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Association of Cumulative Exposure and Dynamic Trajectories of Triglyceride-Total Cholesterol-Body Weight Index with New-Onset Chronic Liver Disease in Middle-Aged and Older Chinese Adults: A Longitudinal Analysis Based on CHARLS

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Article

Keywords: Chronic liver disease, Triglyceride-Total Cholesterol-Body Weight Index (TCBI), Cumulative exposure, Dynamic trajectories, K-means clustering, CHARLS

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Declarations

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Competing interests

The authors declare that they have no competing interests

Authors' contributions

Xingyu Bao:Conceptualization; Data Curation; Formal Analysis; Funding Acquisition; Investigation; Methodology; Project Management; Resources; Software; Supervision; Validation; Visualization;Writing;Editing.

Yan Yao:Review.

Ethics approval and consent to participate

The CHARLS study received approval from the Institutional Review Board of Peking University (IRB00001052-11015) and was performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to their involvement in the CHARLS study. This research adhered to the STROBE guidelines for reporting observational studies in epidemiology.

Consent for publication

Not applicable

Availability of data and materials

The CHARLS datasets are accessible in the CHARLS home website (http://charls.pku.edu.cn/en).

Abstract

Background:

The Triglyceride-Total Cholesterol-Body Weight Index (TCBI) is a novel nutritional index, but its longitudinal association with chronic liver disease (CLD) is unclear. This study examined cumulative TCBI (cuTCBI) and TCBI trajectories in relation to incident CLD risk.

Methods:

Data from the China Health and Retirement Longitudinal Study (CHARLS) included 4,695 participants. TCBI trajectories were identified via K-means clustering. Cox regression, restricted cubic spline (RCS), Kaplan–Meier curves, and ROC analyses assessed associations, with subgroup and sensitivity analyses.

Results:

Over follow-up, 245 (5.2%) developed CLD. Each 1-SD increase in cuTCBI raised CLD risk by 12% (HR=1.12, 95%CI:1.03–1.22). The highest cuTCBI tertile (HR=1.51, 95%CI:1.09–2.09) and quartile (HR=1.68, 95%CI:1.14–2.48) showed increased risk. Three trajectories (low-stable, moderate-stable, high-stable) were identified; the high-stable group had 46% higher risk versus low-stable (HR=1.46, 95%CI:1.03–2.07). RCS revealed a linear dose–response relationship (P-overall<0.0001; P-nonlinear=0.1856). Kaplan–Meier curves showed higher cuTCBI linked to greater CLD incidence ($p<0.05$). Associations were consistent across subgroups and robust in sensitivity analyses.

Conclusions:

Both cuTCBI and persistently elevated TCBI trajectories are associated with increased CLD risk in middle-aged and older adults. Long-term monitoring and maintaining low TCBI levels may aid CLD prevention.

Keywords: Chronic liver disease; Triglyceride-Total Cholesterol-Body Weight Index (TCBI); Cumulative exposure; Dynamic trajectories; K-means clustering; CHARLS

Introduction

Chronic liver disease (CLD) represents a major global public health challenge and is a leading cause of morbidity and mortality worldwide. CLD encompasses a broad spectrum of conditions, including viral hepatitis [1,2], drug-induced liver injury [3], liver cirrhosis [4], autoimmune chronic liver disease [5], alcohol-related chronic liver disease [6], and metabolic dysfunction-associated steatotic liver disease (MASLD)[7], collectively posing a substantial global health burden[8,9]. The burden of CLD is particularly high among the elderly population globally [10]. In China, approximately one-fifth of adults are affected [11]. Therefore, identifying reliable and cost-effective biomarkers for early risk stratification is critical to mitigating this public health crisis.

From a pathophysiological perspective, the development of CLD is not driven by a single pathway but rather by a vicious cycle involving lipid metabolism disorders, insulin resistance, and chronic low-grade inflammation[12–14].Abnormal accumulation of triglycerides (TG) within hepatocytes induces lipotoxicity, activates endoplasmic reticulum stress and mitochondrial dysfunction, and directly leads to hepatocyte apoptosis [15]. Total cholesterol (TC), particularly free cholesterol, promotes hepatic inflammatory responses and hepatic stellate cell activation through an NLRP3 inflammasome-dependent pathway[16].Increased body weight(BW), especially visceral adiposity, further amplifies insulin resistance and systemic inflammation by releasing free fatty acids and pro-inflammatory cytokines (e.g., TNF-α, IL-6) [17]. These three factors synergistically act on the liver, progressively driving the disease from simple steatosis to steatohepatitis, fibrosis, and ultimately cirrhosis[18].Consequently, a composite index that integrates the three dimensions of TG, TC, and BMI

theoretically better approximates the true picture of long-term metabolic burden on the liver than any single indicator.

Based on this mechanistic framework, Doi et al. first proposed the Triglyceride-Total Cholesterol-Body Weight Index (TCBI) as a simple nutritional index for patients with coronary artery disease [19]. However, existing clinical evidence on TCBI is almost entirely derived from cross-sectional designs or single-time-point measurements, and most has focused on cardiovascular outcomes[20–22].To date, prospective cohort evidence on the association of cumulative TCBI exposure (cuTCBI) and its dynamic trajectories with the risk of CLD in middle-aged and older populations remains insufficient. Whether and how cuTCBI is associated with CLD risk is still unclear, and whether distinct longitudinal TCBI trajectories correspond to differential risks of incident CLD has not been established. Exploring cuTCBI and its dynamic change patterns may provide novel insights for CLD risk assessment.

Therefore, this study leveraged data from the China Health and Retirement Longitudinal Study (CHARLS), a national longitudinal cohort, to evaluate the role of cuTCBI and TCBI changes in the risk of CLD among middle-aged and older Chinese adults. The findings will provide evidence for the early identification of high-risk populations for CLD and the development of personalized intervention strategies.

Methods

Study Design and Population

This study analyzed data from the China Health and Retirement Longitudinal Study (CHARLS), a national ongoing cohort study enrolling individuals aged 45 years and

older. CHARLS employs a random sampling design, with the baseline survey conducted in 2011 (Wave 1) and follow-ups performed in 2013, 2015, 2018, and 2020 (Waves 2–5). It collects comprehensive data covering demographics, health, socioeconomic status, and community characteristics, with blood samples collected at baseline and Wave 3. Ethical approval was obtained from the Peking University Institutional Review Board (IRB00001052-11015), and all participants provided written informed consent.The design of the CHARLS study has been described previously [23]. This secondary analysis used CHARLS longitudinal data, setting Wave 1 as the baseline and following participants up to Wave 5.

The exclusion criteria for this study were as follows: (1) missing data for calculating the Triglyceride-Total Cholesterol-Body Weight Index (TCBI) at Wave 1 (2011) (n = 8,874); (2) missing data for calculating TCBI at Wave 3 (2015) (n = 3,816); (3) prevalent chronic liver disease (CLD) before Wave 3 (2015) (n = 233); and (4) age < 45 years (n = 87). The detailed inclusion and exclusion process is shown in Figure 1. Ultimately, 4,695 participants were included in the final analysis.

Figure 1.

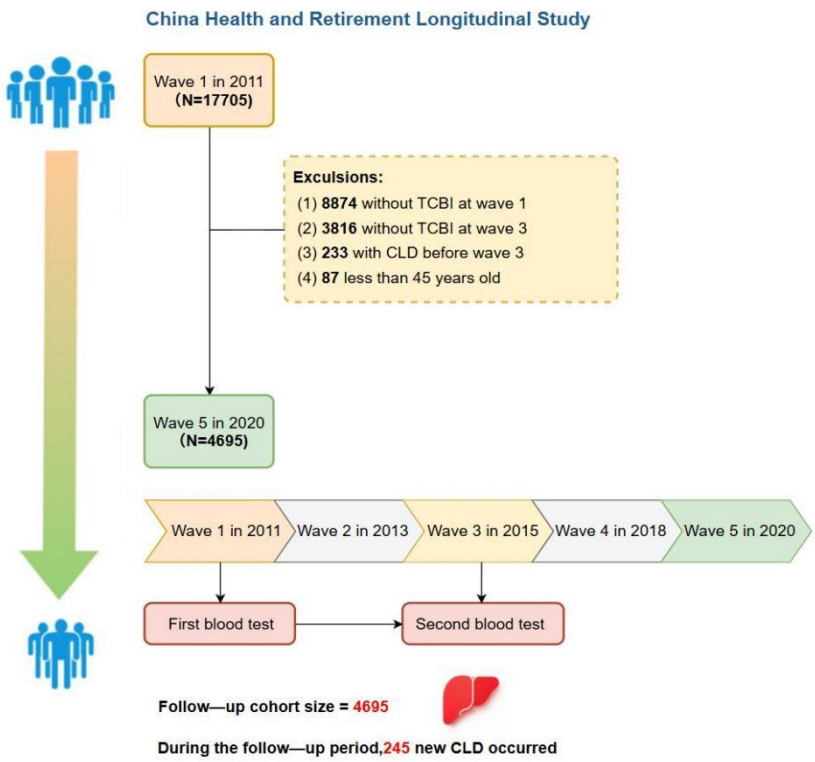


Figure 1. Participant screening process

Assessment of TCBI Change

The exposure variable in this study was the change in the Triglyceride-Total Cholesterol-Body Weight Index (TCBI) from 2011 to 2015. TCBI was calculated as [TG (mg/dL) × TC (mg/dL) × BW (kg)]/1000 [19]. To assess long-term metabolic exposure, a time-weighted average formula was used to compute the cumulative index, cuTCBI = (TCBI2011 + TCBI2015)/2 × time interval (2015–2011). This method assumes a linear change between measurements and has been widely applied in cumulative exposure studies, such as those on CTI and CHG, demonstrating good validity for estimating chronic metabolic burden[24,25].Based on TCBI levels, participants were classified into three trajectory groups using k-means clustering: Cluster 1 (stable low risk), Cluster 2 (moderate increase), and Cluster 3 (stable high risk).

Ascertainment of Incident Chronic Liver Disease (CLD)

After excluding participants with baseline chronic liver disease (CLD), survival analyses started at CHARLS Wave 3 (2015) as the milestone baseline to eliminate immortal time bias, ensuring exposure assessments relied on pre-follow-up data.

Incident CLD was defined via the standardized question of physician-diagnosed chronic liver disease. Positive responses at any survey wave indicated CLD. Prior self-reported CLD was verified in subsequent follow-ups, and inconsistent self-reports were retrospectively corrected.The ascertainment of CLD was consistent with prior studies using CHARLS data [26].

Covariates

Baseline data of the participants were meticulously collected by trained interviewers using a structured questionnaire. The collected data encompassed the following categories: (1) Demographic and lifestyle data: this section included information on sex, age, residence location, education level, marital status, smoking status, and alcohol consumption. (2) Physical measurements: recorded measurements included height, body weight, body mass index (BMI), as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP). (3) Medical history and medication use: this section included hypertension, diabetes, dyslipidemia, heart disease, and stroke. (4) Laboratory measurements: data collected from laboratory tests included fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), C-reactive protein (CRP), high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Hypertension was defined as meeting at least one of the following criteria: (1) systolic blood pressure ≥140 mmHg, (2) diastolic blood pressure ≥90 mmHg, (3) self-reported physician diagnosis of hypertension. Blood pressure was calculated as the average of three measurements taken under standard conditions. Diabetes was defined as meeting at least one of the following criteria: (1) fasting plasma glucose (FPG) ≥126 mg/dL, (2) HbA1c ≥6.5%, (3) self-reported physician diagnosis of diabetes.

Statistical Analysis

Participants were stratified into three groups via k-means clustering. Normally distributed continuous variables were expressed as mean ± standard deviation, and non-normal variables as median (interquartile range). Categorical variables were presented as counts and percentages. Between-group comparisons adopted the chi-square test, one-way ANOVA and Kruskal-Wallis test accordingly. Multiple imputation by chained equations (MICE) with five imputed datasets and Rubin's rules was applied to handle missing covariates.

Longitudinal TCBI trajectories from 2011 to 2015 were classified into three stable patterns (low, moderate, high) using k-means clustering selected by the elbow method. Silhouette Score and Calinski-Harabasz index were calculated to validate clustering performance.

Three Cox proportional hazards models were established to explore the association between cuTCBI and incident CLD: Model 1 (unadjusted), Model 2 (adjusted for demographic factors), and Model 3 (additionally adjusted for lifestyle and comorbidities). Kaplan–Meier curves and the log-rank test were used to compare

cumulative CLD risks across groups. Restricted cubic splines (RCS) with three knots assessed non-linear relationships. The AUC and DeLong test evaluated predictive performance of cuTCBI. Stratified subgroup and interaction analyses, as well as multiple sensitivity analyses, were further conducted.

All statistical analyses were performed using R software (version 4.4.2). A two-sided P-value < 0.05 was considered statistically significant.

Results

K-Means Clustering Analysis of TCBI

To identify distinct longitudinal patterns of TCBI from 2011 to 2015, k-means clustering analysis was performed. Because the raw TCBI values exhibited a right-skewed distribution, log-transformed TCBI (log(TCBI)) values were used to facilitate comparisons. The number of clusters was determined by the elbow method, which showed that the within-cluster sum of squares (WSS) leveled off markedly at k = 3 (Figure 2A). Principal component analysis (PCA) was further applied to visualize cluster separation, demonstrating that the three identified groups were well distributed in the reduced-dimensional space with minimal overlap (Figure 2B). Quantitative validation further supported the choice of the three-cluster solution. The silhouette coefficient was 0.474; previous studies have suggested that a silhouette coefficient > 0.25 indicates reasonably valid clustering[27]. The Calinski-Harabasz index exhibited a pronounced peak at k = 3 (value: 5227.75). Based on this method, participants were classified into three trajectory patterns (Figure 2C): the stable high-risk type (n = 985), which had the highest incidence of chronic liver disease (7%); the moderate increase

type (n = 2058), showing a moderate incidence of chronic liver disease (5.2%); and the stable low-risk type (n = 1652), which had the lowest incidence of chronic liver disease (4.2%). The incidence of chronic liver disease showed an increasing trend across the three groups (Figure 2D). These findings suggest that long-term persistently elevated TCBI levels are more predictive of chronic liver disease incidence than stable low-level exposure.

Figure 2.

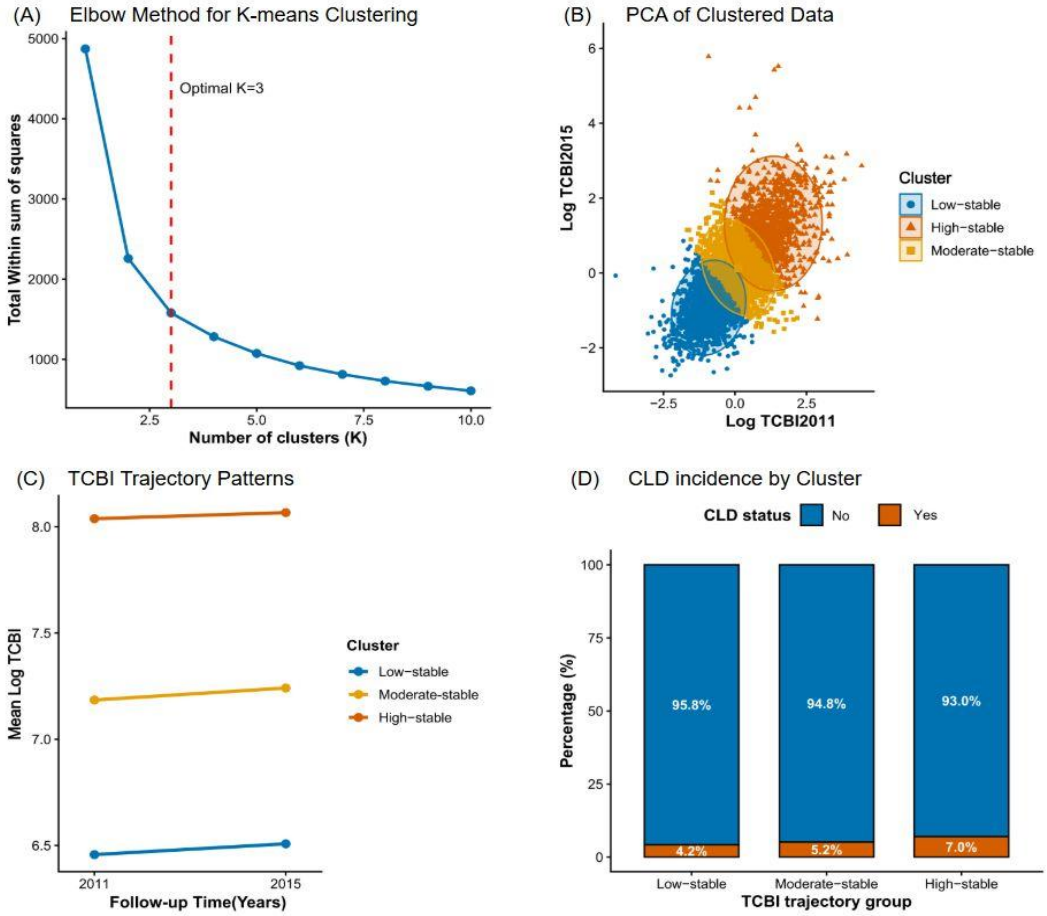


Figure 2. Clustering of TCBI changes from 2012 to 2015. (A) The K value was determined by the elbow method; (B) PCA visualization; (C) Changes in TCBI from 2012 to 2015; (D) Proportion of chronic liver disease in the three TCBI clusters.The TCBI value underwent a logarithmic transformation.

Baseline Characteristics

A total of 4,695 participants were included in this study. Table 1 summarizes the baseline characteristics of participants stratified by three groups based on dynamic TCBI trajectories: Cluster 1 (stable low risk, n = 1,652), Cluster 2 (moderate increase, n = 2,058), and Cluster 3 (stable high risk, n = 985). All variables except alcohol consumption and stroke differed significantly among the three groups ($P < 0.001$). Compared with the low-risk group, participants in the high-risk group were slightly younger, had a higher proportion of urban residents, and exhibited worse metabolic parameters (BMI, blood glucose, lipids, blood pressure, CRP), as well as significantly higher prevalences of hypertension, dyslipidemia, diabetes, and heart disease (all $P < 0.001$). The incidence of CLD increased in a dose-dependent manner: 4.2% in Cluster 1, 5.2% in Cluster 2, and 7.0% in Cluster 3 ($P = 0.008$), suggesting that long-term elevated TCBI is significantly positively associated with CLD risk.

Table 1. Baseline characteristics of the study population based on the change in TCBI

		TCBI trajectory group			
Variable	**Overall N = 4,695**	**Cluster1 N = 1,652**	**Cluster2 N = 2,058**	**Cluster3 N = 985**	***p*-value**
Age (years)	59.0 (52.0–65.0)	60.0 (54.0–67.0)	58.0 (52.0–64.0)	57.0 (51.0–62.0)	<0.001
Gender					<0.001
Female	2,580 (55%)	803 (49%)	1,192 (58%)	585 (59%)	
Male	2,115 (45%)	849 (51%)	866 (42%)	400 (41%)	
Residence					<0.001
Rural	3,988 (85%)	1,470 (89%)	1,738 (84%)	780 (79%)	

Table 1. Baseline characteristics of the study population based on the change in TCBI

Variable	Overall N = 4,695	TCBI trajectory group Cluster1 N = 1,652	Cluster2 N = 2,058	Cluster3 N = 985	*p*-value
Urban	707 (15%)	182 (11%)	320 (16%)	205 (21%)	
Education					<0.001
Illiterate	1,354 (29%)	512 (31%)	608 (30%)	234 (24%)	
Elementary school	1,975 (42%)	734 (44%)	813 (40%)	428 (43%)	
Junior high school and above	1,366 (29%)	406 (25%)	637 (31%)	323 (33%)	
Marital status					<0.001
Married	4,165 (89%)	1,433 (87%)	1,828 (89%)	904 (92%)	
Unmarried	530 (11%)	219 (13%)	230 (11%)	81 (8.2%)	
BMI (kg/m²)	23.4 (21.1–26.0)	21.3 (19.6–23.3)	23.8 (21.7–26.1)	26.1 (23.9–28.6)	<0.001
FPG (mg/dL)	102.4 (94.9–112.1)	99.2 (92.5–107.6)	102.2 (95.4–110.9)	108.9 (100.1–125.3)	<0.001
TG (mg/dL)	104.4 (74.3–152.2)	70.8 (57.5–87.6)	110.6 (89.4–143.4)	203.6 (157.5–283.2)	<0.001
TC(mg/dL)	191.4 (168.2–216.5)	173.6 (153.9–194.5)	195.2 (173.2–219.2)	216.1 (192.9–243.9)	<0.001
HDL (mg/dL)	49.1 (40.6–59.5)	55.7 (47.2–66.5)	48.3 (41.4–58.0)	40.2 (33.2–47.6)	<0.001
LDL (mg/dL)	115.2 (93.9–138.4)	102.8 (86.2–120.6)	122.2 (102.4–145.0)	127.6 (99.4–153.9)	<0.001
CRP(mg/L)	1.0 (0.6–2.1)	0.8 (0.5–1.7)	1.0 (0.6–2.1)	1.4 (0.8–2.6)	<0.001
TCBI 2011	1,159.4 (741.0–1,905.2)	651.0 (519.5–823.9)	1,318.5 (1,016.1–1,686.0)	2,923.0 (2,218.5–4,084.4)	<0.001
log(TCBI 2011)	7.1 (6.6–7.6)	6.5 (6.3–6.7)	7.2 (6.9–7.4)	8.0 (7.7–8.3)	<0.001

Table 1. Baseline characteristics of the study population based on the change in TCBI

Variable	Overall N = 4,695	TCBI trajectory group Cluster1 N = 1,652	Cluster2 N = 2,058	Cluster3 N = 985	*p*-value
TCBI 2015	1,227.6 (781.7–1,986.1)	683.3 (532.5–865.7)	1,382.3 (1,094.1–1,783.1)	3,009.2 (2,300.6–4,218.3)	<0.001
log(TCBI 2015)	7.1 (6.7–7.6)	6.5 (6.3–6.8)	7.2 (7.0–7.5)	8.0 (7.7–8.3)	<0.001
Cumulative TCBI	3,696.2 (2,461.6–5,924.4)	2,134.9 (1,712.6–2,524.4)	4,169.8 (3,491.8–5,132.3)	8,943.0 (7,476.9–12,055.9)	<0.001
SBP (mmHg)	127.3 (114.7–142.0)	122.7 (111.0–138.0)	127.7 (115.7–142.0)	132.7 (120.3–147.0)	<0.001
DBP(mmHg)	75.0 (67.3–83.3)	72.7 (65.0–80.3)	75.0 (67.7–83.3)	78.3 (71.3–87.3)	<0.001
Smoking					<0.001
Yes	1,765 (38%)	708 (43%)	724 (35%)	333 (34%)	
No	2,930 (62%)	944 (57%)	1,334 (65%)	652 (66%)	
Drinking					0.7
No	1,119 (24%)	404 (24%)	481 (23%)	234 (24%)	
Yes	3,576 (76%)	1,248 (76%)	1,577 (77%)	751 (76%)	
Hypertension					<0.001
Yes	1,210 (26%)	277 (17%)	556 (27%)	377 (38%)	
No	3,485 (74%)	1,375 (83%)	1,502 (73%)	608 (62%)	
Dyslipidemia					<0.001
Yes	487 (10%)	83 (5.0%)	199 (9.7%)	205 (21%)	
No	4,208 (90%)	1,569 (95%)	1,859 (90%)	780 (79%)	
Diabetes					<0.001
Yes	274 (5.8%)	64 (3.9%)	112 (5.4%)	98 (9.9%)	
No	4,421 (94%)	1,588 (96%)	1,946 (95%)	887 (90%)	

Table 1. Baseline characteristics of the study population based on the change in TCBI

Variable	TCBI trajectory group				*p*-value
	Overall N = 4,695	**Cluster1 N = 1,652**	**Cluster2 N = 2,058**	**Cluster3 N = 985**	
Heart disease					<0.001
Yes	550 (12%)	161 (9.7%)	228 (11%)	161 (16%)	
No	4,145 (88%)	1,491 (90%)	1,830 (89%)	824 (84%)	
Stroke					0.2
Yes	88 (1.9%)	24 (1.5%)	40 (1.9%)	24 (2.4%)	
No	4,607 (98%)	1,628 (99%)	2,018 (98%)	961 (98%)	
CLD					0.008
Yes	245 (5.2%)	70 (4.2%)	106 (5.2%)	69 (7.0%)	
No	4,450 (95%)	1,582 (96%)	1,952 (95%)	916 (93%)	

Cluster1 represents the stable low-risk group, Cluster2 represents the moderately elevated group, and Cluster3 represents the stable high-risk group.

The raw TCBI values are right-skewed, so log(TCBI) values are shown for ease of comparison.

BMI: body mass index; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; HDL: high density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; CRP: C-reactive protein; TCBI: triglyceride-total cholesterol-body mass index; cuTCBI: cumulative triglyceride-total cholesterol-body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Association Between cuTCBI, TCBI Trajectory, and Risk of Incident Chronic Liver Disease

Three Cox proportional hazards models were constructed to evaluate the association between cuTCBI/TCBI trajectory and the risk of chronic liver disease (Table 2). Across all models, cuTCBI was positively associated with CLD risk. Higher cuTCBI was consistently associated with an increased risk of incident CLD. In the fully adjusted model (Model 3), each 1-standard deviation increase in cuTCBI corresponded to a 12% higher risk (HR = 1.12, 95% CI 1.03–1.22, P = 0.006). Compared with the lowest tertile, the highest tertile was associated with a 51% increased risk (HR = 1.51, 1.09–2.09, P = 0.012; P for trend = 0.006). Results from quartile analysis were similar: the highest quartile showed a 68% higher risk (HR = 1.68, 1.14–2.48, P = 0.008; P for trend = 0.020). Furthermore, the stable high-risk TCBI trajectory group (Cluster 3) had a 46% higher risk of CLD compared with the stable low-risk group (Cluster 1) (HR = 1.46, 1.03–2.07, P = 0.034; P for trend = 0.037). These findings indicate a robust dose-response relationship between cuTCBI and CLD risk.

Table2.Multivariate Cox regression of the relationships between cuTCBI, different clusters of TCBI and the risk of Chronic Liver Disease.

Characteristic	**Model 1 HR (95%CI)**	***p***	**Model 2 HR (95%CI)**	***p***	**Model 3 HR (95%CI)**	***p***
cuTCBI (per 1-SD increase)	1.13 (1.06–1.21)	<0.001	1.13 (1.05–1.22)	<0.001	1.12 (1.03–1.22)	0.006
cuTCBI tertile						
T1	Reference	—	Reference	—	Reference	—
T2	1.12 (0.81–1.57)	0.491	1.12 (0.80–1.56)	0.522	1.08 (0.77–1.51)	0.659

Characteristic	Model 1 HR (95%CI)	*p*	Model 2 HR (95%CI)	*p*	Model 3 HR (95%CI)	*p*
T3	1.67 (1.23–2.27)	<0.001	1.63 (1.19–2.23)	0.002	1.51 (1.09–2.09)	0.012
P for trend		<0.001		<0.001		0.006
cuTCBI quartiles						
Q1	Reference	—	Reference	—	Reference	—
Q2	1.40 (0.95-2.07)	0.091	1.41 (0.95-2.09)	0.085	1.41 (0.95-2.09)	0.085
Q3	1.48 (1.01-2.19)	0.046	1.48 (1.00-2.18)	0.051	1.41 (0.95-2.10)	0.085
Q4	1.87 (1.29-2.71)	<0.001	1.82 (1.25-2.66)	0.002	1.68 (1.14-2.48)	0.008
P for trend		<0.001		0.002		0.020
Change in the TCBI						
Cluster 1 (Low-stable)	Reference	—	Reference	—	Reference	—
Cluster 2 (Moderate-stable)	1.22 (0.90,1.65)	0.2	1.20 (0.89,1.63)	0.2	1.15 (0.85,1.56)	0.4
Cluster 3 (High-stable)	1.68 (1.21,2.34)	0.002	1.60 (1.14,2.25)	0.006	1.46 (1.03,2.07)	0.034
P for trend		0.003		0.007		0.037

Model 1: No variable adjustment; Model 2: Adjusted for Age , Gender, Residence, Education , Marital status; Model 3: Fully adjusted for variables, including Age , Gender,Residence,Education,Marital-status,BMI,Hypertension,Dyslipidemia,Diabetes, Smoking and Drinking.

Restricted Cubic Spline (RCS) Analysis

To investigate the association between cumulative TCBI (cuTCBI) and the risk of chronic liver disease, a restricted cubic spline (RCS) model with three knots was employed based on Model 3. The analysis revealed a significant overall association between cuTCBI and CLD risk ($P < 0.0001$). The test for non-linearity was not significant ($P = 0.1856$), indicating a predominantly linear dose-response relationship with no evidence of a threshold effect (Figure 3).

Figure 3.

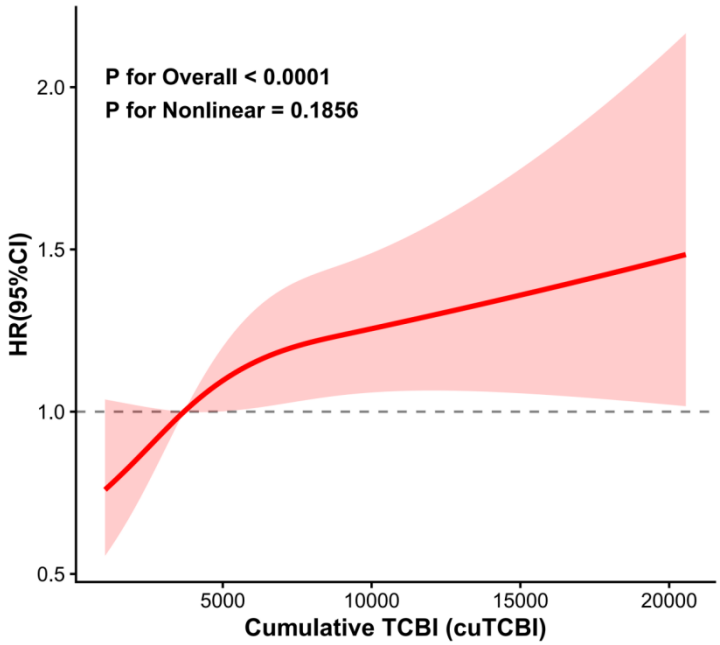


Figure 3.RCS curve between cuTCBI and the incidence of chronic liver disease. HR: hazard ratio; CI: confidence interval; cuTCBI, cumulative triglyceride-total cholesterol-body mass index.

Kaplan–Meier Survival Curve Analysis

Kaplan–Meier analysis (Figure 4) revealed a significant positive association between elevated cuTCBI levels and an increased risk of incident CLD (all log-rank tests $P < 0.05$). Specifically, participants with cuTCBI levels above the median had a significantly higher cumulative incidence of CLD compared with those below the

median (Figure A). Moreover, a clear dose-response relationship was observed across cuTCBI tertiles (Figure B), trajectory clusters (Figure C), and quartiles (Figure D), with individuals in the highest exposure group consistently exhibiting the greatest cumulative incidence burden of CLD.

Figure 4.

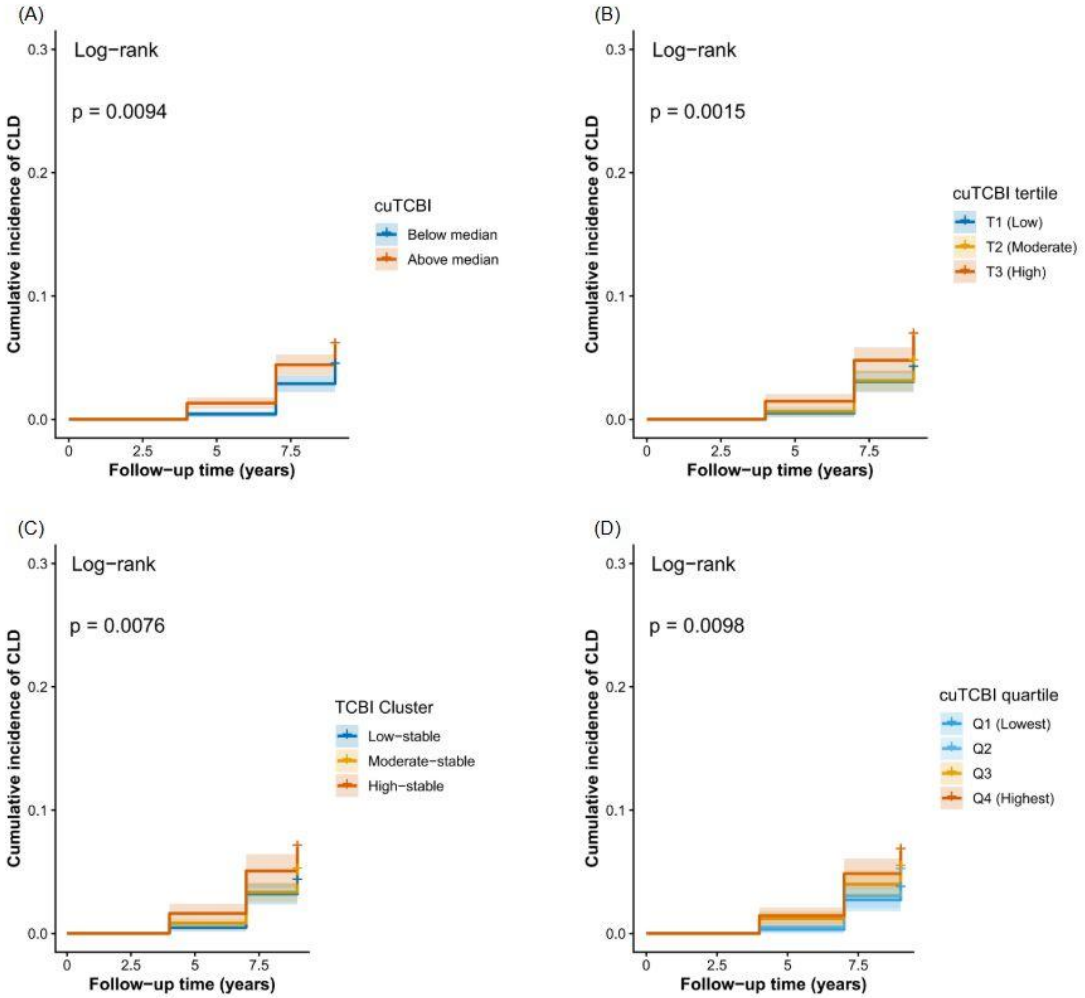


Figure 4. Kaplan-Meier plots of chronic liver disease incidence according to cuTCBI grouping by median (A), tertiles (B), three clusters (C), and quartiles (D).

ROC Curve Analysis

Receiver operating characteristic (ROC) curves were plotted (Figure 5) to evaluate the predictive performance of multiple indicators for incident CLD. The results showed

that cuTCBI outperformed baseline TCBI and its individual components in predicting both 7-year chronic liver disease risk (AUC = 0.589) and 9-year chronic liver disease risk (AUC = 0.594).

Figure 5.

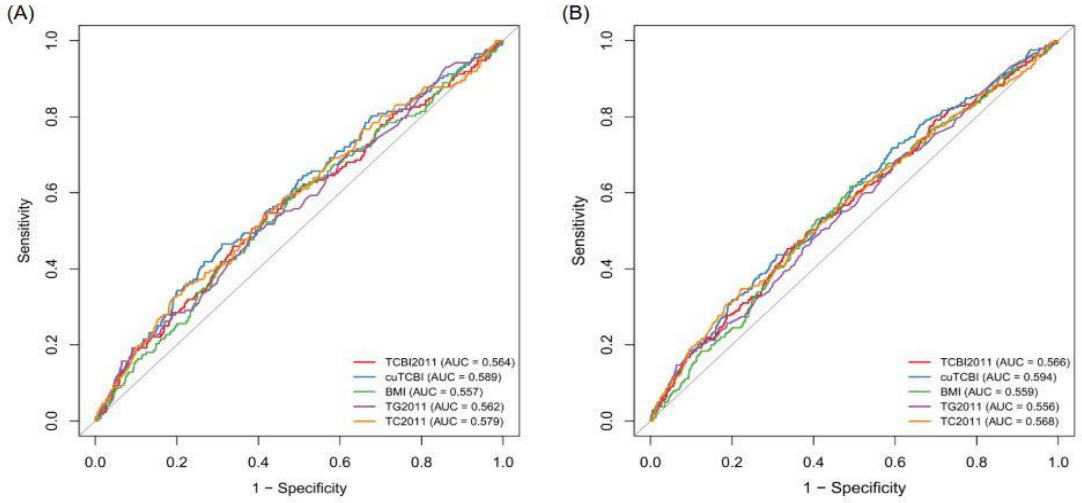


Figure 5. Receiver operating characteristic curves of cuTCBI, TCBI, BMI, TG2011, TC2011 for predicting 7 (A) and 9 (B) years of chronic liver disease.

Subgroup Analysis and Interaction Tests

To evaluate the reliability and stability of the association between cuTCBI and chronic liver disease risk in the fully adjusted Model 3, subgroup analyses and interaction tests were performed. Stratification factors included age, sex, residence location, education level, BMI, alcohol consumption, smoking, diabetes, dyslipidemia, and hypertension. As shown in Figure 6, cuTCBI was associated with an increased risk of chronic liver disease in most subgroups, and no significant interactions were detected across the selected subgroups (all P for interaction > 0.05). These findings underscore the generalizability and robustness of cuTCBI as an independent prognostic marker for chronic liver disease.

Figure 6.

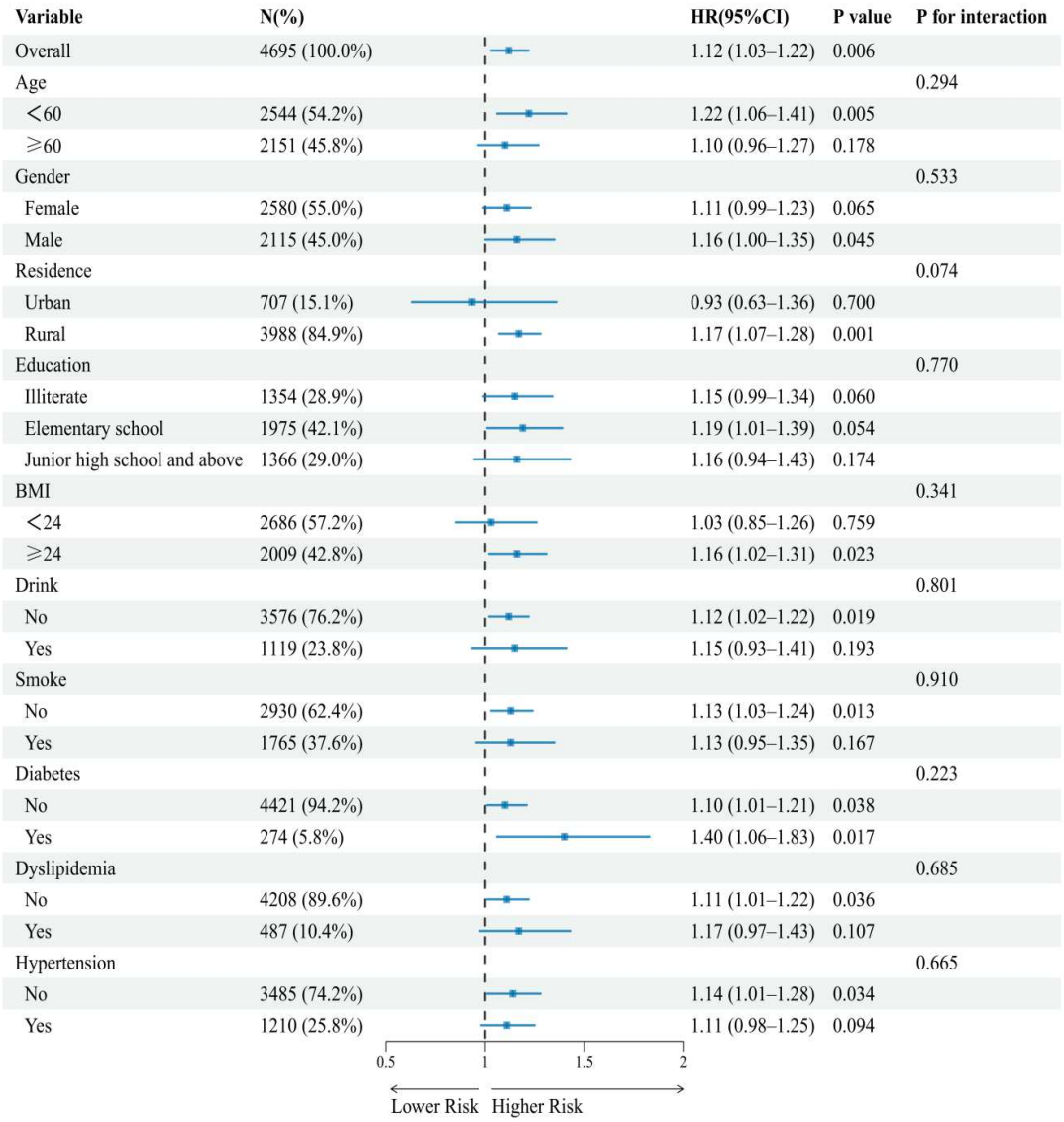


Figure 6. Subgroup and interaction analysis of the association between cuTCBI and chronic liver disease risk. Adjusted for age, sex, residence, education level, marital status, BMI, heart disease, stroke, smoking, and drinking.

Sensitivity Analysis

Multiple sensitivity analyses were conducted to validate the robustness of the results. First, multivariable logistic regression analysis was performed using the same covariates as in the Cox models (Supplementary Table 1). Second, to compare

cumulative versus single-time-point exposure, we re-analyzed the associations using baseline TCBI and TCBI2015 as independent exposure variables (Supplementary Table 2). Third, to ensure that the results were not driven by extreme values, a trimming analysis was performed (Supplementary Table 3), excluding the top and bottom 1% of cuTCBI. Fourth, a complete case analysis (Supplementary Table 4) was performed, excluding participants with any missing covariate data to assess the impact of missing data. Fifth, a lag analysis (Supplementary Table 5) was performed, excluding participants who developed CLD within two years after 2015 to reduce reverse causation. Sixth, to strengthen causal inference and reduce residual confounding, propensity score matching (PSM) at a 1:1 ratio and inverse probability of treatment weighting (IPTW) were used to re-evaluate the association between cuTCBI and CLD, simulating the balance of a randomized controlled trial (Supplementary Table 6; Supplementary Figures 1 and 2). Seventh, the proportional hazards assumption was tested (Supplementary Table 7; Supplementary Figure 3). The smoothed curves of scaled Schoenfeld residuals for all covariates were approximately horizontal and fluctuated around zero, indicating no substantial violation of the proportional hazards assumption. Eighth, restricted cubic spline (RCS) analyses were repeated using four and five knots (Supplementary Figure 4). Ninth, a competing risk analysis was performed. After accounting for non-CLD death and loss to follow-up as competing events using the Fine-Gray model, the association between cuTCBI and CLD risk remained significant (HR = 1.12, 95% CI 1.05–1.21, $P < 0.001$). Cumulative incidence function (CIF) curves are presented in Supplementary

Figure 5. All sensitivity analysis results were consistent with the primary findings, confirming the robustness and reliability of the conclusions.

Discussion

Using data from a nationally representative prospective cohort (CHARLS), this study provides the first comprehensive investigation of the association between cuTCBI and its dynamic trajectory and incident chronic liver disease (CLD). We found that long-term cumulative elevation of TCBI levels and the stable high-risk trajectory pattern were independently associated with an increased risk of CLD in the middle-aged and older population, demonstrating a clear linear dose-response relationship. This association remained robust across multiple sensitivity analyses, and subgroup analyses indicated its generalizability across different populations.

From a pathophysiological perspective, the association between TCBI and CLD risk can be attributed to a vicious cycle involving lipotoxicity, inflammatory activation, and insulin resistance. First, triglycerides (TG) are the primary form of lipid accumulation in the liver [28]. Chronic hypertriglyceridemia implies that hepatic uptake and esterification of free fatty acids exceed their oxidation and export capacity, leading to TG storage as lipid droplets within hepatocytes. Excessive lipid droplet accumulation induces endoplasmic reticulum stress and mitochondrial dysfunction, releasing pro-apoptotic signals (e.g., CHOP, JNK) and directly causing hepatocellular injury [29,30]. Second, total cholesterol (TC), particularly free cholesterol, activates the NLRP3 inflammasome, promoting the maturation and secretion of IL-1β and IL-18, recruiting macrophages and stellate cells, and initiating hepatic inflammation and

fibrogenesis [16,31]. Third, body weight index (BMI) is a simple surrogate for overall and visceral adiposity. In obesity, adipose tissue secretes abundant free fatty acids and pro-inflammatory cytokines (TNF-α, IL-6, leptin) and suppresses adiponectin secretion, further exacerbating insulin resistance [32]. Insulin resistance, in turn, promotes lipolysis and de novo lipogenesis in the liver [33], creating a positive feedback loop. By integrating these three components multiplicatively, TCBI theoretically amplifies their synergistic effects – an elevation in any component is magnified by the others, thereby more sensitively capturing liver risk under the "multiple hits" model.

Beyond the primary findings, the predictive performance of cuTCBI for incident CLD, as measured by the area under the curve (AUC), was modest. Frankly, this discriminatory ability is far from sufficient for cuTCBI to serve as an independent screening or diagnostic tool for CLD. Nevertheless, at an etiological level, it reveals the cumulative effect of long-term metabolic burden on CLD risk, and its performance might improve when combined with other clinical and biomarker data. In clinical practice, even modest improvements in predictive performance can be meaningful, particularly in the complex context of multifactorial diseases [34]. In resource-limited settings, cuTCBI, as a low-cost and easily accessible marker, may help identify high-risk individuals and guide early intervention and clinical management.

This study has several notable strengths. First, it is the first to introduce the concept of "cumulative exposure" into the research framework linking TCBI and CLD. Second,

it is the first to employ k-means clustering to identify longitudinal dynamic trajectories of TCBI, revealing distinct associations between temporal evolution patterns of metabolic burden and CLD risk, thereby capturing long-term metabolic burden and its dynamic changes. Third, the study leveraged data from a nationally representative prospective cohort (CHARLS) with long-term follow-up, enhancing the generalizability of the findings to the middle-aged and older population. Fourth, methodological rigor substantially strengthened the credibility of the conclusions. We implemented nine sensitivity analyses, including multivariable logistic regression, comparison with single-time-point exposures, extreme value trimming, complete case analysis, lag analysis, propensity score matching (PSM), inverse probability of treatment weighting (IPTW), proportional hazards assumption testing, restricted cubic spline (RCS) with varying knot numbers, and competing risk models (Fine-Gray). All results were highly consistent with the primary analysis.

Nevertheless, several limitations should be acknowledged. First, the diagnosis of chronic liver disease was primarily based on self-reported physician diagnosis, which may be subject to recall bias or under-reporting. Second, although we adjusted for a wide range of demographic, lifestyle, and clinical covariates, residual confounding due to unmeasured factors, such as dietary habits or environmental exposures, cannot be completely excluded. Third, the calculation of cuTCBI relied on only two time points (2011 and 2015), which may not fully capture the complexity of long-term exposure trajectories. Fourth, this study was restricted to the middle-aged and older Chinese population, limiting the external generalizability of the findings. Future

studies should validate the results in other populations. Finally, as with all observational studies, our findings demonstrate association, not causation.

Conclusion

Collectively, our findings demonstrate a significant association between cumulative TCBI exposure and its dynamic changes and the risk of chronic liver disease. Specifically, individuals with elevated cuTCBI levels and those with a persistently high TCBI trajectory exhibited a substantially higher risk of CLD. Owing to its low cost and easy accessibility, cuTCBI may effectively identify middle-aged and older adults at high risk of CLD, providing a window for timely individualized intervention to prevent CLD events. Although these results provide preliminary insights, further studies in other cohorts are warranted to validate and extend our findings.

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