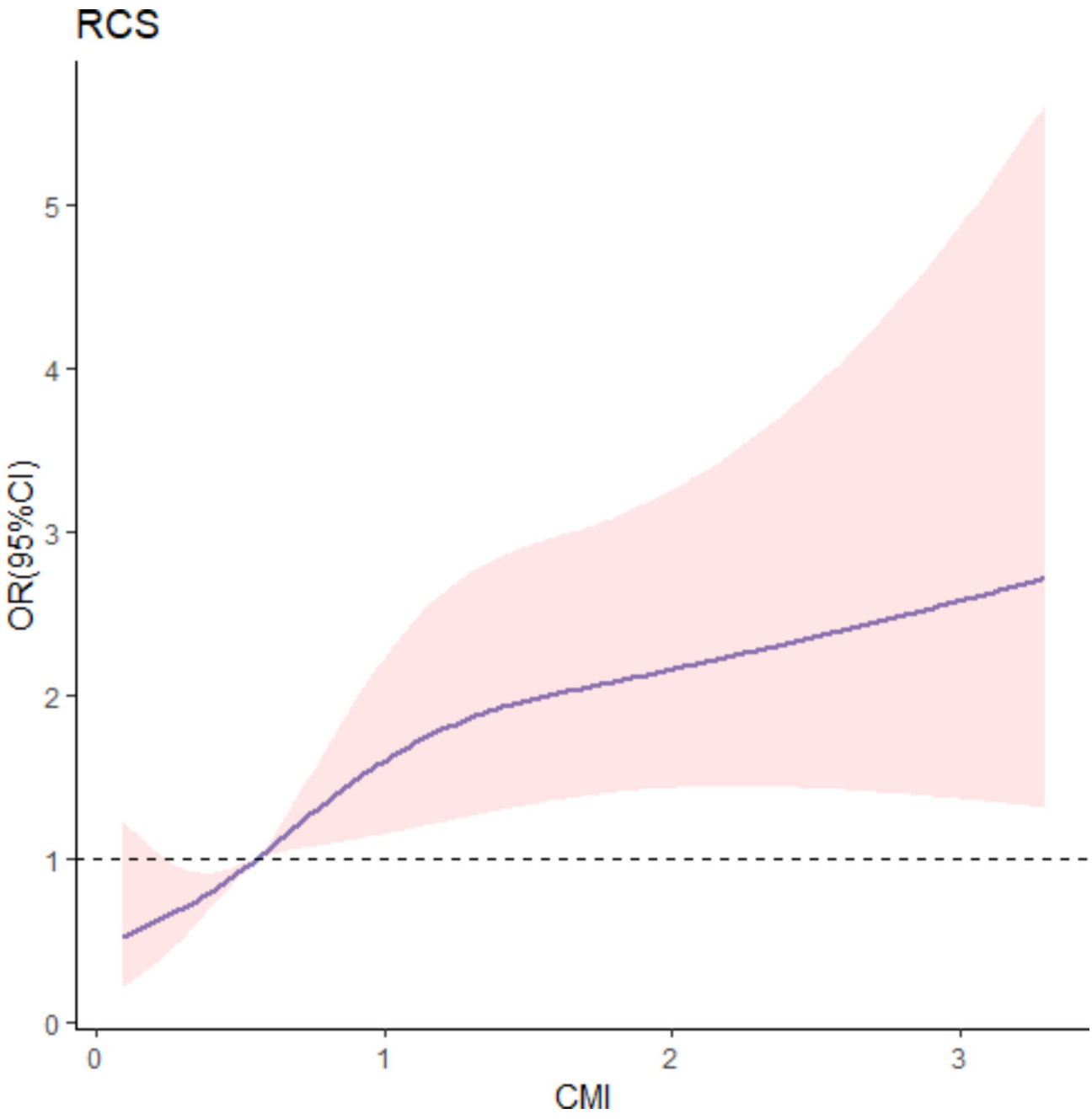

Fig. 2 Association between CMI and new diabetes mellitus from non-alcohol fatty liver disease

Table 3 Threshold effect analysis of the CMI on new diabetes mellitus from non-alcohol fatty liver disease

CMI	Odds ratios (95%CI)	*P*
Turning point (K)	0.5554	
CMI < K	8.821(1.092 ~ 71.321)	0.041
CMI > K	1.505(1.155 ~ 1.962)	0.002
P for log likelihood ratio test		< 0.001

with NAFLD has not been thoroughly examined, rendering our study pioneering in this aspect. Unique to our research is the utilization of data from a large-scale, long-term cohort study, which confirms a significant statistical link between CMI and the onset of diabetes in NAFLD patients. Importantly, even after adjusting for numerous confounding variables, the association persists, emphasizing the close interplay between lipid metabolism and the onset of diabetes in this patient population. Additionally, subgroup analyses strengthen the stability and reliability of our findings across various demographic

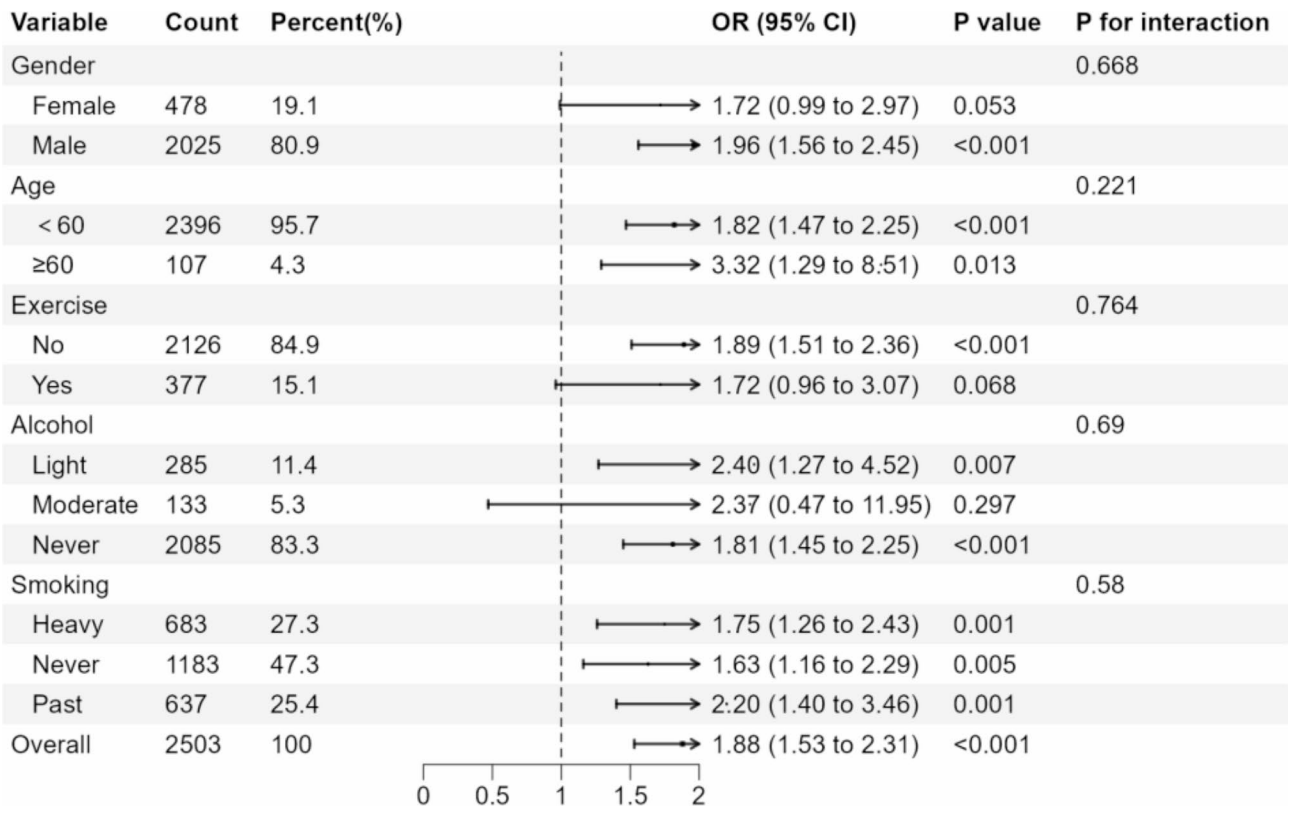

Fig. 3 Subgroup analysis for the association between CMI and new diabetes mellitus from non-alcohol fatty liver disease

factors, including age, gender, exercise habits, and alcohol consumption. These results carry substantial clinical implications. Identifying CMI as a significant predictor of new-onset diabetes in NAFLD patients may promote early intervention strategies. Routine monitoring of CMI could enable healthcare practitioners to pinpoint at-risk individuals and implement preventive measures, potentially enhancing patient outcomes. Moreover, comprehending the pathways linking CMI to diabetes may pave the way for innovative therapeutic strategies aimed at lipid metabolism to reduce diabetes risk. In conclusion, this study reveals a significant non-linear association between CMI and the risk of new-onset diabetes in patients with NAFLD. Elevated CMI levels are linked to an increased clinical risk of diabetes development, highlighting the critical role of lipid metabolism in this context. In this study, the Cardiometabolic Index (CMI) is an emerging comprehensive metric used to assess the metabolic health and cardiovascular risk in diabetes patients. CMI is typically calculated as the ratio of waist circumference to triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), reflecting the state of abdominal obesity, insulin resistance, and lipid metabolism abnormalities [14]. These metabolic disturbances are prevalent in diabetes and are major contributors to cardiovascular diseases and other complications. Studies have shown that diabetes patients with higher CMI are more likely to develop atherosclerosis, hypertension, and coronary heart disease, as well as microvascular complications such as diabetic nephropathy and retinopathy [14, 27, 28, 41]. Additionally, changes in CMI over time may predict disease progression and long-term outcomes. Due to its simplicity and reliance on easily obtainable parameters, CMI has increasingly been recognized as a valuable tool for risk stratification and management in diabetes. Regular assessment of CMI may constitute a vital element in the risk evaluation and prevention of diabetes in patients with NAFLD, ultimately enhancing the management of this widespread condition.

Study strengths and limitations

This investigation represents a secondary analysis of longitudinal data derived from a five-year follow-up involving 15,464 residents in Japan, aimed at investigating independent risk factors for chronic diseases, thus enhancing the scientific credibility of the data. Previous research has only preliminarily established connections between CMI and diabetes or NAFLD independently, without exploring the relationship between CMI and new-onset diabetes in NAFLD. Consequently, this study innovatively investigates this association. Multivariable logistic regression, subgroup analyses, and interaction analyses were employed, further affirming the stability and reliability of the findings. These results offer

significant references for the risk assessment and prevention of diabetes in patients with NAFLD. However, as the data is specific to Japanese residents, the findings may be more applicable to this demographic, presenting limited generalizability to other ethnic groups. Future research will involve the collection of additional data from diverse populations to validate these findings.

Although this investigation presents meaningful observations, several constraints need to be recognized. The analysis focuses on a particular sample group, potentially limiting the applicability of the outcomes to additional populations. Future studies should seek to validate these results across diverse demographic groups and investigate the underlying biological mechanisms mediating the relationship between CMI and new-onset diabetes. In this study, we did not further reduce confounding bias by matching non-MASLD participant cohorts.Our research team will collect localized data in future studies and conduct a separate study using propensity score matching, applying MASLD as the diagnostic criterion, to address the limitations of the current study. Additionally, longitudinal studies tracking CMI changes over time, and their impact on diabetes progression would further clarify the clinical significance of this index.

Conclusion

The results indicate a robust non-linear correlation between CMI and the emergence of new-onset diabetes in individuals with NAFLD, with elevated CMI levels linked to an increased clinical risk for diabetes. Consistent dynamic evaluations of CMI, paired with customized intervention strategies, may assist in managing and mitigating the risk of diabetes among individuals with NAFLD.

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Author contributions
SBH, YQW, ZXW, and HJL were responsible for drafting the manuscript, designing the study, and analyzing the data. HNF, TTZ, YHZ, LXC, and LXZ conducted data verification and cross-checked the manuscript. LXZ, XC, and MD provided support in human resources and contributed to the study design. All authors have read and approved the final manuscript.

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The study was conducted independently by the investigator without any official funding.

Data availability
This investigation is predicated on a secondary statistical analysis of data obtained from the DRYAD database, https://datadryad.org/stash/dataset/doi:10.5061/dryad.8q0p192#citations.

Declarations

Ethics approval and consent to participate
The study followed the Declaration of Helsinki and the implementation of the NAGALA project was authorized by the Murakami Memorial Hospital Ethics Committee, and informed consent for data usage was obtained from each participant. The original dataset used in this research, as well as the original study, received ethical approval from the Ethical Committee of Murakami Memorial Hospital in Japan. Participants in the original study provided written informed consent prior to enrollment in the research. As this study is a secondary analysis based on the publicly available dataset published by Okamura, additional ethical review was not required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Golabi P, Bush H, Younossi ZM. Treatment strategies for nonalcoholic fatty liver disease and Nonalcoholic Steatohepatitis. Clin Liver Dis. 2017;21(4):739–53. https://doi.org/10.1016/j.cld.2017.06.010.
2. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the diagnosis and management of nonalcoholic fatty liver Disease in Primary Care and Endocrinology Clinical Settings: co-sponsored by the American Association for the study of Liver diseases (AASLD). Endocr Pract. 2022;28(5):528–62. https://doi.org/10.1016/j.eprac.2022.03.010.
3. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2021;18(4):223–38. https://doi.org/10.1038/s41575-020-00381-6.
4. Grander C, Grabherr F, Tilg H. Non-alcoholic fatty liver disease: pathophysiological concepts and treatment options. Cardiovasc Res. 2023;119(9):1787–98. https://doi.org/10.1093/cvr/cvad095.
5. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11–20. https://doi.org/10.1038/nrgastro.2017.109.
6. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. J Hepatol. 2018;69(4):896–904. https://doi.org/10.1016/j.jhep.2018.05.036.
7. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol. 2015;62(5):1148–55. https://doi.org/10.1016/j.jhep.2014.11.034.
8. Mikolasevic I, Milic S, Turk Wensveen T, Grgic I, Jakopcic I, Stimac D, et al. Nonalcoholic fatty liver disease - A multisystem disease? World J Gastroenterol. 2016;22(43):9488–505. https://doi.org/10.3748/wjg.v22.i43.9488.
9. Liu J, Ren ZH, Qiang H, Wu J, Shen M, Zhang L, et al. Trends in the incidence of diabetes mellitus: results from the global burden of Disease Study 2017 and implications for diabetes mellitus prevention. BMC Public Health. 2020;20(1):1415. https://doi.org/10.1186/s12889-020-09502-x.
10. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. https://doi.org/10.1016/j.diabres.2021.109119.
11. Liu Lele S, Bei W. Effect of saxagliptin on naive type 2 diabetes mellitus with non-alcoholic fatty liver disease. Chronic Disease Prev Control China.

2021;29(09):692–5. https://doi.org/10.16386/j.cjpccd.issn.1004-6194.2021.09.012.
12. Zhang M, Zhou J, Liu Y, Sun X, Luo X, Han C, et al. Risk of type 2 diabetes mellitus associated with plasma lipid levels: the rural Chinese cohort study. Diabetes Res Clin Pract. 2018;135:150–7. https://doi.org/10.1016/j.diabres.2017.11.011.
13. Wakabayashi I, Sotoda Y, Hirooka S, Orita H. Association between cardiometabolic index and atherosclerotic progression in patients with peripheral arterial disease. Clin Chim Acta. 2015;446:231–6. https://doi.org/10.1016/j.cca.2015.04.020.
14. Shi WR, Wang HY, Chen S, Guo XF, Li Z, Sun YX. Estimate of prevalent diabetes from cardiometabolic index in general Chinese population: a community-based study. Lipids Health Dis. 2018;17(1):236. https://doi.org/10.1186/s12944-018-0886-2.
15. Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. Int J Obes (Lond). 2019;43(1):139–48. https://doi.org/10.1038/s41366-018-0076-3.
16. Hashimoto Y, Hamaguchi M, Kojima T, Ohshima Y, Ohbora A, Kato T, et al. Modest alcohol consumption reduces the incidence of fatty liver in men: a population-based large-scale cohort study. J Gastroenterol Hepatol. 2015;30(3):546–52. https://doi.org/10.1111/jgh.12786.
17. Ryu S, Chang Y, Kim DI, Kim WS, Suh BS. Gamma-glutamyltransferase as a predictor of chronic kidney disease in nonhypertensive and nondiabetic Korean men. Clin Chem. 2007;53(1):71–7. https://doi.org/10.1373/clinchem.2006.078980.
18. Hamaguchi M, Kojima T, Itoh Y, Harano Y, Fujii K, Nakajima T, et al. The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. Am J Gastroenterol. 2007;102(12):2708–15. https://doi.org/10.1111/j.1572-0241.2007.01526.x.
19. Wang M, Li S, Zhang X, Li X, Cui J. Association between hemoglobin glycation index and non-alcoholic fatty liver disease in the patients with type 2 diabetes mellitus. J Diabetes Investig. 2023;14(11):1303–11. https://doi.org/10.1111/jdi.14066.
20. Liu J, Fu Q, Su R, Liu R, Wu S, Li K, et al. Association between nontraditional lipid parameters and the risk of type 2 diabetes and prediabetes in patients with nonalcoholic fatty liver disease: from the national health and nutrition examination survey 2017–2020. Front Endocrinol (Lausanne). 2024;15:1460280. https://doi.org/10.3389/fendo.2024.1460280.
21. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. Gut. 2021;70(5):962–9. https://doi.org/10.1136/gutjnl-2020-322572.
22. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(1):20–30. https://doi.org/10.1016/S2468-1253(22)00317-X. Epub 2022 Nov 16.
23. Agoritsas T, Merglen A, Shah ND, O'Donnell M, Guyatt GH. Adjusted analyses in studies addressing therapy and harm: users' guides to the Medical Literature. JAMA. 2017;317(7):748–59. https://doi.org/10.1001/jama.2016.20029.
24. VanderWeele TJ. Principles of confounder selection. Eur J Epidemiol. 2019;34(3):211–9. https://doi.org/10.1007/s10654-019-00494-6.
25. Mullee A, Romaguera D, Pearson-Stuttard J, Viallon V, Stepien M, Freisling H, et al. Association between Soft Drink Consumption and mortality in 10 European countries. JAMA Intern Med. 2019;179(11):1479–90. https://doi.org/10.1001/jamainternmed.2019.2478.
26. Wakabayashi I, Daimon T. The cardiometabolic index as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus. Clin Chim Acta. 2015;438:274–8. https://doi.org/10.1016/j.cca.2014.08.042.
27. Wang H, Chen Y, Guo X, Chang Y, Sun Y. Usefulness of cardiometabolic index for the estimation of ischemic stroke risk among general population in rural China. Postgrad Med. 2017;129(8):834–41. https://doi.org/10.1080/00325481.2017.1375714.
28. Eslam M, Sanyal AJ, George J. International Consensus Panel.MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease., Gastroenterology. 2020 Feb 8: S0016–5085 (20) 30171–2. https://doi.org/10. 1053/ j. gastro. 2019. 11. 312.
29. Kupriyanova Y, Zaharia OP, Bobrov P, Karusheva Y, Burkart V, Szendroedi J, et al. GDS group. Early changes in hepatic energy metabolism and lipid content in recent-onset type 1 and 2 diabetes mellitus. J Hepatol. 2021;74(5):1028–37. https://doi.org/10.1016/j.jhep.2020.11.030.
30. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: an update. Metabolism. 2016;65(8):1109–23. https://doi.org/10.1016/j.metabol.2016.05.003. Epub 2016 May 13.
31. Zou Y, Zhong L, Hu C, Zhong M, Peng N, Sheng G. LDL/HDL cholesterol ratio is associated with new-onset NAFLD in Chinese non-obese people with normal lipids: a 5-year longitudinal cohort study. Lipids Health Dis. 2021;20(1):28. https://doi.org/10.1186/s12944-021-01457-1.
32. Zaharia OP, Strassburger K, Strom A, Bönhof GJ, Karusheva Y, Antoniou S, German Diabetes Study Group, et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. Lancet Diabetes Endocrinol. 2019;7(9):684–94. https://doi.org/10.1016/S2213-8587(19)30187-1.
33. Imai Y, Cousins RS, Liu S, Phelps BM, Promes JA. Connecting pancreatic islet lipid metabolism with insulin secretion and the development of type 2 diabetes. Ann N Y Acad Sci. 2020;1461:53–72. https://doi.org/10.1111/nyas.14037.
34. Vogel A, Brunner JS, Hajto A, Sharif O, Schabbauer G. Lipid scavenging macrophages and inflammation. Biochim Biophys Acta Mol Cell Biol Lipids. 2022;1867(1):159066. https://doi.org/10.1016/j.bbalip.2021.159066.
35. Suren Garg S, Kushwaha K, Dubey R, Gupta J. Association between obesity, inflammation and insulin resistance: insights into signaling pathways and therapeutic interventions. Diabetes Res Clin Pract. 2023;200:110691. https://doi.org/10.1016/j.diabres.2023.110691.
36. Heard ME, Melnyk SB, Simmen FA, Yang Y, Pabona JM, Simmen RC. High-Fat Diet Promotion of endometriosis in an Immunocompetent Mouse Model is Associated with altered peripheral and Ectopic Lesion Redox and inflammatory status. Endocrinology. 2016;157(7):2870–82. https://doi.org/10.1210/en.2016-1092.
37. Dursun M, Besiroglu H, Otunctemur A, Ozbek E. Association between cardiometabolic index and erectile dysfunction: a new index for predicting cardiovascular disease. Kaohsiung J Med Sci. 2016;32(12):620–3. https://doi.org/10.1016/j.kjms.2016.10.003.
38. Wang H, Chen Y, Sun G, Jia P, Qian H, Sun Y. Validity of cardiometabolic index, lipid accumulation product, and body adiposity index in predicting the risk of hypertension in Chinese population. Postgrad Med. 2018;130(3):325–33. https://doi.org/10.1080/00325481.2018.1444901.
39. Wang HY, Shi WR, Yi X, Wang SZ, Luan SY, Sun YX. Value of reduced glomerular filtration rate assessment with cardiometabolic index: insights from a population-based Chinese cohort. BMC Nephrol. 2018;19(1):294. https://doi.org/10.1186/s12882-018-1098-8.
40. Zou J, Xiong H, Zhang H, Hu C, Lu S, Zou Y. Association between the cardiometabolic index and non-alcoholic fatty liver disease: insights from a general population. BMC Gastroenterol. 2022;22(1):20. https://doi.org/10.1186/s12876-022-02099-y.
41. Xu B, Wu Q, Yin G, Lu L, La R, Zhang Y, et al. Associations of cardiometabolic index with diabetic statuses and insulin resistance: the mediating role of inflammation-related indicators. BMC Public Health. 2024;24(1):2736. https://doi.org/10.1186/s12889-024-20048-0.

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