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The mediating role of the TyG index in the relationship between circadian syndrome and cancer among middle-aged and elderly Chinese

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Abstract

Background Circadian Syndrome (CircS) is a significant marker of metabolic imbalance and has been linked to various chronic diseases. However, its relationship with cancer risk remains underexplored. This research aims to explore the relationship between CircS and cancer, while also assessing the possible mediating role of the triglyceride glucose (TyG) index.

Methods Baseline data from the 2011 China Health and Retirement Longitudinal Study (CHARLS) and follow-up data from 2015 were analyzed, including participants' sociodemographic characteristics, health behaviors, and metabolic indicators. Linear regression, mediation analysis, and logistic regression were employed to explore relationships between CircS, cancer risk, and the TyG index, with a dose-response analysis conducted on TyG index and cancer risk.

Results Among 7,864 middle-aged and elderly participants, CircS was significantly and positively associated with cancer risk ($r=0.17$, $P<0.001$). The TyG index showed a significant correlation with both CircS ($r=0.52$, $P<0.001$) and cancer ($r=0.15$, $P<0.001$). Mediation modeling indicated that the TyG index partially mediated the association between CircS and cancer, accounting for 23% of this relationship. Additionally, a significant nonlinear dose-response relationship was observed between the TyG index and cancer risk ($P_{nonlinear} = 0.0024$).

Conclusion Circadian syndrome is associated with increased cancer risk, with the TyG index partially mediating this relationship.

Keywords Circadian syndrome, Cancer, TyG index, Risk, Mediation analyses

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Introduction

The circadian system is one of the key mechanisms regulating human health and metabolism [1]. It maintains homeostasis in the body by precisely coordinating important physiological functions such as gene expression, hormone secretion, thermoregulation, behavioral activity patterns and energy expenditure [2, 3]. Thus, disruption of circadian rhythms can have profound effects on a wide range of metabolic processes. With the increased understanding of individual biological rhythms, abnormal sleep patterns and depressive symptoms have also been found to be highly correlated with circadian disorders [4]. The concept of Circs has gradually taken shape, which is based on the interactions of Metabolic Syndrome (MetS) with short sleep duration and depressive symptoms, emphasizing that disruptions of biological rhythms can lead to a profound effect on body homeostasis [5]. Disorders of circadian rhythms can lead to imbalances in homeostasis, which in turn can lead to a variety of physiological dysfunctions. Dysregulation of circadian rhythms is not only an important driver of chronic diseases such as obesity [6], diabetes [7], and heart disease [8, 9], but also has a complex relationship with cancer [10–12]. Long-term evidence from epidemiologic studies and laboratory experiments have shown that disruption of the biological clock is significantly associated with the development of cancer [13].

Systemic and tissue-specific disruption of circadian rhythms leads to abnormal cellular functions, such as altered cell division and metabolism, both of which are closely associated with cancer development and progression [14, 15]. Evidence from studies in different cell types and in vivo models suggests that the core circadian genes play a key role in tumorigenesis and progression [16–18]. On the other hand, metabolic dysfunction triggered by circadian dysregulation may play a driving role in carcinogenesis and tumor progression. Several metabolic pathways that are closely related to the metabolic survival of cancer cells show oscillatory properties of circadian rhythms [19, 20]. It is hypothesized that disruption of circadian rhythms may enhance the viability of cancer cells by enhancing the efficiency of their utilization of available energy sources and by facilitating lipogenesis [21]. The Circs is the result of metabolic disturbances in the body, this results in the buildup of body fat and disrupts the regulation of glucose and insulin, subsequently affecting hormonal balance and ultimately heightening cancer risk [22, 23]. Currently, the TyG index is regarded as a more practical and dependable indicator of insulin resistance (IR), additionally, the triglyceride glucose index-waist circumference (TyG-WC) demonstrates significant predictive value in assessing cardiovascular risk and respiratory diseases [24], and is also strongly correlated with morbidity and mortality in a variety of cancers including colorectal cancer [25], breast cancer [26], and gastric cancer [27]. The use of this index not only helps to identify metabolic abnormalities at an early stage, but also provides an important reference for cancer prevention and intervention.

Given the association between the TyG index, MetS, and cancer, recent reports have revealed a connection between Circs and MetS. Nonetheless, it is still uncertain if the TyG index is a significant factor in the connection between Circs and cancer. In addition, to our knowledge, no research has investigated the mediating effect of the TyG index on the relationship between CircS and cancer risk. Therefore, the first aim was to explore the connection between Circs and cancer. The secondary aim was to evaluate the possible mediating effect of the TyG index in the relationship between Circs and cancer, and to provide a comprehensive assessment of TyG index to provide new insights for stratified management of cancer risk.

Method

Data resources

In this prospective cohort investigation, we examined the initial data from the 2011 CHARLS database (http://charls.pku.edu.cn/) along with cancer follow-up information collected in 2015. This interdisciplinary survey utilized nationally representative and high-quality data, conducting a survey of people aged 45 and above from 450 villages and communities throughout 28 provinces, including autonomous regions and municipalities. Participants were selected through multistage stratified probability-proportional sampling and underwent one-on-one interviews using structured questionnaires that gathered comprehensive information on demographics, household composition, physical health status, healthcare access and insurance coverage, employment and pension details, income and expenses, housing conditions, laboratory tests, among other relevant data. Follow-ups for all participants occurred biennially after the baseline assessment, details regarding the study design, inclusion criteria, and specific aspects of the questionnaire have been previously reported [28]. The baseline sample included 17,705 participants. During the follow-up period, data exclusions were made due to missing information caused by incomplete follow-up or delayed laboratory tests. Specifically, participants were excluded for the following reasons: age ≤ 45 years ($n = 370$); missing sociodemographic data, including gender, educational attainment, marital status, and residential location ($n = 4,156$); absence of blood test parameters ($n = 6,071$); missing Circs diagnostic information ($n = 3,357$); and lack of cancer history data ($n = 3,176$). Ultimately, a total of 7,864 eligible participants were included (Figure S1).

Definition of cancer

All participants were posed the question, "Have you ever received a diagnosis of cancer or a malignant tumor (excluding minor skin cancers) from a physician?" and/or self-reported with the query, "Have you ever been diagnosed with cancer or a malignant tumor?" Those who answered yes to either question were classified as cancer patients. Additionally, individuals who died during the survey and had cancer listed as their cause of death were also classified as having cancer.

Diagnostic criteria for circs

Circs were defined by several criteria, including abdominal obesity (waist ≥ 85 cm for men, ≥ 80 cm for women), hypertension (sbp ≥ 130 mmHg and/or dbp ≥ 85 mmHg), hyperglycemia (glucose ≥ 100 mg/dl), triglycerides (≥ 150 mg/dl), low HDL-C (< 40 mg/dl), depression (CESD score ≥ 10), and insufficient sleep duration (< 6 h per day) [29]. Participants were diagnosed with Circs if they met four or more criteria.

TyG index

Blood specimens were collected by a health care professional in the fasting state, blood samples were stored at -80 °C and measured in a central laboratory using an enzyme colorimetric assay. TyG index = Ln (Glucose mg/dL] x TG [mg/dL]/2).

Covariate assessment

In the baseline survey, covariates for sociodemographic characteristics included sex, age, highest level of education (primary, high school, and college), marital (unmarried or married), and living residence (city or village). Health-related behavior variables, including smoking status (no, yes), alcohol use (no, yes), the count of chronic diseases (0, 1, ≥ 2), and body mass index (BMI), were gathered via self-report questionnaires. The number of chronic conditions was evaluated based on 14 self-reported non-communicable diseases, such as hypertension, hyperlipidemia, diabetes, chronic lung disease, liver disease, heart disease, stroke, kidney disease, asthma, mental health issues, digestive disorders, memory problems, and arthritis. BMI was calculated using standardized questions regarding height and weight.

Statistical analysis

We employed means and standard deviations for continuous variables, while percentages were used for categorical data to characterize baseline variables, and for variables that were not normally distributed, we applied medians along with interquartile ranges (IQR) to represent the overall sample. Spearman's correlation analysis was performed to evaluate the associations between the primary variables. To avoid the influence of multicollinearity, all variables were evaluated using the Variance Inflation Factor (VIF) diagnostic. Variables with VIF > 5 were considered unsuitable for inclusion in the Cox regression model. Using linear regression analysis, we separately explored the associations between Circs and cancer as well as Circs and the TyG index. Through a mediation model, we further analyzed the mediating role of the TyG index in the relationship between Circs and cancer. Subsequently, we included the TyG index as a mediator in exploring its relationship with Circs and cancer [30]. The mediation model proposed by Baron and Kenny was applied to examine the mediating effect of the TyG index on the association between CircS and cancer risk: (1) a significant direct relationship was observed between CircS and cancer risk; (2) CircS was significantly associated with the TyG index; (3) after including the TyG index in the model, the association between CircS and cancer risk remained significant. A total of 1,000 resamplings were executed using a nonparametric bootstrap method to evaluate total, indirect, and direct effects, the significance was evaluated using bias-corrected confidence intervals (BC-CI) [31]. We applied three logistic regression models to determine how TyG—considered both continuously (per IQR) or categorically (by quartiles)—is associated with cancer outcomes; results were reported as OR along with 95% CIs. Additionally, restricted cubic splines were used to examine potential nonlinear relationships while visualizing the dose-response association of the TyG index with cancer risk. A multivariable restricted cubic spline model was used to examine the association between the TyG index and cancer incidence, with four selected knots at the 5th, 35th, 65th, and 95th percentiles. To explore potential effect modification, interaction terms (TyG × covariates) were introduced. To assess the robustness of the findings, a sensitivity analysis was conducted by grouping participants based on the TyG index median. This analysis verified the consistency of the direction and significance of the results. All statistical analyses were conducted with R software (version 4.4.1), considering a two-tailed P-value < 0.05 as statistically significant.

Result

Baseline characteristics of the population

Table 1 presents the baseline characteristics of the study sample. A total of 7864 participants were included (males = 3691 (46.9%), females = 4173 (53.1%)), of which 275 (3.5%) of the participants were with cancer at the time of participation. A total of 2476 (31.5%) of all participants had Circs, of which 203 also had cancer. Demographic characterization of the participants found that cancer patients had more women compared to non-cancer patients and had a greater prevalence of smoking, alcohol consumption, BMI, number of chronic diseases,

Table 1 Baseline characteristics of the study population by cancer status at follow-up

	Total (n = 7864)	Non_CA (n = 7589)	CA (n = 275)	*P*
Age	59.0 (9.0)	59.0 (9.0)	59.3 (9.7)	0.607
Gender				
Female	4173 (53.1)	3997 (52.7)	176 (64.0)	< 0.001
Male	3691 (46.9)	3592 (47.3)	99 (36.0)	
Education				
College	96 (1.2)	95 (1.3)	1 (0.4)	0.185
High shcool	676 (8.6)	658 (8.7)	18 (6.5)	
Primary	7092 (90.2)	6836 (90.1)	256 (93.1)	
Marital				
Married	6664 (84.7)	6429 (84.7)	235 (85.5)	0.803
Unmarried	1200 (15.3)	1160 (15.3)	40 (14.5)	
Location				
City	546 (6.9)	523 (6.9)	23 (8.4)	0.411
Village	7317 (93.1)	7065 (93.1)	252 (91.6)	
Smoking				
No	4783 (60.8)	4589 (60.5)	194 (70.5)	0.001
Yes	3080 (39.2)	2999 (39.5)	81 (29.5)	
Drinking				
No	5264 (66.9)	5058 (66.6)	206 (74.9)	0.005
Yes	2600 (33.1)	2531 (33.4)	69 (25.1)	
BMI	23.6 (3.9)	23.6 (3.9)	24.5 (4.3)	< 0.001
Chronic Disease				
>=2	3035 (38.6)	2897 (38.2)	138 (50.2)	< 0.001
1	2371 (30.2)	2295 (30.2)	76 (27.6)	
0	2458 (31.3)	2397 (31.6)	61 (22.2)	
Comprehensive components of Crics				
Sbp	130.1 (21.2)	130.0 (21.2)	130.3 (20.4)	0.835
Dbp	75.7 (12.0)	75.8 (12.1)	73.5 (10.7)	0.002
Sleep Time	6.3 (1.9)	6.4 (1.9)	5.9 (1.9)	< 0.001
Waist	84.3 (12.6)	84.2 (12.6)	87.9 (12.1)	< 0.001
Glucose	109.8 (35.1)	109.1 (33.8)	129.4 (58.2)	< 0.001
TG	134.0 (110.4)	131.1 (104.6)	214.8 (201.2)	< 0.001
HDL	51.2 (15.3)	51.5 (15.3)	45.1 (16.2)	< 0.001
Depression				
No	4892 (62.2)	4754 (62.6)	138 (50.2)	< 0.001
Yes	2972 (37.8)	2835 (37.4)	137 (49.8)	
Circs				
No	5388 (68.5)	5316 (70.0)	72 (26.2)	< 0.001
Yes	2476 (31.5)	2273 (30.0)	203 (73.8)	
TyG	8.7 (0.7)	8.7 (0.7)	9.2 (0.9)	< 0.001
Quartiles of TyG				
Q1	1966 (25.0)	1930 (25.4)	36 (13.1)	< 0.001
Q2	1966 (25.0)	1924 (25.4)	42 (15.3)	
Q3	1966 (25.0)	1920 (25.3)	46 (16.7)	
Q4	1966 (25.0)	1815 (23.9)	151 (54.9)	

CA: cancer, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, Circs: Circadian Syndrome, TG: triglyceride, HDL: high-density lipoprotein, TyG: triglyceride glucose

Table 2 Correlations among Circs, TyG index and cancer

Variables	Circs	TyG	Cancer
Circs	1.00		
TyG	0.52***	1.00	
Cancer	0.17***	0.15***	1.00

*** *P*-value < 0.001

waist circumference, blood glucose, TG, depression, and prevalence of Circs, and less HDL and sleep duration. The mean baseline TyG for all participants was 8.7 (SD = 0.7).

Associations of key variables

After mediation analysis of the associations between Circs, cancer, and TyG index, we found that the prevalence of Circs at baseline was positively associated with the prevalence of cancer at follow-up ($r = 0.17$, $P < 0.001$). The TyG index was positively associated with Circs at baseline ($r = 0.52$, $P < 0.001$) as well as positively associated with cancer ($r = 0.15$, $P < 0.001$). Table 2 demonstrates the correlation between the three.

Mediating role of the TyG index

After adjusting for all covariates, we found that Circs was significantly associated with cancer ($\beta = 9.732$, $P < 0.001$, Table S1). As shown in Table 3, Model 1 indicated that Circs was significantly associated with TyG ($\beta = 46.762$, $P < 0.001$). After using TyG index as a mediator in Model 2, the association between Circs and cancer remained significant ($\beta = 0.12$, $P < 0.001$). This suggests that the TyG index partially mediated the association between Circs and cancer. Bootstrap analyses additionally indicated that the overall effect of Circs on cancer was 0.067 ($P < 0.001$). The mediating effect of the TyG index was 0.016 ($P < 0.001$). Bootstrap analysis revealed that the total effect of CircS on cancer was 0.067 (95% BC-CI [0.057–0.08], $P < 0.001$), with the mediating effect of the TyG index estimated at 0.016 (95% BC-CI [0.009–0.02], $P < 0.001$). The percentage of bootstrapped samples containing zero was 0, indicating that the mediation effect was significant. The TyG index served as a significant mediator in the relationship between CircS and cancer, accounting for 23% of the total effect (Fig. 1).

Dose-response relationship between TyG index and cancer

Table 4 illustrates the relationship between the TyG index and cancer risk, along with its inter-quartile distribution. The likelihood of developing cancer rose steadily with higher quartiles of the TyG index ($P_{Trend} < 0.001$). Following adjustments for age, sex, education, marital, location, smoking habits, alcohol consumption, BMI, chronic diseases, sbp, dbp, sleep duration, waist, glucose, TG, HDL, and depression status compared to the first quartile of the TyG index (Q1), those in the highest quartile

Table 3 Circs and TyG indices in relation to cancer risk

	Model 1				Model 2			
	B	SE	β	*P*	B	SE	β	*P*
Circs	0.695	0.0149	46.762	***	0.0527	0.0052	9.906	***
TyG					0.0224	0.0036	6.277	***
Age	-0.0016	0.0008	-2.124	*	-0.0002	0.0002	-0.639	0.523
Gender(Ref = Female)	-0.0554	0.0189	-2.939	**	-0.0019	0.006	-0.318	0.75
Education(Ref = colleage)								
High shcool	0.0789	0.0625	1.263	0.2067	0.0163	0.0198	0.826	0.409
Primary	0.0374	0.0594	0.629	0.5296	0.0226	0.0188	1.203	0.229
Marital(Ref = Married)	-0.0735	0.0184	-3.996	***	-0.0055	0.0058	-0.949	0.343
Location(Ref = City)	-0.0561	0.026	-2.162	*	-0.0064	0.0082	-0.786	0.432
Smoking(Ref = No)	0.0459	0.0184	2.493	*	-0.0074	0.0058	-1.277	0.201
Drinking(Ref = No)	0.0123	0.016	0.784	0.4328	-0.0031	0.0049	-0.616	0.538
BMI	0.0221	0.0018	12.333	***	-0.0012	0.0006	-2.086	*
Chronic Disease(Ref=>=2)								
0	-0.0196	0.0159	-1.23	0.2187	-0.0068	0.005	-1.357	0.175
1	0.0063	0.0158	0.401	0.6882	-0.0059	0.0049	-1.184	0.237

Model 1: without mediator; Model 2: with mediator. Note: *** *P*-value < 0.001, * *P*-value < 0.05, Ref: reference

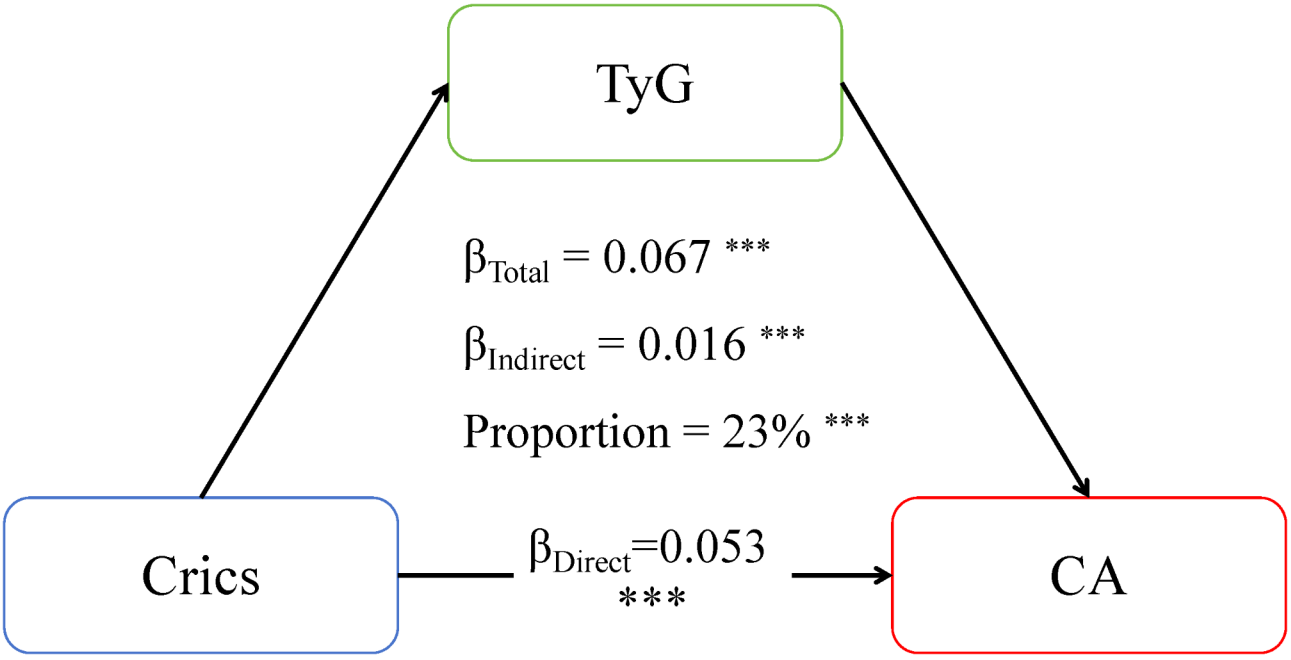

Fig. 1 Path diagram of the mediated relationship between Circs and cancer risk

Table 4 Association of TyG index with the risk of cancer

	Model 1	*P*	Model 2	*P*	Model 3	*P*
TyG_per_IQR	1.034(1.029–1.039)	< 0.001	1.033(1.028–1.038)	< 0.001	1.0003(1.0001–1.0004)	< 0.001
Quartiles of TyG						
Q1	Ref		Ref		Ref	
Q2	1.003(0.992–1.015)	0.599	1.002(0.991–1.013)	0.79	0.9941(0.9826–1.0056)	0.308
Q3	1.005(0.994–1.017)	0.381	1.002(0.990–1.014)	0.738	0.9864(0.9743–0.9987)	0.241
Q4	1.060(1.048–1.072)	< 0.001	1.056(1.043–1.068)	< 0.001	1.0126(1.0037–1.0216)	0.006
P for trend		< 0.001		< 0.001		< 0.01

Model 1 was crude model. Model 2 was adjusted for age, gender, education, marital, location, smoking, drinking, BMI and chronic disease. Model 3 was adjusted for age, gender, education, marital, location, smoking, drinking, BMI, chronic disease, sbp, dbp, sleep time, waist, glucose, TG, HDL and depression. Note: IQR: interquartile range

(Q4) showed an increased risk of cancer development (OR = 1.0126; 95% CI = 1.0037–1.0216). The TyG index remained significantly linked to cancer risk ($P < 0.001$) when considered as a continuous variable. After adjusting for confounding factors, the restricted cubic spline analysis demonstrated a significant non-linear dose-response relationship between the TyG index and cancer risk (P non-linear = 0.0024Fig. . 2). This indicates that an increase in the TyG index is associated with a non-linear upward trend in cancer risk.

Subgroup analysis and sensitivity analysis

We performed subgroup analyses based the participant's age, gender, education, location, marital, smoking, alcohol consumption, number of chronic diseases, and presence of Circs, to further explore whether the TyG index had a different effect on the risk of cancer in different subgroups. The impact of the TyG index on cancer risk remained consistent across subgroups, and interaction analyses revealed significant interactions between the TyG index and factors such as sex, marital status, smoking, and CircS status ($P < 0.05$, Fig. 3). Furthermore, sensitivity analysis, conducted after regrouping based on the median TyG index, demonstrated that the relationship between the TyG index and cancer risk remained stable (HR: 1.007, 95% CI: 1.002–1.013, $P < 0.001$, Table S2).

Discussion

This study investigate the mediating effect of Circs on the association between cancer prevalence risk and the TyG index within a Chinese cohort of middle-aged and elderly individuals, utilizing baseline data from CHALS. Furthermore, the study sought to investigate how different levels of the TyG index correlate with cancer risk in a dose-response manner. Our results indicated that participants diagnosed with Circs had a higher prevalence of cancer, which was significantly linked to cancer risk according to follow-up data, aligning with our hypotheses. The results of the bootstrap method further supported that the TyG index partially mediated the relationship between CircS and cancer risk. The analysis revealed a positive correlation between TyG index levels and the risk of cancer; after controlling for confounding variables, there was a significant increase in cancer risk linked to higher IQRs of the TyG index (OR = 1.0003; 95% CI [1.0001–1.0004]; $P < 0.001$). Moreover, dose-response curves demonstrated a nonlinear association between TyG index levels and new cancer risks, indicating an increase in incidence as the TyG index rose. Interaction analysis indicated that CircS status may moderate the relationship between the TyG index and cancer risk. This finding highlights the need for subgroup-specific risk assessments in clinical practice.

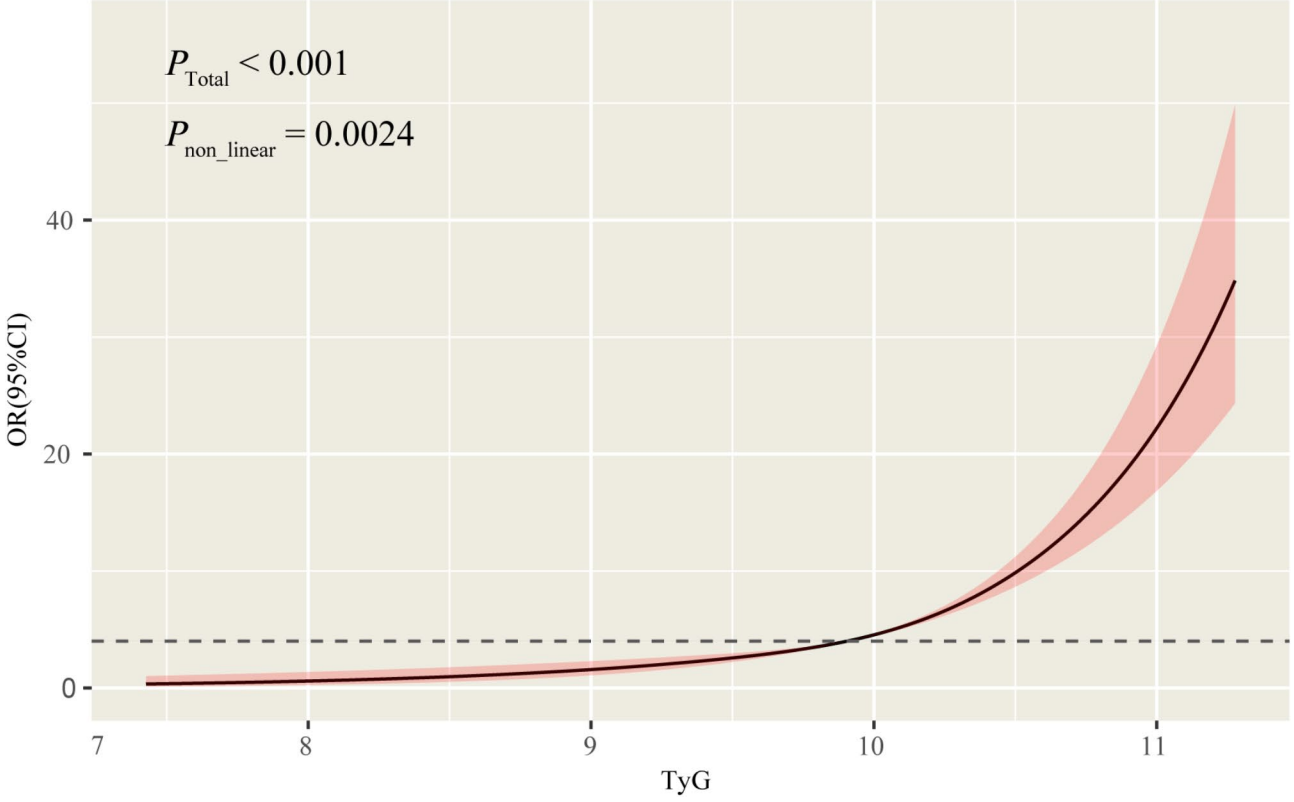

Fig. 2 Restricted cubic spline analysis of the association between TyG index and cancer risk. The model adjusted for age, gender, education, marital, location, smoking, drinking, BMI, number of chronic diseases, sbp, dbp, sleep time, waist, glucose, TG, HDL and depression

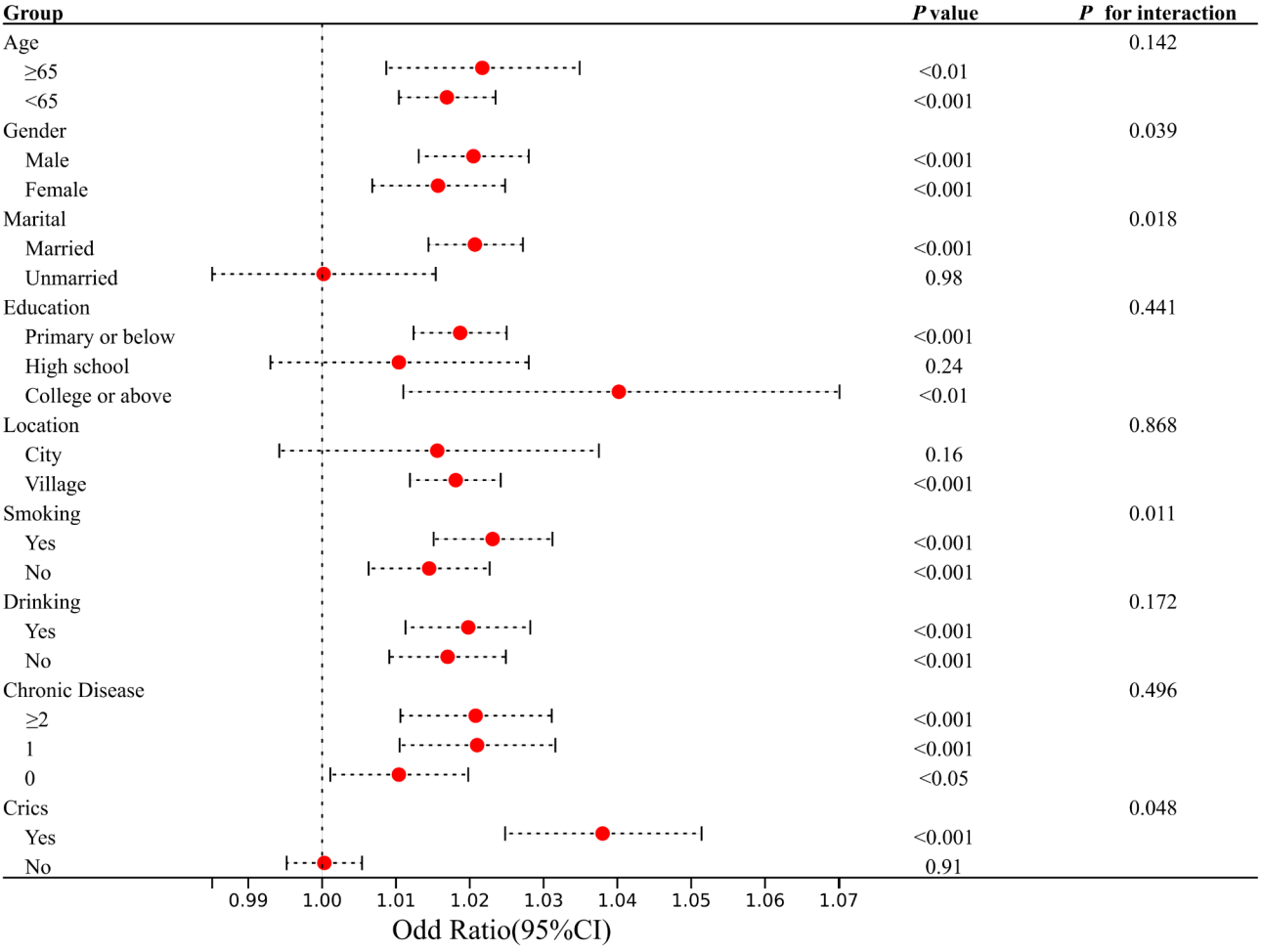

Fig. 3 Forest plot for subgroup analysis and interaction test of TyG index with increased cancer risk

Currently, Circs has been shown to be an important predictor of cardiovascular disease [8] and is considered a better alternative predictor of MetS in the Chinese population [29], however, the relationship between Circs and cancer risk has not been clarified. In this study, we found that patients with Circs in the middle-aged and elderly population in China have a corresponding increased risk of cancer. We hypothesize that this may be related to the fact that Circs causes metabolic dysfunction in the body, which in turn leads to cancer. It is well known that the circadian system is one of the core mechanisms regulating human health and metabolic functions, affecting almost every aspect of the body. An increasing amount of evidence indicates that the disruption of circadian rhythms is linked not only to key elements of metabolic syndrome, including obesity, dysglycemia, and dyslipidemia, but also with its major complications, including sleep disorders, depression, nonalcoholic steatohepatitis, and cancers [32, 33]. MetS could be linked to the overall risk of cancer or specifically related to the onset of certain types of cancers, including liver and colorectal cancer [34]. It has been hypothesized that the link between MetS and cancer lies in the imbalance between lipocalin and leptin. Lipocalin is a hormone with anti-inflammatory and anti-tumor properties, whereas in patients with MetS, lipocalin levels are usually reduced, accompanied by an increase in leptin secretion, and this hormonal imbalance tends to promote hyperinsulinemia, production of vascular endothelial growth factor, enhancement of cellular proliferation, and inhibition of apoptosis, thus providing favorable conditions for cancer development and progression [35, 36]. Since circadian rhythm disruption is an important potential causative factor for Mets, a positive association between Circs and cancer may likewise exist. The prevailing view is that disruption of the circadian system is crucial for the proliferation of cancer cells, senescence, metabolism, and DNA damage by leading to aberrant expression of genes related to the biological clock (e.g., BMAL1, REV-ERB, and DEC12) [37, 38], suggesting that metabolic disturbances in cancer may originate from the disruption of the biological clock.

In addition, the core features of MetS, insulin resistance and chronic low-grade inflammatory state, may also play an important role in cancer initiation, progression, and metastasis [39]. The TyG index has emerged as a novel alternative to insulin resistance as an important marker for predicting chronic metabolic diseases at present, previous studies have demonstrated that a higher TyG index is associated with an increased risk of chronic kidney disease [40, 41]. Therefore, we included the TyG index as a mediator to analyze the Circs mediating role between Circs and cancer risk. In this study, we discovered that the TyG index acted as a mediator in the relationship between CircS and cancer risk. When treated as a continuous variable, our analysis indicated a nonlinear association with cancer risk. Elevated levels of the TyG index may contribute to an increased likelihood of developing cancer. This finding provides new evidence to existing studies that CircS may promote cancer by increasing the risk of metabolic disorders further by raising the TyG index. Circs as a more strictly defined Mets, although TyG index can be a valid diagnostic factor for Mets [42], he mechanism of its correlation with cancer risk remains unclear. Research has indicated that insulin may be crucial in the malignant transformation of different cell types, and also in the processes of cancer development and metastasis, through its binding to and activation of the structurally similar receptor, insulin-like growth factor-1 (IGF-1) [43–45]. Moreover, hyperglycemia increases the sensitivity of cells to IGF-1 [46], which further promotes cancer development and progression. At the same time, blood glucose abnormalities exacerbate oxidative stress, leading to the persistence of a chronic inflammatory response, which provides a favorable microenvironment for tumor growth, promotes angiogenesis, and inhibits apoptosis [47]. This finding provides new evidence for the promotion of carcinogenesis by CircS through the TyG index, and it also reveals the potential application of the TyG index in cancer prediction.

The strength of this study lies within its broad representativeness based on prospective cohort data from the middle-aged and elderly population in China, which provides a solid foundation for exploring the association between CircS, TyG index and cancer risk. In addition, the study used multivariate adjustment and mediation modeling analysis to reveal the partial role of TyG index as a mediator between CircS and cancer risk, which complements existing studies and provides a new perspective for future studies exploring Circs and cancer. While our study focuses on middle-aged and elderly Chinese individuals, the findings may have broader applicability due to the universal nature of circadian and metabolic processes. The mechanisms linking CircS and the TyG index to cancer risk are not population-specific and could potentially apply to other ethnic or age groups experiencing similar circadian and metabolic disruptions. However, there are some limitations of this study. First, as a cancer diagnosis based on self-report, there may be information bias that affects the accuracy of the conclusions. Second, although the study revealed associations between CircS, TyG index and cancer risk, it did not delve into the biological mechanisms behind these associations. Finally, due to the relatively short follow-up period, the effect of long-term Circs on cancer risk could not be fully assessed, which needs to be further validated in future studies.

Conclusion

This study examines the association between CircS and cancer risk and reveals the mediating role of the TyG index in this correlation. The likelihood of developing cancer rose with higher TyG index levels, exhibiting a nonlinear relationship. This finding provides new evidence for a potential bridging role of CircS between metabolic dysfunction and cancer development.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13816-7.

Supplementary Material 1

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Author contributions
ZB designed the study. DC, JL, YN and SW performed data analysis. ZB drafted the manuscript. DC revised the manuscript. All authors read and approved the final manuscript.

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Data availability
More information regarding obtaining data for research use can be found at the CHARLS database (http://charls.pku.edu.cn/).

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles of the Declaration of Helsinki. The CHARLS protocol was approved by the Biomedical Ethics Review Board of Peking University (IRB00001052-11015). Informed written consent was obtained from all participants at the time of enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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