Cardiovascular Diabetology

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Association between triglyceride glucose-body mass index and the trajectory of cardio-renal-metabolic multimorbidity: insights from multi-state modelling

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Abstract

Background Although some studies have examined the association between the triglyceride glucose-body mass index (TyG-BMI) and cardiovascular outcomes in the cardio-renal-metabolic (CRM) background, none have explored its role in the progression of CRM multimorbidity. In addition, prior research is limited by small sample sizes and a failure to account for the competitive effects of other CRM diseases.

Methods In this study, data obtained from the large-scale, prospective UK Biobank cohort were used. CRM multimorbidity was defined as the new-onset of ischemic heart disease, type 2 diabetes mellitus, or chronic kidney disease during follow-up. Multivariable Cox regression was used to analyse the independent association between TyG-BMI and each CRM multimorbidity (first, double, or triple CRM diseases). The C-statistic was calculated for each model, and a restricted cubic spline was applied to assess the dose–response relationship. A multi-state model was used to investigate the association between TyG-BMI and the trajectory of CRM multimorbidity (from baseline [without CRM disease] to the first CRM disease, the first CRM disease to double disease, and double disease to triple disease), with disease-specific analyses.

Results This study included 349,974 participants, with a mean age of 56.05 (standard deviation [SD], 8.08), 55.93% of whom were female. Over a median follow-up of approximately 14 years, 56,659 (16.19%) participants without baseline CRM disease developed at least one CRM disease, including 8451 (14.92%) who progressed to double CRM disease and 789 (9.34%) who further developed triple CRM disease. In the crude model, each SD increase in TyG-BMI was associated with a 47% higher risk of the first CRM disease, a 72% higher risk of double CRM disease, and a 95% higher risk of triple CRM disease, with C-statistics of 0.625, 0.694, and 0.764, respectively. Multi-state model analysis showed a 32% increased risk of new CRM disease, a 24% increased risk of progression to double CRM disease, and a

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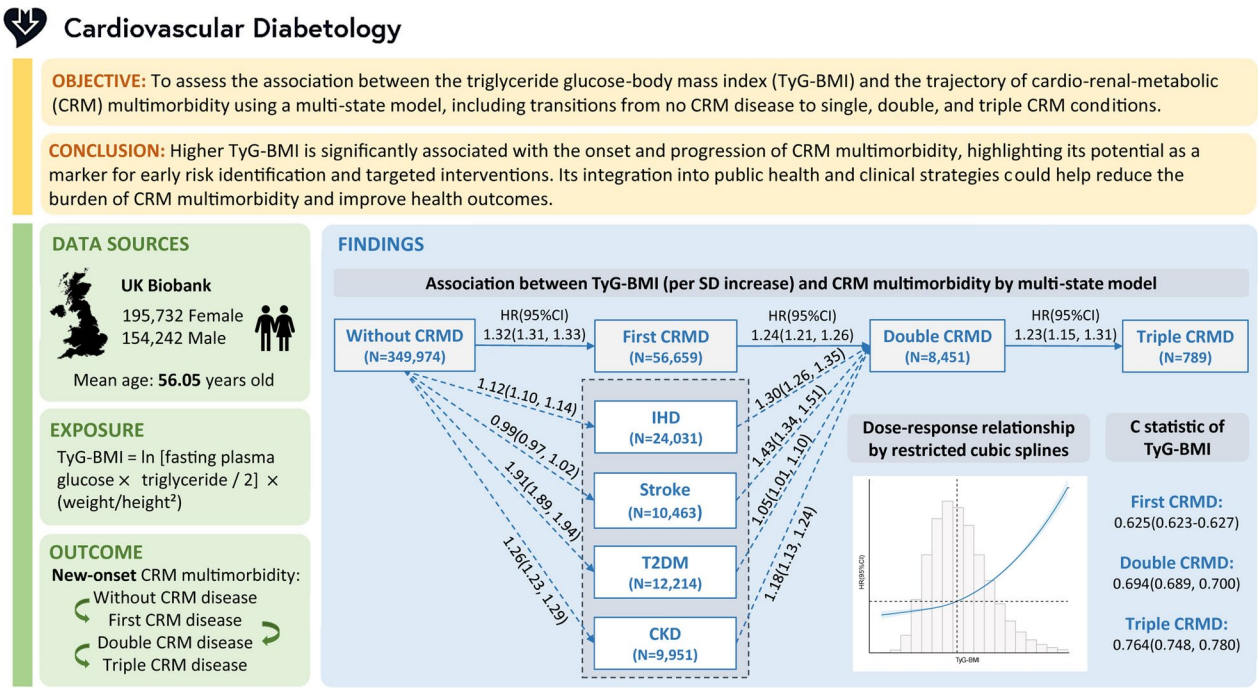
23% increased risk of further progression for those with double CRM diseases. TyG-BMI was significantly associated with the onset of all individual first CRM diseases (except for stroke) and with the transition to double CRM disease. Significant interactions were also observed, but TyG-BMI remained significantly associated with CRM multimorbidity across subgroups. Sensitivity analyses, including varying time intervals for entering states and an expanded CRM definition (including atrial fibrillation, heart failure, peripheral vascular disease, obesity, and dyslipidaemia), confirmed these findings.

Conclusion TyG-BMI remarkably influences the onset and progression of CRM multimorbidity. Incorporating it into CRM multimorbidity prevention and management could have important public health implications.

Graphical abstract



Keywords Triglyceride glucose-body mass index, Cardio-renal-metabolic multimorbidity, Multi-state model, UK Biobank

Introduction

Cardio-renal-metabolic (CRM) conditions share common underlying mechanisms and they frequently coexist [1–5]. These conditions interact at the pathophysiological level, creating a detrimental cycle that accelerates disease progression. As individuals accumulate diagnoses over time, multimorbidity tends to develop sequentially, leading to increasing incidence of multi-organ dysfunction and adverse cardiovascular outcomes [5, 6]. Therefore, understanding the accumulation of diseases over time and identifying key factors associated with this process is crucial.

The triglyceride glucose (TyG) index, which is a surrogate marker of insulin resistance (IR), has been shown to correlate with the occurrence and prognosis of fatal and non-fatal cardiovascular diseases (CVD) [7–11]. Previous studies, including our own, reported that combining the TyG index with obesity-related indicators such as body mass index (BMI) enhances the effectiveness of IR assessment and improves the ability to predict related health outcomes [12–15].

Previous studies which primarily focused on the association between the TyG index (or obesity-related indicators) and CVD outcomes within the context of CRM have typically examined a single trajectory (i.e., from the absence to the presence of disease). However, no studies have explored the role of the TyG-BMI index in the progression of CRM multimorbidity, which includes transitions from no CRM disease to the first CRM disease (newly diagnosed CVD, type 2 diabetes [T2DM] or chronic kidney disease [CKD]), followed by further progression to double or triple CRM diseases (the presence of any two or all three conditions). This definition has been referenced in previous literature [4, 6, 16].

In addition, earlier research has been limited by small sample sizes and a failure to account for the competing effects of other CRM diseases.

By utilizing a large prospective sample of approximately 350,000 individuals from the UK Biobank (UKB), this study aims to address the abovementioned gaps by analysing the association between TyG-BMI and the trajectory of CRM multimorbidity through a multistate model. The findings of this study will provide new insights into the prevention and management of CRM multimorbidity.

Methods

Study design

The UKB is a prospective cohort study involving over 500,000 participants from England, Scotland, and Wales, recruited between 2006 and 2010 [17]. Socio-demographic, medical, and lifestyle information was collected through questionnaires, interviews, and health records, with physical measurements and biological samples obtained using standardized protocols. This study was approved by the North West Multicenter Research Ethics Committee, with all participants providing a written informed consent. This research was conducted under UKB application number 205837.

As shown in Fig. 1A, participants from the UKB cohort who had CVD (including ischemic heart disease [IHD] and stroke), T2DM or CKD at baseline were excluded from the study (n = 63,822). In addition, participants with unavailable data for calculating TyG-BMI or for the follow-up of new-onset CRM disease were excluded (n = 64,504), as well as those missing relevant covariates (n = 23,837). Finally, 349,974 participants were included in the analysis.

Calculation of TyG-BMI and follow-up for CRM multimorbidity

TyG-BMI was defined as the product of the TyG index and BMI. The TyG index was calculated as ln [fasting plasma glucose (mg/dL) × triglyceride (mg/dL)/2], and BMI (kg/m^2) was calculated as weight/height^2 [18].

The primary outcome of interest was the incidence of new-onset CRM multimorbidity amongst participants. Outcomes were defined accordance with the International Classification of Diseases, 10th Edition. CRM multimorbidity was defined in accordance with previous literature [4, 6, 16]. The First CRM disease was defined as the first occurrence of any of the following during follow-up: CVD (including IHD [I20–I25] and stroke [I60–I69]), T2DM (E11) or CKD (N18) [19, 20]. Double CRM disease was defined as the occurrence of any two of these diseases, and triple CRM disease was defined as the occurrence of all three. All participants were followed from the date of their consent to join the UKB study until the earliest occurrence of an outcome event, loss to follow-up, or the end of the follow-up period.

Covariates

On the basis of previous studies and clinical experience [21, 22], we included the following covariates were included: age, sex, race, education level, Townsend deprivation index, smoking status, drinking status, history of hypertension, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and creatinine levels.

Sex was categorized as female and male. Race was categorized as White European, Mixed, Asian, Black, or Other. Education level was classified as high (college or university degree, nursing, teaching and others), intermediate (A [advanced]/AS levels or equivalent, O [ordinary] levels/General Certificate of Secondary Education or equivalent and Certificate of Secondary Education or equivalent), low (National Vocational Qualification or Higher National Diploma or equivalent) or other (none of the above) [23]. The Townsend deprivation index incorporates information on social class, employment, car availability, and housing [24]. Smoking and drinking status were categorized as never, previous, or current. Hypertension history was defined as self-reported doctor-diagnosed hypertension, the current use of antihypertensive medications, or a repeated measurement of average systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

Statistical analysis

Baseline characteristics were categorized by TyG-BMI quartile groups. Continuous variables were reported as means ± standard deviations (SD) for normally distributed variables, or as medians with interquartile ranges for skewed variables. Categorical variables were presented as numbers and percentages (%). Group differences were analysed using analysis of variance, the Kruskal–Wallis H test, and chi-square tests.

Multivariable Cox regression was applied to analyse the association between TyG-BMI (entered as a continuous variable per SD increase) and CRM multimorbidity (first/double/triple CRM disease), as well as CRM components (IHD, stroke, T2DM, and CKD), adjusting for age, sex, race, education, Townsend deprivation index, smoking and drinking status, hypertension history, LDL cholesterol, HDL cholesterol, and creatinine. The C-statistic was calculated for each model to assess predictive performance. In addition, restricted cubic splines (with four knots) were used to visualize the dose–response relationship between TyG-BMI and outcomes.

The multi-state model is an extension of the competing risk model, which can be used to comprehensively understand the effects of risk factors on different disease

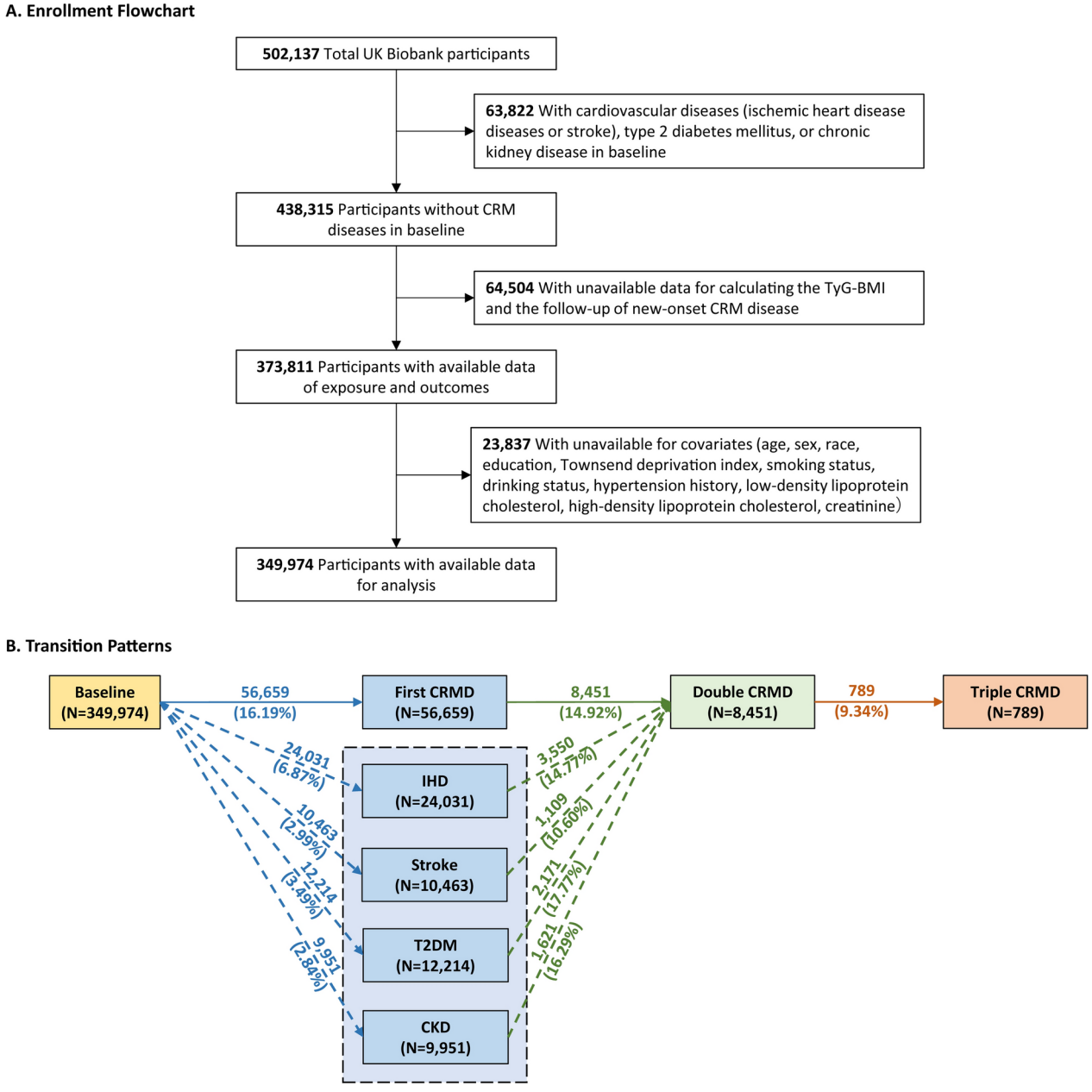


Fig. 1 Study design and criteria. Abbreviations: *CKD* chronic kidney disease, *CRMD* cardio-renal-metabolic disease, *IHD* ischemic heart disease, *T2DM* type 2 diabetes mellitus

stages (e.g., progression or prognosis). The methodology has been previously described in the literature [19, 25]. The multi-state model was used in this study to analyse the role of TyG-BMI in the temporal progression of CRM multimorbidity, from no CRM disease to first, double, and triple CRM diseases. As shown in Fig. 1B, three transition stages were constructed on the basis of the progression trajectory of CRM multimorbidity: (1) baseline (without CRM disease) to first CRM disease, (2) first to double CRM disease, and (3) double to triple CRM disease. For participants entering different stages on the same date, the entry date of the prior stage was defined as 0.5 days earlier than the entry date of the subsequent stage, which is in line with previous studies [19, 26]. For example, the entry date for the first CRM disease was set as 0.5 days before the entry date for double CRM disease. In secondary analyses, the differential associations of TyG-BMI with progression were further examined by the subtype of the first CRM disease (IHD, stroke, T2DM, and CKD), constructing nine transition paths. The relative risks of patients transitioning from baseline to each individual first CRM disease paths were also compared.

Subgroup analyses were conducted to examine whether the association between TyG-BMI and CRM multimorbidity differed across age groups, sex, race, education level, smoking and drinking status, and hypertension history. Likelihood ratio tests were used to assess interactions [27].

Two sensitivity analyses were performed evaluate the stability of the results. Firstly, the entry date of the prior state we calculated using different time intervals (0.5 years, 1 year, 5 years, or excluded directly) for participants entering different states on the same day. Secondly, the definition of outcomes we expanded to include additional cardiac (atrial fibrillation: I48, heart failure: I50, peripheral vascular diseases: I70, I73) and metabolic (diabetes: E10-E14, obesity: E66, dyslipidaemia: E78) outcomes [19, 28, 29]. After excluding participants with these conditions at baseline, relevant analyses were repeated.

All analyses were conducted using R (version 4.4.1) and Free Statistics software (version 2.0). The multi-state model was performed using the "mstate" package. Statistical tests were two-sided, with significance set at $P < 0.05$.

Results

Baseline characteristics of the participants

As shown in Table 1, this study included 349,974 participants with a mean age of 56.05 years (SD, 8.08), of whom 55.93% were female. Compared with participants in the lowest quartile of TyG-BMI, those in the highest quartile had a lower proportion of individuals with higher education levels, a higher Townsend deprivation index and potential smoking or alcohol consumption history. They also had a higher prevalence of hypertension, higher LDL cholesterol, lower HDL cholesterol, and higher creatinine levels. During a median follow-up of approximately 14 years, 56,659 participants (16.19%) developed any new CRM disease, 8451 participants (2.41%) developed two or more CRM diseases, and 789 participants (0.23%) developed all three. As TyG-BMI levels increased, the prevalence of CRM multimorbidity and its individual components also increased.

Association of TyG-BMI with CRM multimorbidity

As shown in Table 2, in the crude model, for each SD increase in TyG-BMI, the risk of developing first, double, and triple CRM disease increased by 47%, 72%, and 95%, respectively. The C-statistics for each model were approximately 0.625, 0.694, and 0.764. After adjusting for covariates, the association between TyG-BMI and CRM multimorbidity remained significant, with a marked increase in C-statistics. Dose–response relationship between TyG-BMI and CRM multimorbidity was shown in Fig. 2. In the crude model, for each SD increase in TyG-BMI, the risk of developing IHD, stroke, T2DM, and CKD increased by 31%, 13%, 106%, and 40%, respectively, with C-statistics of approximately 0.595, 0.541, 0.771, and 0.612. After adjustment, the association between TyG-BMI and stroke was no longer significant.

Amongst individuals without any CRM disease at baseline, 56,659 (16.19%) developed any type of CRM disease, with 8451 (14.92%) further progressing to double CRM disease, and 789 (9.34%) progressing to triple CRM disease (Fig. 1B). Multi-state model analysis showed that for each SD increase in TyG-BMI, the risk of developing any CRM disease from baseline increased by 32% (Table 3). Amongst those with any CRM disease, each SD increase in TyG-BMI was associated with a 24% increased risk of progressing to double CRM disease. For individuals with double CRM disease, the risk of further progression increased by 23%.

Further secondary analysis revealed that 24,031 participants (6.87%) developed first CRM disease as IHD, 10,463 (2.99%) as stroke, 12,214 (3.49%) as T2DM, and 9951 (2.84%) as CKD (Fig. 1B). Compared with the transition from baseline to CKD, the risk of transitioning to IHD, stroke, and T2DM was 2.41, 1.05, and 1.23 times higher, respectively (Supplementary Table 1). Except for stroke, TyG-BMI was significantly associated with the occurrence of each individual first CRM disease. Amongst those whose first CRM disease was IHD, 3550 (14.77%) participants developed double CRM disease, 1109 (10.60%) participants for stroke, 2171 (17.77%) participants for T2DM and 1621 (16.29%) participants for CKD (Fig. 1B). TyG-BMI was significantly associated with the progression of each individual first CRM disease to double CRM disease (Table 3).

Subgroup and sensitivity analyses

The results of subgroup analysis are shown in Supplementary Table 2. The interaction effects of TyG-BMI with age, race, education level, smoking status, and hypertension history were observed (P for interaction < 0.05). However, the association between TyG-BMI and CRM multimorbidity remained significant in all subgroups. Sensitivity analyses revealed that similar conclusions were drawn, whether different time intervals were set for participants entering different states on the same day or the definition of CRM diseases was expanded (Supplementary Tables 3–5).

Discussion

In this large prospective study, TyG-BMI was significantly associated with and predicted the trajectory of CRM multimorbidity, including transitions from baseline (without CRM disease) to the first CRM disease, from the first CRM disease to double CRM disease, and from double CRM disease to triple CRM disease. In disease-specific analyses, TyG-BMI was significantly associated

Table 1 Characteristics of participants

Characteristic	Overall (N = 349,974)	Quartile 1 (N = 87,494)	Quartile 2 (N = 87,493)	Quartile 3 (N = 87,493)	Quartile 4 (N = 87,494)	*P* value
TyG-BMI						< 0.001
Mean (SD)	236.16 (47.13)	183.03 (14.42)	216.53 (7.92)	245.51 (9.27)	299.56 (34.81)	
Age, years						< 0.001
Mean (SD)	56.05 (8.08)	54.55 (8.22)	56.45 (8.06)	56.85 (7.98)	56.35 (7.87)	
Sex, n (%)						< 0.001
Female	195,732 (55.93)	62,606 (71.55)	48,534 (55.47)	40,911 (46.76)	43,681 (49.92)	
Male	154,242 (44.07)	24,888 (28.45)	38,959 (44.53)	46,582 (53.24)	43,813 (50.08)	
Race, n (%)						< 0.001
Asian	6458 (1.85)	1669 (1.91)	1741 (1.99)	1729 (1.98)	1319 (1.51)	
Black	5109 (1.46)	1011 (1.16)	1184 (1.35)	1416 (1.62)	1498 (1.71)	
Mixed	2114 (0.60)	640 (0.73)	512 (0.59)	453 (0.52)	509 (0.58)	
Others	2874 (0.82)	676 (0.77)	684 (0.78)	742 (0.85)	772 (0.88)	
White	333,419 (95.27)	83,498 (95.43)	83,372 (95.29)	83,153 (95.04)	83,396 (95.32)	
Education level, n (%)						< 0.001
High	170,824 (48.81)	49,197 (56.23)	44,186 (50.50)	40,778 (46.61)	36,663 (41.90)	
Intermediate	105,055 (30.02)	25,794 (29.48)	25,890 (29.59)	26,072 (29.80)	27,299 (31.20)	
Low	20,146 (5.76)	3390 (3.87)	4881 (5.58)	5638 (6.44)	6237 (7.13)	
Other	53,949 (15.42)	9113 (10.42)	12,536 (14.33)	15,005 (17.15)	17,295 (19.77)	
Townsend deprivation index						< 0.001
Median (Q1, Q3)	− 2.24 (− 3.69, 0.28)	− 2.30 (− 3.74, 0.18)	− 2.39 (− 3.78, − 0.05)	− 2.31 (− 3.70, 0.16)	− 1.93 (− 3.51, 0.84)	
Smoking status, n (%)						< 0.001
Current	35,853 (10.24)	9168 (10.48)	8668 (9.91)	8995 (10.28)	9022 (10.31)	
Never	196,399 (56.12)	53,405 (61.04)	50,324 (57.52)	47,278 (54.04)	45,392 (51.88)	
Previous	117,722 (33.64)	24,921 (28.48)	28,501 (32.58)	31,220 (35.68)	33,080 (37.81)	
Drinking status, n (%)						< 0.001
Current	325,314 (92.95)	81,571 (93.23)	81,958 (93.67)	81,589 (93.25)	80,196 (91.66)	
Never	13,608 (3.89)	3227 (3.69)	3090 (3.53)	3278 (3.75)	4013 (4.59)	
Previous	11,052 (3.16)	2696 (3.08)	2445 (2.79)	2626 (3.00)	3285 (3.75)	
Hypertension history, n (%)						< 0.001
No	168,668 (48.19)	58,747 (67.14)	45,850 (52.40)	37,131 (42.44)	26,940 (30.79)	
Yes	181,306 (51.81)	28,747 (32.86)	41,643 (47.60)	50,362 (57.56)	60,554 (69.21)	
LDL cholesterol, mmol/L						< 0.001
Mean (SD)	3.65 (0.83)	3.37 (0.76)	3.65 (0.81)	3.78 (0.84)	3.80 (0.85)	
HDL cholesterol, mmol/L						< 0.001
Mean (SD)	1.47 (0.38)	1.71 (0.39)	1.53 (0.35)	1.39 (0.33)	1.27 (0.29)	
Creatinine, μmol/L						< 0.001
Mean (SD)	71.45 (14.39)	67.09 (12.60)	71.37 (13.97)	73.83 (14.98)	73.51 (14.89)	
First CRM disease, n (%)						< 0.001
No	293,315 (83.81)	79,790 (91.19)	75,837 (86.68)	72,396 (82.74)	65,292 (74.62)	
Yes	56,659 (16.19)	7704 (8.81)	11,656 (13.32)	15,097 (17.26)	22,202 (25.38)	
Double CRM disease, n (%)						< 0.001
No	341,523 (97.59)	86,813 (99.22)	86,194 (98.52)	85,374 (97.58)	83,142 (95.03)	
Yes	8451 (2.41)	681 (0.78)	1299 (1.48)	2119 (2.42)	4352 (4.97)	
Triple CRM disease, n (%)						< 0.001
No	349,185 (99.77)	87,465 (99.97)	87,413 (99.91)	87,315 (99.80)	86,992 (99.43)	
Yes	789 (0.23)	29 (0.03)	80 (0.09)	178 (0.20)	502 (0.57)	
New-onset IHD, n (%)						< 0.001
No	323,176 (92.34)	83,652 (95.61)	81,502 (93.15)	79,927 (91.35)	78,095 (89.26)	
Yes	26,798 (7.66)	3842 (4.39)	5991 (6.85)	7566 (8.65)	9399 (10.74)	
New-onset stroke, n (%)						< 0.001
No	336,777 (96.23)	84,897 (97.03)	84,252 (96.30)	83,953 (95.95)	83,675 (95.64)	
Yes	13,197 (3.77)	2597 (2.97)	3241 (3.70)	3540 (4.05)	3819 (4.36)	

Table 1 (continued)

Characteristic	Overall (N = 349,974)	Quartile 1 (N = 87,494)	Quartile 2 (N = 87,493)	Quartile 3 (N = 87,493)	Quartile 4 (N = 87,494)	*P* value
New-onset T2DM, n (%)						< 0.001
No	334,887 (95.69)	86,863 (99.28)	85,961 (98.25)	84,196 (96.23)	77,867 (89.00)	
Yes	15,087 (4.31)	631 (0.72)	1532 (1.75)	3297 (3.77)	9627 (11.00)	
New-onset CKD, n (%)						< 0.001
No	336,458 (96.14)	85,731 (97.99)	84,605 (96.70)	83,755 (95.73)	82,367 (94.14)	
Yes	13,516 (3.86)	1763 (2.01)	2888 (3.30)	3738 (4.27)	5127 (5.86)	

CRM cardio-renal-metabolic, *CKD* chronic kidney disease, *IHD* ischemic heart disease, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *T2DM* type 2 diabetes mellitus, *TyG-BMI* triglyceride glucose-body mass index

Table 2 Association between TyG-BMI and CRM multimorbidity

	Crude model			Adjusted model		
	HR (95% CI)	*P* value	C statistic (95% CI)	HR (95% CI)	*P* value	C statistic (95% CI)
CRM multimorbidity						
First CRM disease	1.47 (1.46, 1.48)	< 0.001	0.625 (0.623, 0.627)	1.32 (1.31, 1.33)	< 0.001	0.720 (0.718, 0.722)
Double CRM diseases	1.72 (1.70, 1.75)	< 0.001	0.694 (0.689, 0.700)	1.54 (1.51, 1.57)	< 0.001	0.806 (0.802, 0.810)
Triple CRM diseases	1.95 (1.87, 2.04)	< 0.001	0.764 (0.748, 0.780)	1.79 (1.69, 1.89)	< 0.001	0.872 (0.861, 0.883)
CRM components						
IHD	1.31 (1.30, 1.33)	< 0.001	0.595 (0.592, 0.598)	1.13 (1.12, 1.15)	< 0.001	0.712 (0.710, 0.715)
Stroke	1.13 (1.11, 1.14)	< 0.001	0.541 (0.536, 0.546)	1.01 (0.99, 1.03)	0.26	0.718 (0.714, 0.722)
T2DM	2.06 (2.04, 2.08)	< 0.001	0.771 (0.767, 0.775)	1.86 (1.84, 1.89)	< 0.001	0.807 (0.804, 0.810)
CKD	1.40 (1.38, 1.42)	< 0.001	0.612 (0.608, 0.617)	1.28 (1.26, 1.30)	< 0.001	0.782 (0.779, 0.786)

TyG-BMI was entered as a continuous variable per standard deviation increase. The crude model did not account for covariates, while the adjusted model accounted for age, sex, race, education, Townsend deprivation index, smoking status, drinking status, hypertension history, LDL cholesterol, HDL cholesterol, and creatinine

CI confidence interval, *CRM* cardio-renal-metabolic, *CKD* chronic kidney disease, *HR* hazard ratio, *IHD* ischemic heart disease, *T2DM* type 2 diabetes mellitus, *TyG-BMI* triglyceride glucose-body mass index

with the occurrence of each individual first CRM disease, except for stroke. Moreover, TyG-BMI was associated with the progression of each individual first CRM disease to double CRM disease. Subgroup and sensitivity analyses, including an expanded definition of CRM diseases, confirmed the robustness of these findings.

Study review

In general, previous studies have focused on the association between TyG and its related derived indicators with health outcomes, often examining the association with a single trajectory. Few studies have assessed their role in the progression of health outcomes, especially in the context of a group of diseases with remarkable mutual interactions. For example, Li et al., based on the China Health and Retirement Longitudinal Study with 7376 participants (mean age: 59.17 ± 9.28 years; 52.62% female), found that in participants with cardiovascular-kidney-metabolic (CKM) syndrome stages 0–3 (i.e., including individuals with or without metabolic risk factors and CKD, as defined by the American Heart Association [AHA]), each 10-unit increase in TyG-BMI was associated with a 6.5% higher risk of CVD [21]. Although no significant interaction was observed, this association was more significant in participants at stages 2 and 3 probably because of the smaller sample size. Furthermore, Li et al. did not account for the potential competitive relationships and interactions between newly developed CRM diseases during disease progression. Based on prospective large-scale data, this study successfully demonstrated the crucial role of TyG-BMI in the occurrence and progression of CRM diseases using a multi-state model, providing strong evidence for the utility of TyG-BMI in detecting CRM multimorbidity.

Although similar limitations exist, several previous studies have demonstrated the significant associations between TyG and new-onset CKD [30–32], the development of CVD in patients with CKD [33] and the development of CKD in patients with CVD [34]. In addition, TyG has been linked to new-onset CVD or CVD-related mortality in individuals with DM or metabolic syndrome [35–40]. These findings further support the bidirectional and causal associations amongst CRM diseases.

Mechanisms

The mechanisms through which hyperglycaemia damages the cardio-renal system are well-documented. The excessive intracellular glucose flux triggers mitochondrial superoxide production, which intensifies oxidative stress and is thought to be the primary initiating factor in diabetes-induced organ damage [5, 41]. The bidirectional interaction between the cardio-renal systems has

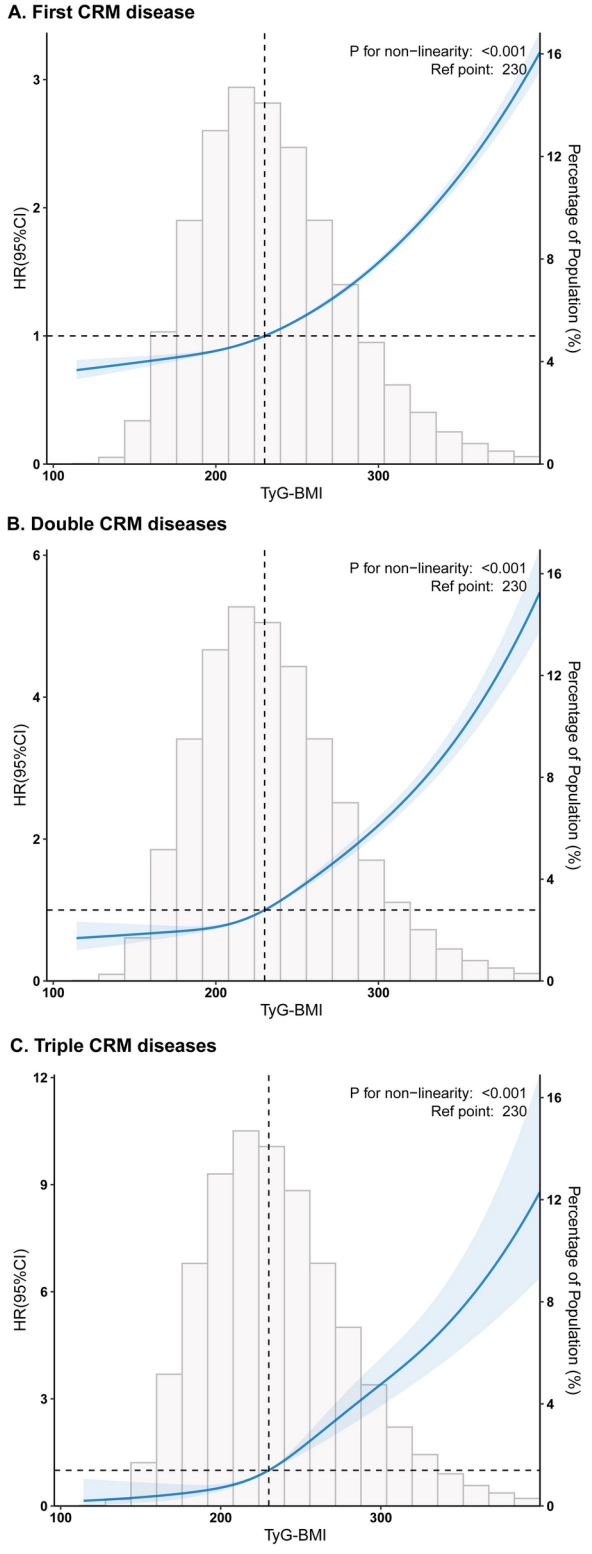


Fig. 2 Dose–response relationship between TyG-BMI and CRM multimorbidity using restricted cubic splines. Abbreviations: CRM, cardio-renal-metabolic. Only participants with TyG-BMI within the 99.5% upper limit were included in the plot. All models were adjusted for age, sex, race, education, Townsend deprivation index, smoking status, drinking status, hypertension history, LDL cholesterol, HDL cholesterol, and creatinine

Table 3 Association between TyG-BMI and the trajectory of CRM multimorbidity by multi-state model

Transition	HR (95% CI)	*P* value
Model 1: Baseline → First CRM disease → Double CRM diseases → Triple CRM diseases		
Baseline → First CRM diseases	1.32 (1.31, 1.33)	< 0.001
First CKM diseases → Double CRM diseases	1.24 (1.21, 1.26)	< 0.001
Double CKM diseases → Triple CRM diseases	1.23 (1.15, 1.31)	< 0.001
Model 2: Baseline → First CRM disease subtypes (IHD, Stroke, T2DM, and CKD) → Double CRM diseases → Triple CRM diseases		
Baseline → IHD	1.12 (1.10, 1.14)	< 0.001
Baseline → Stroke	0.99 (0.97, 1.02)	0.53
Baseline → T2DM	1.91 (1.89, 1.94)	< 0.001
Baseline → CKD	1.26 (1.23, 1.29)	< 0.001
IHD → Double CRM diseases	1.30 (1.26, 1.35)	< 0.001
Stroke → Double CRM diseases	1.43 (1.34, 1.51)	< 0.001
T2DM → Double CRM diseases	1.05 (1.01, 1.10)	0.01
CKD → Double CRM diseases	1.18 (1.13, 1.24)	< 0.001
Double CRM diseases → Triple CRM diseases	1.23 (1.15, 1.31)	< 0.001

TyG-BMI was entered as a continuous variable per standard deviation increase. All models were adjusted for age, sex, race, education, Townsend deprivation index, smoking status, drinking status, hypertension history, LDL cholesterol, HDL cholesterol, and creatinine

CI confidence interval, *CRM* cardio-renal-metabolic, *CKD* chronic kidney disease, *HR* hazard ratio, *IHD* ischemic heart disease, *T2DM* type 2 diabetes mellitus, *TyG-BMI* triglyceride glucose-body mass index

been extensively explored, with hemodynamic disturbances, neurohormonal dysfunction, and inflammation identified as potential contributors [42, 43]. However, the exact mechanism by which CVD and CKD contribute to metabolic dysregulation remains controversial [5]. IR may be a key factor in this context. Previous studies have shown a bidirectional relationship between IR, which is a central metabolic abnormality in T2DM, and endothelial dysfunction, which is a common initiating event in CVD [44]. IR is also commonly observed in the early stages of CKD, potentially driven by chronic inflammation, oxidative stress, and post-translational modifications of signal-transduction proteins. In addition, factors such as metabolic acidosis [45], vitamin D deficiency (17,091,124), and metabolic toxins accumulation [46] may exacerbate glucose metabolism disturbances in patients with CKD. Based on large-scale epidemiological data, this study highlights the important role of the TyG-BMI index, which is a marker of IR, in the progression of CRM diseases, providing further insights into the underlying mechanisms.

Burden and prevention of CRM multimorbidity

CRM diseases are highly prevalent in the population. Based on the National Health and Nutrition Examination Survey from January 2015 to March 2020, Ostrominski et al. found that more than one-fourth of adults in the

United States had a CRM disease, with nearly one in 10 participants experiencing overlapping CRM diseases [4]. Among individuals aged 65 or older, more than half had at least one CRM disease, and nearly one-fourth exhibited overlapping diseases. The prevention and management of CRM diseases are crucial. As shown in previous research by Zhang et al., maintaining a healthy lifestyle (encompassing a balanced diet, limited alcohol consumption, smoking cessation, regular physical activity, reduced sedentary behaviour, adequate sleep, and strong social connections) can slow the progression of CRM diseases [6]. Furthermore, the use of novel glucose-lowering medications with cardiovascular and renal benefits has been shown to be advantageous.

Highlights and limitations

The current study holds important public health implications. By using a multi-state model, the role of TyG-BMI in the onset and progression of CRM multimorbidity has been demonstrated. Apart from providing strong validation of previous research, our findings also offer new insights for the prevention and management of CRM diseases. However, several limitations should be considered. Firstly, given the observational nature of this study and the potential impact of confounding factors, causal inferences should be made with caution. Secondly, considering that the sample is derived from a European population, further research in more diverse populations is necessary. Thirdly, the participants from the UKB tend to be healthier and have higher education levels, and the self-reported nature of some study covariates may introduce selection bias [47]. Fourthly, this study focuses more on the overlapping conditions of CVD, T2D, and CKD, rather than the CKM syndrome as defined by AHA. This relatively simpler definition has been widely used in previous studies. Despite its advantages with regard to clinical convenience and speed, it lacks a certain degree of precision. Furthermore, given the large sample size of the UKB (500,000 participants), conducting long-term dynamic assessments of various clinical and laboratory indicators to accurately determine the progression of CKM syndrome stages throughout participants' life course is challenging and unrealistic. However, future research should aim to address this limitation.

Conclusions

Our study demonstrates that TyG-BMI plays a crucial role in the onset and progression of CRM multimorbidity. As a sensitive marker of metabolic health, TyG-BMI may facilitate the early identification of individuals at high risk and identify targeted prevention and management strategies. Incorporating TyG-BMI into public health interventions could help mitigate the burden of CRM multimorbidity and improve long-term health outcomes. Thus, further research is warranted to evaluate its applicability across diverse populations and assess its integration into clinical practice and health policies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02693-w.

Additional file1 (DOCX 36 kb)

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Author contributions

Conceptualization: H.T., J.H., Y.C.; Data Management and Analysis: H.T., JT.H., X.Z.; Figure Creation: H.T., X.Z., X.C., Q.Y.; Writing-Original Draft Preparation: H.T., JT.H., X.Z., X.C., Q.L., N.L., H.L., JN.H., S.W.; Writing-Review and Editing: JN.H., S.W., C.T, M.L., J.W., P.C., L.J., Y.Z.; Provided Critical Revisions to the Manuscript: K.Y., X.T., Y.C.; Project Management: K.Y., X.T., Y.C.

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Data availability

The dataset supporting the conclusions of this article is available in the public UK Biobank Resource (www.ukbiobank.ac.uk/). This research was conducted using data from the UK Biobank Resource under application number [205837].

Declarations

Ethical approval and consent to the participate

The UK Biobank was approved by the North West Multicenter Research Ethics Committee, with all participants providing written informed consent. Ethical approval and informed consent were waived as the UK Biobank data is publicly available and does not include identifiable information.

Competing interests

The authors declare no competing interests.

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