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Long-term dual-trajectories of TyG and LAP and their association with cardiometabolic multimorbidity in midlife: the CARDIA study

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Abstract

Background Insulin resistance and central obesity are major risk factors for cardiometabolic diseases. The triglyceride-glucose index (TyG) and lipid accumulation product (LAP) are markers that independently predict cardiometabolic risk. However, their combined long-term trajectories and impact on cardiometabolic multimorbidity (CMM) development remain unclear.

Methods This cohort study utilized data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, which tracked 3467 participants at baseline. Dual-trajectory of TyG and LAP were identified using a group-based dual-trajectory model. Cox proportional hazards models were employed to assess the relationships between dual-trajectory groups and primary cardiometabolic outcomes, including first cardiometabolic disease (FCMD), CMM (two or more conditions such as type 2 diabetes, coronary heart disease, or stroke), and all-cause mortality. Multi-state models were performed to assess the associations of dual-trajectory with CMM development.

Results The study included 3467 participants with a mean age of 25.08 years (SD = 3.59). Of these, 43.4% ($n = 1505$) were male, and 53.2% ($n = 1561$) were White. Three distinct dual-trajectory groups were identified: low-increasing (61.5%), high-amplitude fluctuation (7.6%), and high-increasing (30.9%). After multivariate adjustment, compared with the low-increasing group, the high-amplitude fluctuation group exhibited significantly higher risks for FCMD (hazard ratio [HR] 1.38, 95% confidence interval [CI]: 1.08–1.77), CMM (HR 2.63, 95% CI 1.21–5.71), and all-cause mortality (HR 2.16, 95% CI 1.30–3.56), as well as elevated risks for transitions from baseline to FCMD (HR 1.41, 95% CI 1.17–1.63), FCMD to CMM (HR 2.07, 95% CI 1.53–3.96), CMM to death (HR 2.87, 95% CI 1.19–7.62). The high-increasing group showed similar results.

Conclusions Elevated and fluctuating trajectories of TyG and LAP from early adulthood are associated with increased risks of CMM development in midlife.

Keywords Triglyceride–glucose index, Lipid accumulation product, Dual-trajectory, Cardiometabolic multimorbidity, Cohort study

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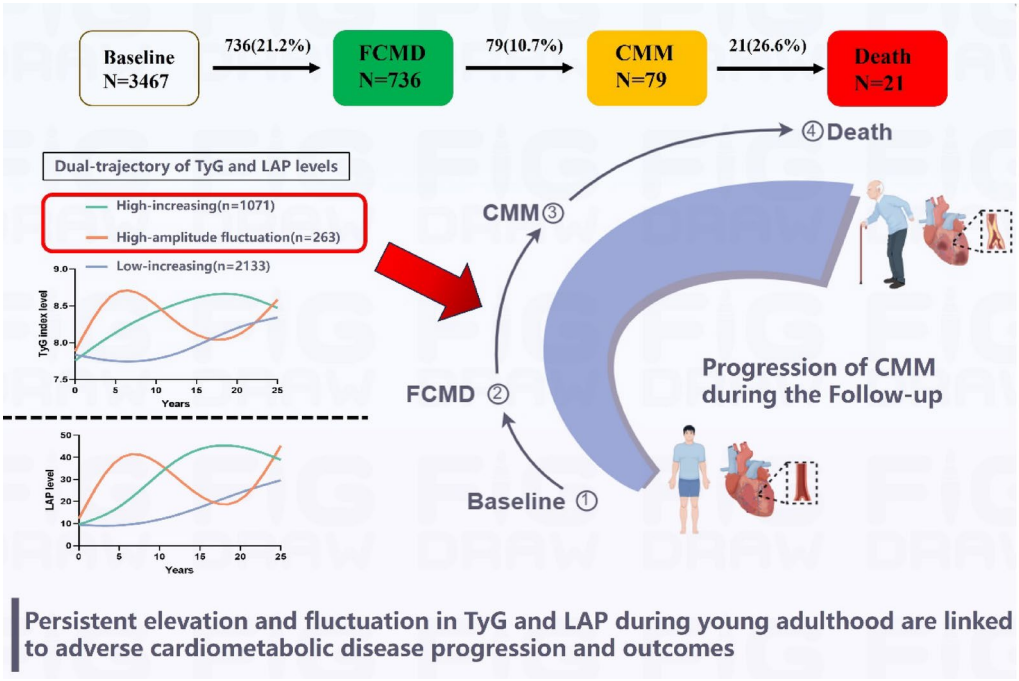
Graphical abstract



Introduction

Multimorbidity, characterized by an individual having at least two chronic metabolic conditions, has emerged as a critical global health challenge [1–3]. Among the different forms of multimorbidity, cardiometabolic multimorbidity (CMM), which involving the simultaneous combination of two or more cardiometabolic diseases (CMDs) such as stroke, type 2 diabetes (T2D), and coronary heart disease (CHD), is particularly worrisome [4]. A Canadian study reported that 22% of individuals with diabetes, 32.2% of those with heart disease, and 48.4% of stroke patients have one additional cardiometabolic condition [5]. Moreover, the coexistence of multiple CMDs significantly escalates mortality risk and markedly reduces life expectancy compared to the presence of a single CMD [3, 6]. Therefore, early identification of potential risk factors contributing to CMM development is crucial.

Insulin resistance (IR) is a key risk factor linked to numerous cardiovascular and metabolic diseases, including CHD, stroke, hypertension, atherosclerosis, T2D, and atrial fibrillation [4, 7]. Recently, the triglyceride-glucose index (TyG) has emerged as a reliable indicator of IR and its progression [8]. Numerous studies have validated the TyG's utility in predicting stroke risk [9], the incidence of diabetes [10], cardiovascular disease (CVD) risk [11], and adverse cardiovascular outcomes [12, 13]. Moreover, obesity, particularly central obesity, is another known contributor to CMDs, with strong associations to premature mortality [14, 15]. Unlike BMI, which cannot distinguish between lean mass and fat mass, the lipid accumulation product (LAP) serves as a more precise indicator of visceral adiposity and metabolic risk [15, 16]. Empirical evidence further supports the utility of LAP in independently predicting conditions such as metabolic syndrome and CMDs, underscoring its value as a crucial metric for improving survival assessments in obese populations [17, 18]. In addition, visceral fat not only directly increases the risk of CMDs but also induces lipotoxicity, chronic inflammation, and adipokine imbalance, exacerbating cardiometabolic risk [19, 20]. These pathways indicate that visceral fat can impact CMDs both as an independent factor and through its interaction with IR. Although TyG and LAP have been extensively studied as independent predictors of cardiometabolic diseases, their potential combined utility for assessing CMM risk remains underexplored. Thus, combining these markers will offers a more comprehensive assessment of cardiometabolic risk.

Furthermore, most existing studies have focused on older populations, often neglecting younger individuals. Nevertheless, metabolic changes during young adulthood have a major impact on future cardiometabolic outcomes, underscoring the importance of focusing on younger cohorts. Additionally, the dynamic nature of TyG and LAP over time suggests that static, single-point assessments may provide only limited insights. Trajectory modeling, in contrast, allows for the examination of temporal changes, the identification of distinct risk

trajectories, and the facilitation of more precise, individualized prevention and intervention strategies [21]. Finally, prior studies have predominantly examined the existence of one or two CMDs, thereby failing to fully address the complex interactions involved in the progression of CMM, which limits the comprehensive utility of TyG and LAP in assessing cardiometabolic disease risk.

In light of these gaps, this study aimed to utilize data from the Coronary Artery Risk Development in Young Adults (CARDIA) study to describe the longitudinal trajectory patterns of TyG and LAP levels during young adulthood, and to evaluate their combined effect on CMM development in middle age.

Methods

Study design and population

Between 1985 and 1986 (year 0), the CARDIA study recruited over 5115 participants aged 18 to 30 from urban areas in four U.S. cities: Minneapolis (Minnesota), Birmingham (Alabama), Oakland (California), and Chicago (Illinois). As a prospective, multi-center study, CARDIA was established to track CVD risk progression and contributing factors from young adulthood to midlife. Data have been collected over nine follow-up intervals, starting with the initial baseline assessment and continuing with further exams at 2, 5, 7, 10, 15, 20, 25, and 30 years. Detailed methodology and examination procedures are documented in previously published reports [22].

For this study, participants with prevalent diabetes, stroke or CHD ($n = 356$) at baseline, missing baseline waist circumference (WC), fast plasma glucose (FPG) and TG values ($n = 121$), having fewer than three valid follow-up observations for WC, FPG, and TG ($n = 831$) and missing other covariates ($n = 168$) were excluded. We also excluded individuals with prevalent cancer ($n = 172$) at baseline to ensure data reliability by minimizing confounding factors, competing risks, and metabolic effects related to cancer and its treatments [23, 24]. A total of 3,467 participants were ultimately included to study the association between TyG and LAP dual-trajectory and CMM development (Fig. 1). To further assess potential selection bias due to missing data, we compared the incidence rates of FCMD, CMM, and all-cause mortality between included and excluded participants. No significant differences in outcomes incidence were observed (Additional file 1: Table S10).

Assessment of the TyG and LAP

The FPG was measured using the hexokinase UV method [22]. TG concentrations in fasting sample blood were assessed by calibration and enzymatic analysis [22]. The TyG was computed using the following formula: Ln [fasting TG (mg/dL) × FPG (mg/dL)/2] [25].

Measurements of weight, height, and WC were gathered according to standardized procedures outlined in earlier studies [26]. WC was measured at the midpoint between the iliac crest and the lowest rib laterally, and between the xiphoid process and the umbilicus anteriorly, with measurements recorded to the nearest 0.5 cm. LAP was calculated using the formula (WC(cm)-65) × TG (mmol/L) for man, and (WC(cm)-58) × TG (mmol/L) for women [27].

Other covariates

At baseline, demographic data and cardiometabolic risk factors—including age, sex, race, education, physical activity, smoking and drinking status, and use of antihypertensive medications—were gathered using standardized protocols [22].

Blood pressure was measured three times following a 5 min rest period, and the mean of the three readings was recorded. Hypertension was defined as having a systolic

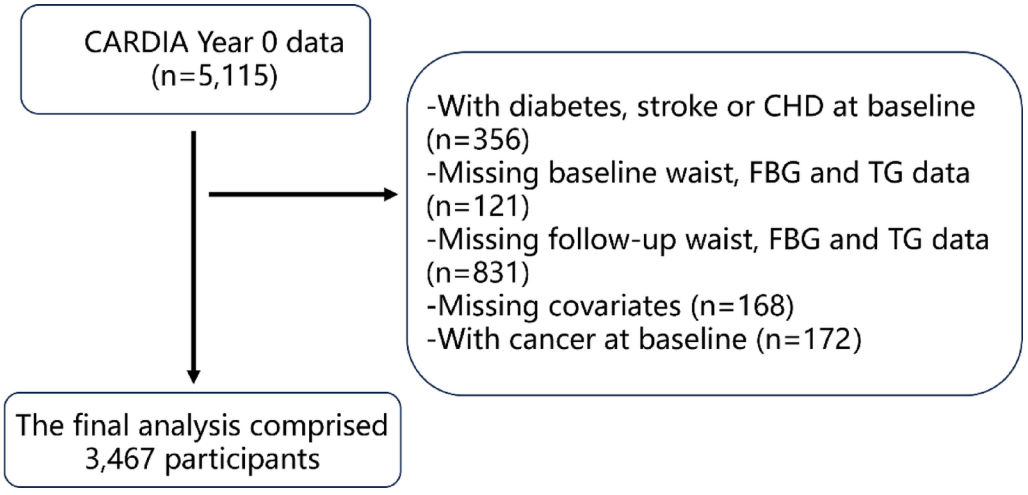


Fig. 1 Flow chart of participant selection

blood pressure (SBP) of 140 mmHg or above, a diastolic blood pressure (DBP) of 90 mmHg or above, or the use of antihypertensive drugs. BMI was derived by dividing body weight (kg) by the square of height (m), expressed as kg/m². Protocols for measuring serum total cholesterol, High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). were detailed in prior studies [28]. Smoking status was categorized into three classes: current, former, or never. Physical activity was measured using the validated CARDIA questionnaire, which quantified 13 exercise categories over the past year and converted them into exercise units (EU), with 300 EU equivalent to 150 min of moderate-intensity exercise weekly [29].

Outcomes

The primary outcomes in this study were defined as first cardiometabolic disease (FCMD), CMM and all-cause mortality.

In accordance with established criteria from previous research, we defined CMM as the coexistence of at least two of the following three CMDs—T2D, CHD, and stroke—with the first occurring CMD identified as the FCMD [24, 30]. To define T2D, criteria included an FPG level reaching 126 mg/dL or more, a 2-hour post-challenge glucose level of ≥ 11.1 mmol/L (200 mg/dL), HbA1c at 48 mmol/mol (6.5%) or higher, or the administration of antidiabetic drugs. Participants were confirmed to be free of diabetes by Year 0, based on assessments of medication use and fasting glucose levels conducted at baseline.

Tracking of cardiovascular and cerebrovascular incidents, which including CHD and stroke, as well as mortality, was conducted from the initial assessment until August 31, 2014. For individuals who underwent hospitalization or outpatient vascular procedures, corresponding medical documentation was collected. Vital status updates were obtained every six months, with next-of-kin consent acquired for access to medical and death records as needed. Each reported event was reviewed independently by two physicians from the CARDIA Endpoints Surveillance and Adjudication Subcommittee, adhering to predefined criteria for cardiovascular incidents described in prior publications [31–33]. In cases of disagreement, the full committee conducted a review. Participants without events who remained in the study were censored as of August 31, 2014.

Statistical analysis

Continuous variables were reported as mean ± SD, and categorical variables as frequency (percentage). Participants were divided into quartiles according to their baseline TyG and LAP levels. Group differences were analyzed using ANOVA, Kruskal-Wallis test, and χ^2 test, as appropriate. Follow-up time was calculated as the duration from the baseline assessment (Year 0, 1985–1986) to the examination visit where incidences (FCMD, CMM or mortality) was identified or until the censoring time (loss to follow-up, or end of cohort surveillance), whichever came first.

To explore the relationships between baseline TyG and LAP levels and FCMD, CMM, and all-cause mortality, Cox proportional hazards models were employed. Hazard ratios (HRs) with 95% confidence interval (CI) were reported to estimate relative risks associated with different levels of TyG and LAP. The fully adjusted models accounted for baseline age, sex, race, BMI, education, physical activity, SBP, hypertension, antihypertensive medication use, smoking status, alcohol consumption, and LDL-C.

A group-based dual-trajectory model with a semi-parametric approach was used to examine the temporal trends of TyG and LAP levels over the follow-up duration (from year 0 to year 25). This method enables the simultaneous analysis of both indicators' dynamics, evaluating the likelihood of LAP trajectories corresponding to specific TyG trajectories. According to recommendations of Nagin [34], to select the optimal model, a two-stage approach was applied. Firstly, we identified the optimal number of trajectories for the model, exploring options from 2 to 5 clusters. In the following stage, the trajectory shapes were refined by adjusting the polynomial order, specifying them as linear, quadratic, or cubic. Selection of the best-fit dual-trajectory model was guided by three main criteria [35]: (1) minimum Bayesian Information Criterion (BIC) value; (2) each trajectory group included at least 5% of the participants; and (3) mean posterior probability greater than 0.7.

Participants were further grouped by dual-trajectory of TyG and LAP. We employed Cox proportional hazards models to assess the associations of dual-trajectory groups with FCMD, CMM, and all-cause mortality, and calculated HRs and 95% CI to evaluate risk. The Cox models included the same set of baseline covariates for full adjustment as in the previous Cox models. To further evaluate the potential collinearity between TyG and LAP, we calculated the variance inflation factor (VIF), across all fully adjusted Cox models for FCMD, CMM, and mortality.

Subsequently, multi-state models, an extension of Cox proportional hazards models, were utilized to investigate the role of dual-trajectory groups at multiple phases of CMM progression, beginning from a baseline without CMDs to the development of FCMD, progression to CMM, and ultimately, mortality. The primary advantage of multi-state models lies in their ability to incorporate multiple sequential or competing events as transition states, enabling a comprehensive evaluation of risk factors across various phases of disease progression with consideration for competing risks [36, 37]. In accordance

with prior research [24, 38], five key transition stages were identified(Fig. 2): (1) baseline to FCMD (21.2%), (2) FCMD to CMM (10.7%), (3) baseline to death (1.6%), (4) FCMD to death (8.0%), and (5) CMM to death (26.6%). The initiation of CMM was defined by the occurrence date of a second CMD. For participants transitioning between different states on the same data, and in alignment with prior research methodologies, the theoretical entry date for the preceding state is estimated by subtracting 0.5 days from the entry date of the subsequent state [24]. For instance, in patients newly diagnosed with CMM, the entry date into FCMD is derived as 0.5 days prior to the recorded date of CMM diagnosis. Given the relatively low number of events in some transitions, we further applied Bootstrap resampling (1000 iterations) to estimate bias-corrected and accelerated (BCa) confidence intervals, improving the precision of risk estimates and ensuring robustness in the presence of small sample sizes.

Sensitivity analyses were conducted to assess the robustness of our findings. First, given the potential confounding effect of LDL-C, a sensitivity analysis was performed in participants with LDL-C < 4.144 mmol/L. Second, to account for the influence of cardiovascular medications, individuals taking antihypertensive, cardiac, or both types of medications at baseline were excluded. Third, to evaluate the impact of pre-existing malignancies, a sensitivity analysis including participants with baseline cancer was conducted. Forth, to examine whether the associations between dual-trajectory groups and CMM remained consistent across individual CMM components, a sensitivity analysis was performed by assessing the associations between dual-trajectory groups and each CMM component separately. Finally, to assess whether the association between dual-trajectory groups and all outcomes was independent of baseline fasting glucose levels, we conducted a sensitivity analysis adjusted for baseline FPG.

We constructed time-dependent Cox proportional hazards models to further validate the associations between dual-trajectory groups and the risks of FCMD, CMM, and all-cause mortality while dynamically accounting for longitudinal changes in key metabolic risk factors. Using the counting-process framework (i.e., Surv (start time, stop time, event)), we incorporated time-updated covariates for body weight, physical activity, systolic blood pressure, smoking status, alcohol consumption and LDL-C, measured at Years 0, 5, 10, 15, 20, and 25. This approach allowed us to better capture the temporal variability of these clinically relevant exposures over the 25-year follow-up.

We further conducted subgroup analyses stratified by sex, race, BMI, smoking status, LDL-C levels, and hypertension to examine potential effect modifications in the associations between dual-trajectory groups and outcomes.

Analyses were carried out in R (version 4.1.3), with the group-based dual-trajectory model fitted by the "lcmm" package and the multi-state models by "mstate". All statistical tests were two-sided, with p-values below 0.05 considered statistically significant in all analyses.

Results

Baseline characteristics of TyG and LAP quartiles and outcomes

This study included 3,467 participants with a baseline mean age of 25.08 ± 3.59 years, among whom 43.4% were male and 53.2% were white. Participants were separated into four quartile groups by TyG and LAP levels.

In the TyG quartile grouping (Additional file 1: Table S1), participants with higher TyG levels were older and more likely to be male, White, smokers, and daily alcohol consumers. They also had greater WC, BMI, SBP, DBP, TG, TC, LDL-C, FPG, LAP, and a higher prevalence of hypertension, while HDL-C was significantly lower. The LAP quartiles showed a similar trend (Additional file 1:

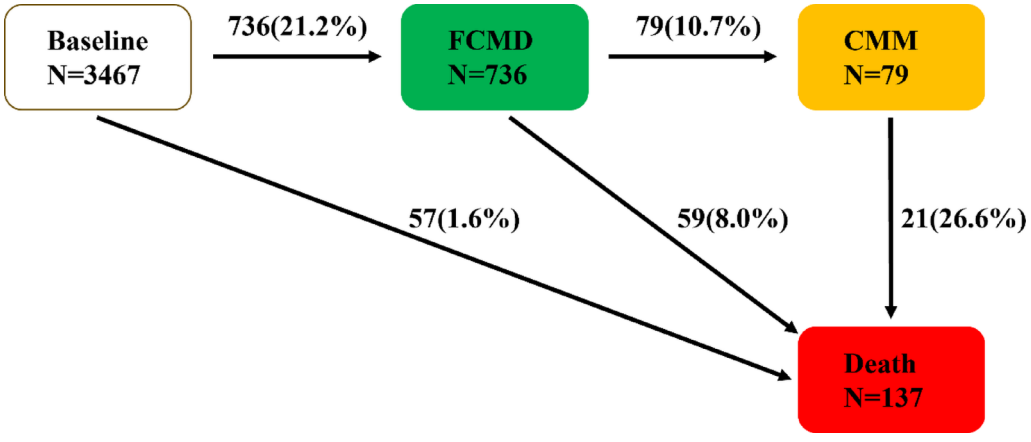


Fig. 2 Counts and percentages of participants in the five transition stages of cardiometabolic outcomes

Table S2). With increasing LAP levels, participants demonstrated higher age, a greater proportion of males, and higher rates of smoking and alcohol intake. They also exhibited elevated WC, BMI, SBP, DBP, TG, TC, LDL-C, FPG, TyG, as well as a higher prevalence of hypertension and antihypertensive medication use, with notably reduced HDL-C levels.

Furthermore, (Additional file 1: Figure S1) illustrates the associations between TyG levels, LAP levels, and outcomes including FCMD, CMM, and all-cause mortality. Elevated baseline TyG levels were associated with an increased risk of FCMD (HR = 1.51, 95% CI 1.31–1.75, $P < 0.001$), CMM (HR = 1.88, 95% CI 1.20–2.94, $P = 0.006$), and all-cause mortality (HR = 1.46, 95% CI: 1.06–2.01, $P = 0.022$). Similarly, higher baseline LAP levels were positively associated with FCMD (HR = 1.007, 95% CI: 1.003–1.009, $P < 0.001$), CMM (HR = 1.008, 95% CI: 1.000-1.016, $P = 0.047$), and all-cause mortality (HR = 1.008, 95% CI 1.003–1.017, $P = 0.002$).

Baseline characteristics based on dual-trajectory groups

In dual-trajectory analysis, a three-group model was identified as the best-fit pattern. (Additional file 1: Table S3). We identified 3 discrete dual-trajectory groups, denoted as low-increasing group (group 1, 61.5%), high-amplitude fluctuation group (group 2, 7.6%), and high-increasing group (group 3, 30.9%). The mean posterior probabilities for Groups 1, 2, and 3 were 0.86, 0.87, and 0.92, respectively. As shown in Fig. 3, these groups displayed distinct trajectories throughout the follow-up period. Group 1 demonstrated a stable and gradual increase in TyG and LAP levels. Group 2 showed pronounced fluctuations, characterized by an initial rapid increase reaching a peak around Year 5, followed by a marked decline to a nadir between Years 15 and 20, and subsequently rebounding with a sharp upward trend. In contrast, group 3 displayed a consistently rapid and steady increase in TyG and LAP levels over the entire follow-up. The median (interquartile range) changes in TyG and LAP levels from Year 0 to Year 25 were 0.5 (0.46–0.57) for the low-increasing TyG group, 0.7 (0.7–0.92) for the high-amplitude fluctuation TyG group, and 0.71 (0.62–0.79) for the high-increasing TyG group. For LAP levels, the changes over this period were 20.27 (11.28–35.71) in the low-increasing group, 33.12 (19.16–64.1) in the high-amplitude fluctuation group, and 29.49 (16.88–48.02) in the high-increasing group (Additional file 1: Table S4).

Table 1 shows the baseline characteristics of dual-trajectory groups. Compared with group 1, participants in groups 2 and 3 were more often male and exhibited higher values in cardiometabolic markers, including WC, BMI, SBP, DBP, TC, TG, and LDL-C, while having significantly lower HDL-C levels. Additionally, group 2 had the highest rates of smoking (38.0%, $P = 0.001$) and alcohol

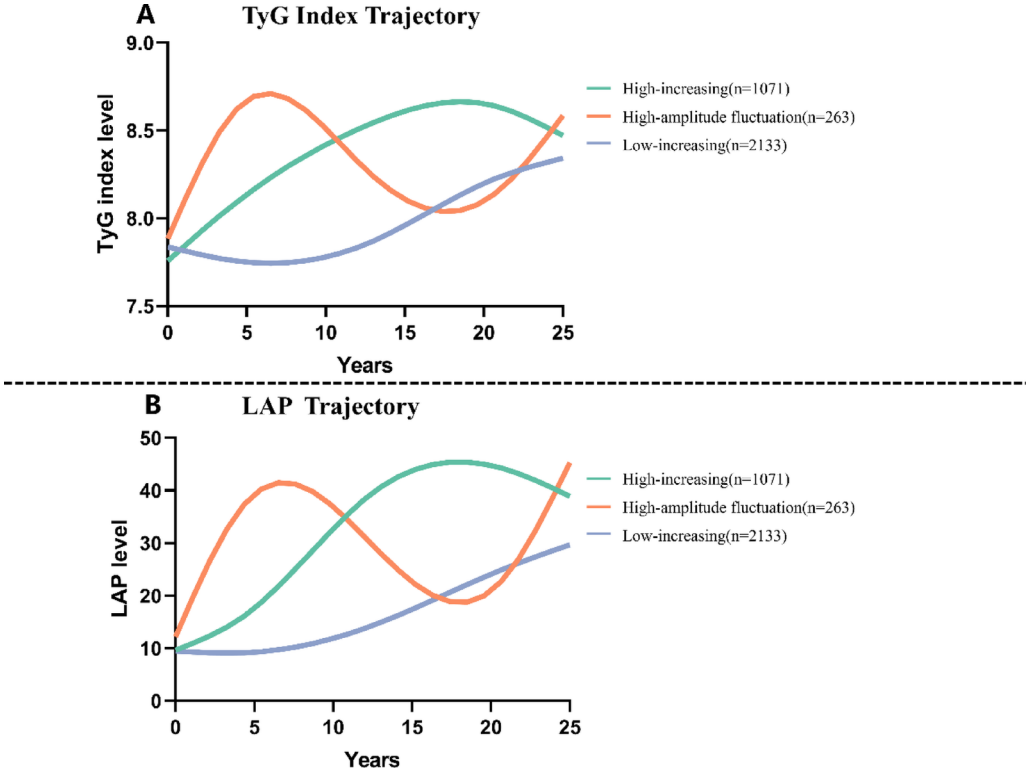


Fig. 3 Dual-trajectory of TyG and LAP levels over 25 years

Table 1 Baseline characteristics of participants stratified by dual-trajectory groups

Characteristics	Dual-trajectory group				
	Total (*n* = 3467)	Group 1 (*n* = 2133)	Group 2 (*n* = 263)	Group 3 (*n* = 1071)	*P* value
Age, mean (SD), years	25.08 (3.59)	25.05 (3.58)	25.30 (3.57)	25.08 (3.62)	0.585
Male, no (%)	1505 (43.40)	763 (35.80)	143 (54.40)	599 (55.90)	< 0.001
White, no (%)	1845 (53.20)	1151 (54.00)	120 (45.60)	574 (53.60)	0.036
Waist circumference, mean (SD), cm	77.49 (10.70)	76.59 (10.68)	80.83 (11.27)	78.46 (10.36)	< 0.001
BMI, mean (SD), kg/m^2	24.42 (4,71)	24.19 (4.65)	25.61 (4.96)	24.59 (4.71)	< 0.001
SBP, mean (SD), mmHg	109.82 (10.65)	109.02 (10.44)	111.70 (11.67)	110.96 (10.66)	< 0.001
DBP, mean (SD), mmHg	68.05 (9.19)	67.71 (9.05)	69.35 (9.43)	68.39 (9.38)	0.008
Smoking status, No. (%)					0.001
Current smoker	942 (27.20)	547 (25.60)	100 (38.00)	295 (27.50)	
Former smoker	1040 (30.00)	662 (31.00)	71 (27.00)	307 (28.70)	
Never smoker	1485 (42.80)	924 (43.30)	92 (35.00)	469 (43.80)	
Alcohol consumption, median (SD), ml/day	11.47 (19.87)	11.09 (19.93)	14.32 (20.32)	11.55 (19.59)	0.045
Educational level, mean (SD), year	13.82 (1.83)	13.89 (1.82)	13.22 (1.86)	13.83 (1.83)	< 0.001
Physical activity, mean (SD), EU	419.07 (297.39)	410.89 (294.60)	432.29 (286.74)	432.12 (305.09)	0.123
TC, mean (SD), mg/dL	177.53 (32.96)	176.95 (32.88)	180.77 (35.99)	177.88 (32.33)	0.189
TG, mean (SD), mg/dL	72.62 (47.82)	73.08 (46.06)	83.01 (66.31)	69.15 (45.44)	< 0.001
LDL-C, mean (SD), mg/dL	109.81 (30.87)	108.38 (30.66)	113.25 (33.04)	111.81 (30.57)	0.002
HDL-C, mean (SD), mg/dL	53.20 (12.84)	53.97 (12.73)	50.92 (12.41)	52.24 (13.05)	< 0.001
FPG, mean (SD), mg/dL	81.93 (10.87)	81.98 (10.39)	83.19 (19.69)	81.53 (8.50)	0.083
TyG, mean (SD)	7.86 (0.51)	7.87 (0.50)	7.95 (0.61)	7.80 (0.51)	< 0.001
LAP, mean (SD)	15.01 (19.07)	14.56 (17.29)	21.35 (31.85)	14.36 (17.97)	< 0.001
Hypertension, no (%)	300 (8.70)	183 (8.60)	27 (10.30)	90 (8.40)	0.617
Antihypertensive medication, no (%)	71 (2.00)	49 (2.30)	7 (2.70)	15 (1.40)	0.183

Group 1: Low-increasing trajectory group; Group 2: High-amplitude fluctuation trajectory group; Group 3: High-increasing trajectory group

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcium; FPG, fasting plasma glucose; TyG, triglyceride-glucose index; LAP, lipid accumulation product

consumption ($P = 0.045$). In contrast, group 1 exhibited the lowest levels of the aforementioned metabolic burden and unhealthy lifestyle factors.

Dual-trajectory and outcomes

Over a mean follow-up of 24.04 ± 3.32 years, 736 (21.2%) individuals developed FCMD, including 428 with T2D, 168 with CHD, and 140 with stroke. Additionally, 79 (2.3%) progressed to CMM, and 137 (4.0%) experienced mortality. The Cox proportional hazards models revealed significant positive associations between dual-trajectory groups and risks of all three aforementioned outcomes. (Table 2). Compared with the low-increasing group, risks for all three outcomes were significantly elevated in the high-amplitude fluctuation group. For instance, in the unadjusted model, the HR for FCMD in the high-amplitude fluctuation group was 1.78 (95% CI 1.40–2.26, $P < 0.001$); after adjusting for demographics and cardiometabolic risk factors (model 2), the HR decreased to 1.39 (95% CI 1.09–1.78, $P = 0.008$), and further adjustment for baseline TyG and LAP levels (model 3) yielded an HR of 1.38(95% CI 1.08–1.77, $P = 0.01$). For CMM risk, HRs (95% CI) for the high-amplitude fluctuation group across models 1 to 3 were 3.27(1.68–6.38), 2.61(1.27–5.34), and 2.63(1.21–5.71), respectively ($P < 0.05$). Similarly, in terms of mortality, the HRs (95% CI) were 3.05(1.87–4.98), 2.17(1.32–3.58), and 2.16(1.30–3.56) across the three models ($P < 0.05$).

The high-increasing group also demonstrated significantly higher risks than the low-increasing group. The HR (95%CI) for FCMD increased from 1.54(1.31–1.79) in model 1 to 1.59(1.36–1.87) in model 3($P < 0.05$). For CMM, HR (95%CI) rose from 2.00(1.23–3.26) in model 1 to 2.68(1.57–4.56) in model 3. Similarly, for all-cause mortality, the HR decreased slightly from 1.85 (1.28–2.66) in model 1 to 1.77 (1.21–2.59) in model 3 ($P < 0.05$). In addition, the VIF values for TyG and LAP ranged from 1.76 to 2.36 across models, all well below the commonly accepted threshold of 5. These findings indicate low

Table 2 Risk of FCMD, CMM and all-cause mortality for dual-trajectory groups

Dual-trajectory groups	No. events/total	Model 1		Model 2		Model 3	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
FCMD							
Low-increasing	382/2133	Reference	1.0	Reference	1.0	Reference	1.0
High-amplitude fluctuation	80/263	1.78(1.40–2.26)	< 0.001	1.39(1.09–1.78)	0.008	1.38(1.08–1.77)	0.01
High-increasing	274/1071	1.54(1.31–1.79)	< 0.001	1.48(1.27–1.74)	< 0.001	1.59(1.36–1.87)	< 0.001
CMM							
Low-increasing	33/2133	Reference	1.0	Reference	1.0	Reference	1.0
High-amplitude fluctuation	12/263	3.27(1.68–6.38)	< 0.001	2.61(1.27–5.34)	0.008	2.63(1.21–5.71)	0.01
High-increasing	34/1071	2.00(1.23–3.26)	0.005	2.33(1.38–3.91)	0.001	2.68(1.57–4.56)	< 0.001
Death							
Low-increasing	63/2133	Reference	1.0	Reference	1.0	Reference	1.0
High-amplitude fluctuation	27/263	3.05(1.87–4.98)	< 0.001	2.17(1.32–3.58)	0.002	2.16(1.30–3.56)	0.003
High-increasing	47/1071	1.85(1.28–2.66)	0.001	1.68(1.16–2.45)	0.006	1.77(1.21–2.59)	0.003

Model 1: Unadjusted

Model 2: Adjusted for baseline age, race, sex, body mass index, education, physical activity, systolic blood pressure, hypertension, antihypertensive medication use, smoking status, alcohol consumption and low-density lipoprotein cholesterol

Model 3: Adjusted for model 2 covariates plus TyG and LAP at year 0

Abbreviation: HR, hazard ratio; CI, confidence interval; FCMD, first cardiometabolic disease; CMM, cardiometabolic multimorbidity

Table 3 Associations between the dual-trajectory groups and CMM transition patterns

Transition pattern	Case	HR (95%CI)*	*P* value
Low-increasing			
Baseline → FCMD	382	Reference	1.0
FCMD → CMM	33	Reference	1.0
CMM → Death	9	Reference	1.0
FCMD → Death	24	Reference	1.0
Baseline → Death	30	Reference	1.0
High-amplitude fluctuation			
Baseline → FCMD	80	1.41 (1.17–1.63)	0.015
FCMD → CMM	12	2.07 (1.53–3.96)	0.023
CMM → Death	6	2.87 (1.19–7.62)	0.041
FCMD → Death	12	2.71 (1.58–5.04)	0.007
Baseline → Death	9	1.14 (0.81–3.15)	0.179
High-increasing			
Baseline → FCMD	274	1.51 (1.33–1.72)	< 0.001
FCMD → CMM	34	1.87 (1.12–2.96)	0.019
CMM → Death	6	1.05 (0.54–3.78)	0.731
FCMD → Death	23	1.54 (0.78–2.34)	0.256
Baseline → Death	18	1.26 (0.84–2.38)	0.079

Models adjusted for baseline age, race, sex, body mass index, education, physical activity, systolic blood pressure, hypertension, antihypertensive medication use, smoking status, alcohol consumption and low-density lipoprotein cholesterol. Abbreviations as in Table 2

*Hazard ratios and 95% confidence intervals were estimated using Bootstrap resampling (1,000 iterations) with bias-corrected and accelerated intervals

multicollinearity and confirm that TyG and LAP provide independent information in relation to cardiometabolic outcomes.

Multi-state analysis

A multi-state analysis was utilized to investigate the role of dual-trajectory groups in shaping transition dynamics across each stage of CMM development. Figure 2 illustrates a gradual increase in mortality risk with the progression of CMM. Table 3 further details the transition risks across trajectory groups. Compared with the low-increasing group, the high-amplitude fluctuation group exhibited significantly higher risks at all stages, including baseline to FCMD (HR 1.41, 95% CI 1.17–1.63, $P = 0.015$), FCMD to CMM (HR 2.07, 95% CI 1.53–3.96, $P = 0.023$), CMM to death (HR 2.87, 95% CI 1.19–7.62, $P = 0.041$), and FCMD to death (HR 2.71, 95% CI 1.58–5.04, $P = 0.007$). In contrast, the high-increasing group exhibited elevated risk primarily in the earlier stages, including baseline to FCMD (HR 1.51, 95% CI 1.33–1.72, $P < 0.001$) and FCMD to CMM (HR 1.87, 95% CI: 1.12-2.96, $P = 0.019$), with no significant differences observed in subsequent mortality stages (CMM to death, HR 1.05, $P = 0.731$; FCMD to death, HR 1.54, $P = 0.256$).

Sensitivity analysis

In participants whose baseline LDL-C was < 4.144 mmol/L, the risks for FCMD, CMM, and all-cause mortality remained significantly elevated in the high-amplitude fluctuation and high-increasing groups, in alignment with the primary analysis (Additional file 1: Table S5). Second, individuals on antihypertensive, cardiac, or both medications were excluded, and this exclusion did not alter the risk patterns observed across dual-trajectory groups (Additional file 1: Table S6). Furthermore, including baseline cancer patients in the analysis showed that elevated risks for FCMD, CMM, and all-cause mortality remained significant in high-amplitude fluctuation and high-increasing groups, underscoring the robustness of these findings (Additional file 1: Table S7). The sensitivity analysis examining dual-trajectory group associations with individual CMM components showed that the

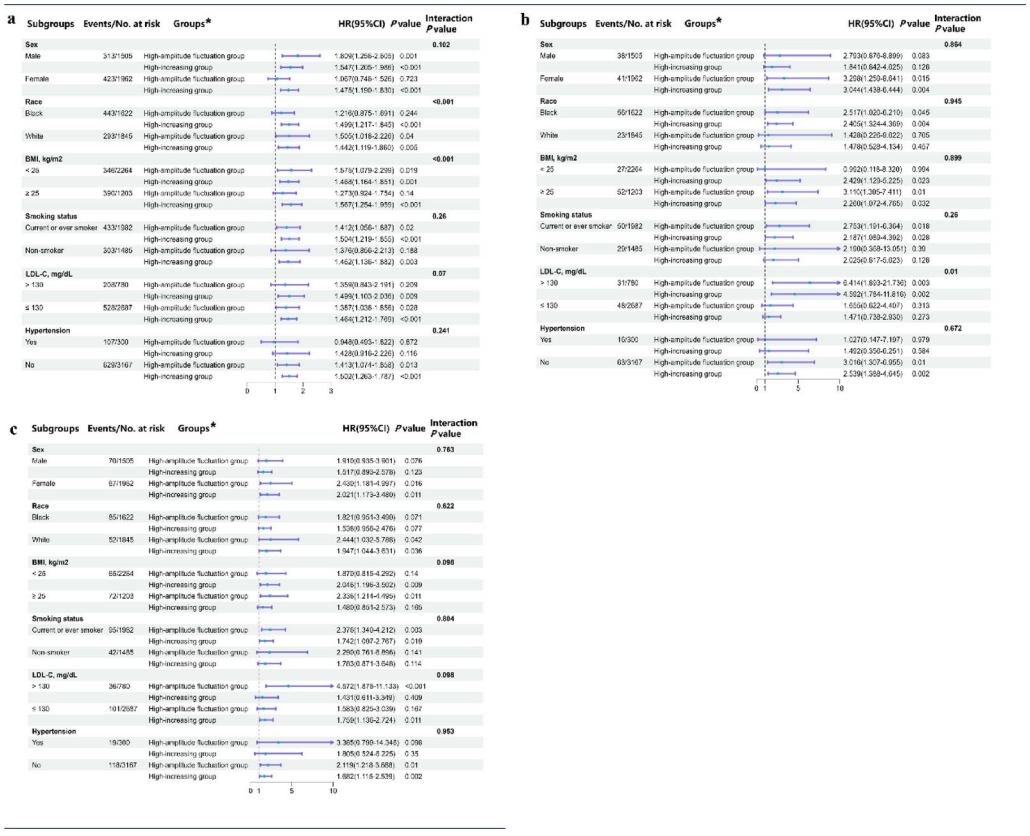


Fig. 4 Association between TyG and LAP dual-trajectory and cardiometabolic outcomes in subgroup analysis. **a** subgroup analysis of the association between Dual-trajectory and FCMD. **b** subgroup analysis of the association between Dual-trajectory and CMM. **c** subgroup analysis of the association between Dual-trajectory and all-cause mortality. Models were adjusted for baseline age, race, sex, body mass index, education, physical activity, systolic blood pressure, hypertension, antihypertensive medication use, smoking status, alcohol consumption and low-density lipoprotein cholesterol. *HR and 95% CI were derived from Cox regression models and low Low-increasing trajectory group was used as the reference in each subgroup analysis

high-increasing group had the higher risk for T2D and stroke, while the high-amplitude fluctuation group was strongly associated with all outcomes (Additional file 1: Table S8). Finally, after adjusted for baseline FPG, the risks for all outcomes remained significantly elevated in the high-amplitude fluctuation and high-increasing groups (Additional file 1: Table S9).

Time-dependent Cox analysis

Additionally, we conducted time-dependent Cox regression analyses to examine whether the associations between dual-trajectory groups and outcomes remained robust after accounting for longitudinal changes in key risk factors. The results showed that, compared with the low-increasing group, individuals in the high-amplitude fluctuation group exhibited significantly elevated risks of FCMD (HR = 1.46, 95% CI 1.14–1.86), CMM (HR = 3.01, 95% CI 1.49–6.08), and all-cause mortality (HR = 2.35, 95% CI 1.43–3.86). Similarly, the high-increasing group also showed significantly increased risks of FCMD (HR = 1.34, 95% CI 1.14–1.57), CMM (HR = 2.42, 95% CI 1.44–4.09), and mortality (HR = 1.71, 95% CI: 1.18–2.50) (Additional file 1: Table S11).

Subgroup analysis

After stratifying participants sex, race, BMI, smoking status, lipid levels, and hypertension revealed that the link between dual-trajectory groups and outcomes remained similar (Fig. 4). For CMM risk, all subgroup interaction effects were non-significant except for the LDL-C subgroup, which showed a significant interaction ($P = 0.01$). Similarly, subgroup analysis for all-cause mortality risk showed high stability, with non-significant interaction P-values across all subgroups ($P > 0.05$). However, FCMD risk exhibited some variability within the BMI and race subgroups, with both showing significant interaction P-values ($P < 0.001$).

Discussion

In this study, based on data from a prospective cohort, we found that elevated baseline TyG and LAP levels in young adulthood were associated with increased risks of FCMD, CMM, and mortality in middle age. We also identified

three distinct dual-trajectory groups for TyG and LAP levels in young adults: low-increasing, high-amplitude fluctuation, and high-increasing. We further found that high-amplitude fluctuation trajectories and high-increasing trajectories of TyG and LAP are significantly associated with the increased risk of FCMD, CMM, and mortality. Unlike traditional single-time measurements, trajectory patterns more intuitively capture the dynamic changes in metabolic status, emphasizing the cumulative impact of insulin resistance and lipid metabolism disorders.

Our findings align with previous studies that have shown elevated TyG and LAP levels to be predictive of cardiometabolic disorders [12, 18, 39, 40]. However, compared with baseline models, dual-trajectory modeling yielded stronger and more consistent associations, particularly for long-term outcomes. For example, the high-amplitude fluctuation group demonstrated over a twofold increased risk of both CMM and mortality, even after adjustment for baseline TyG and LAP levels. These results indicate that the dual-trajectory approach provides additional predictive value by capturing cumulative metabolic exposure and long-term variability, which single-timepoint measurements may fail to reflect. This modeling strategy enables the identification of individuals at persistently elevated or unstable metabolic states—patterns that confer greater risk yet may remain undetected in conventional static assessments. Furthermore, few studies have clarified the co-evolution patterns of these two markers. Given that each of these markers independently predicts cardiometabolic risk, exploring their combined trajectory is crucial to understanding the full extent of metabolic dysregulation. Our research identified a synchronous trend in the dual trajectories of TyG and LAP, which revealed a systemic nature of metabolic imbalance that went beyond single measurements. Several mechanisms may partially account for this synchronous trend. IR disrupts lipid and glucose metabolic pathways, leading to visceral fat accumulation, elevated circulating free fatty acids (FFA), and persistently high levels of pro-inflammatory cytokines like TNF-α and IL-6 [8, 41]. This metabolic dysregulation accelerates triglyceride and glucose production, thereby raising TyG levels, while FFA accumulation further promotes visceral fat deposition, increasing the LAP [42]. Additionally, chronic low-grade inflammation induced by IR exacerbates systemic lipid and glucose metabolic disturbances, reinforcing the link between TyG and LAP [8, 43]. Addressing these disturbances in glucose and lipid metabolism may be crucial for interrupting this cycle and preventing CMM development. These findings underscore the combined impact of TyG and LAP, highlighting the importance of dynamic monitoring of blood glucose, lipids, and fat distribution for effective cardiometabolic health management. Building upon these insights, we further investigated whether the observed associations between trajectory groups and adverse outcomes could be explained by concurrent changes in key metabolic risk factors. To this end, we conducted time-dependent Cox regression analyses incorporating time-updated covariates. Notably, the high-amplitude fluctuation and high-increasing groups remained significantly associated with elevated risks of FCMD, CMM, and mortality. These findings suggest that dual-trajectory patterns reflect a broader and more persistent metabolic imbalance, beyond the effects of individual time-varying risk exposures. Clinically, this reinforces the need for long-term, multi-dimensional risk management strategies aimed at sustaining metabolic stability and reducing cumulative exposure to dynamic stressors.

Numerous studies have demonstrated a link between higher long-term trajectory of TyG and LAP and adverse cardiovascular outcomes [44–49]. However, these studies have primarily concentrated on a single disease stage, without assessing the impact of long-term trajectory of TyG and LAP across various transition stages in the entire progression of CMM-namely, from being CMD-free to developing FCMD, progressing to CMM, and eventually leading to mortality. To overcome these limitations, we utilized a multi-state model that accounts for competing risks as well as transitions across different cardiometabolic stages. Our findings suggest that both the high-amplitude fluctuation and high-increasing groups could impact entire progression of CMM. Furthermore, we found distinct risk distribution patterns between the high-amplitude fluctuation and high-increasing groups. The high-amplitude fluctuation group presents a higher risk that intensifies in all stages of disease progression, while the high-increasing group has a greater impact on the earlier stages. This distinction is likely due to the instability, cumulative metabolic damage, and lack of gradual adaptation caused by metabolic fluctuations. A prospective cohort study revealed that revealed greater TyG variability were causally related to higher incidence of CVD [50]. The underlying mechanism between the high-amplitude fluctuation group and the overall progression of CMM is not fully understood, and we have hypothesized several plausible mechanisms. Frequent fluctuations result in significant changes in insulin resistance, blood glucose, and lipid levels, which place the cardiovascular system in a prolonged state of stress. Thereby the likelihood of systemic inflammation, oxidative stress, endothelial dysfunction and plaque instability is increased which raise the risk of CMM and all-cause mortality [51, 52]. With disease progression, cumulative metabolic damage increases, leading individuals in the high-amplitude fluctuation group to experience multiple fluctuation cycles, repeated stress, and metabolic disorders. Consequently, they are more prone to severe

complications, organ failure, and a significantly higher risk of death [53]. In contrast, although the metabolic indicators of individuals in the high-increasing group continued to rise, the steady upward trend enabled the body to gradually adapt to this metabolic burden, reducing the accumulated inflammation and stress [54]. Therefore, the risk in the high-increasing group is mainly concentrated in the early stages when the cardiovascular system had not fully adapted to metabolic stress, and FCMD and CMM were more likely to occur. With disease progression, metabolic adaptation provides some protection in later stages, resulting in no significant difference in the progression from CMM to mortality or FCMD to mortality. This finding suggests that late-stage intervention has limited effects, emphasizing the importance of early intervention to address metabolic abnormalities and maintain a stable metabolic state, thereby reducing the risks of cardiometabolic disease and all-cause mortality. Adjusting lifestyle factors (e.g., diet management, increased exercise, stable daily routine) and pharmacological intervention to improve IR and reduce visceral fat accumulation may help delay the progression of cardiometabolic disease. Given the high metabolic fluctuation in some individuals, a single time-point intervention may be insufficient for long-term effects. Thus, a dynamic monitoring and individualized management approach is recommended to stabilize metabolic fluctuations and mitigate cumulative systemic stress.

Our analysis also indicates that individuals with higher baseline TyG and LAP levels, as well as those with high-increasing and high-amplitude fluctuation trajectories, display a significantly higher proportion of males, highlighting gender differences in metabolic trajectories. Males are more susceptible to fat accumulation in the visceral area, a pattern linked to lipid metabolism disorders and elevated LAP [55]. Additionally, androgens, such as testosterone, can promote visceral fat accumulation and increase pro-inflammatory factors, thus exacerbating IR and elevating TyG levels [56–58]. Female estrogen, to a certain extent, inhibits the accumulation of visceral fat and plays a protective role [57]. Males also tend to consume a high-calorie diet, which can lead to visceral fat accumulation and metabolic burden [59]. In response to environmental stress or dietary changes, males exhibit greater sensitivity to IR and inflammation, leading to higher metabolic fluctuations [60, 61]. These sex-specific metabolic responses and lifestyle differences jointly contribute to the higher likelihood of males following high-risk metabolic trajectories under increased metabolic load. Furthermore, our subgroup analyses revealed a significant interaction between LDL-C levels and metabolic trajectories in relation to CMM risk. This suggests that LDL-C may amplify the adverse effects of metabolic instability and overload, accelerating systemic inflammation, oxidative stress, and endothelial dysfunction [62]. Further studies are warranted to validate these findings and elucidate potential mechanisms.

This study has several limitations. As an observational cohort study, residual confounding may still exist despite adjustments for multiple factors, and the relatively homogeneous sample may limit generalizability. A potential concern is retrospective classification bias in trajectory modeling, particularly regarding the inclusion of glucose in both TyG and T2D diagnosis. However, this bias was minimized as group-based trajectory modeling classified individuals based on longitudinal patterns rather than predefined disease status, and model selection was guided by BIC and posterior probability to ensure robust classification. Additionally, sensitivity analyses adjusting for baseline FPG confirmed that the associations between dual trajectories and outcomes were independent of baseline glucose levels. The dual-trajectory approach further mitigates concerns by incorporating LAP, a marker of lipid accumulation and visceral fat, reflecting broader metabolic dysfunction beyond hyperglycemia alone. Another limitation is the relatively small number of events in certain transition states, particularly for later-stage transitions, which may introduce variability in risk estimates. This is partly because the cohort is still in midlife, resulting in fewer mortality events at this stage. Bootstrap resampling was employed to enhance the precision of risk estimates. Lastly, the timing of T2D diagnosis was based on periodic assessments and may not reflect the true onset of disease. This delayed ascertainment could lead to imprecise event timing, particularly for transitions to FCMD or CMM. Nonetheless, because all participants were assessed under the same follow-up schedule, any such misclassification is likely to be non-differential and would bias the results conservatively. Future studies with extended follow-up durations, larger and more diverse populations, and alternative trajectory modeling strategies are warranted to validate these findings and further assess the robustness of TyG and LAP as long-term predictors of cardiometabolic multimorbidity.

Conclusion

This study demonstrates that higher TyG and LAP levels in early adulthood are associated with an increased risk of FCMD, CMM, and mortality by midlife. Additionally, chronic exposure to elevated and fluctuating TyG and LAP levels in young adulthood is associated with increased CMM risk, with fluctuating TyG and LAP levels showing higher risks across all stages of CMM development, while consistently high levels primarily impact earlier stages. These findings emphasize the critical role of early intervention and sustained monitoring of insulin resistance and lipid accumulation to mitigate long-term cardiometabolic risks.

Abbreviations

TyG	Triglyceride–glucose index
LAP	Lipid accumulation product
CHD	Coronary heart disease
T2D	Type 2 diabetes
CMDs	Cardiometabolic diseases
CMM	Cardiometabolic multimorbidity
FCMD	First cardiometabolic disease
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	Cardiovascular disease
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
BMI	Body mass index
WC	Waist circumference
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TG	Triglyceride
FPG	Fasting plasma glucose
CRP	C-reactive protein
IR	Insulin resistance
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

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Additional file 1.

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Author contributions

YYZ had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. YYZ, LQZ and JJW contributed to the study design and inception. LQZ, JJW, and ZRZ contributed to the acquisition, analysis, interpretation of data, and drafted the manuscript. QG and LJW contributed to the analysis of the data and interpretation. HZ and ZYZ revised the manuscript. All authors provided a revision of the manuscript for critically important intellectual content and approved the final version of the manuscript.

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Data availability

Data documentation for CARDIA is publicly available at cardia.dopm.uab.edu.

Declarations

Ethics approval and consent to participate

The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Institutional Review Board at Sun Yat-sen Memorial Hospital. Written informed consent was obtained from all participants for data collection.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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