Zhu *et al. Cardiovascular Diabetology* (2025) 24:102
https://doi.org/10.1186/s12933-025-02652-5

Cardiovascular Diabetology

RESEARCH

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Associations of triglyceride glucose-body mass index and the combination of sedentary behavior and physical activity with risks of all-cause mortality and myocardial infarction: a cohort study from the UK biobank

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Abstract

Background Triglyceride glucose-body mass (TyG-BMI) index, sedentary behavior (SB) and physical activity (PA) are independently associated with all-cause mortality and myocardial infarction (MI). However, it remains unclear whether TyG-BMI index and the combination of SB and PA exhibit joint effects on all-cause mortality and MI.

Methods Among 502 356 participants from the UK Biobank, 297 761 eligible participants were selected. The Cox proportional hazards model and the restricted cubic spline regression model were used to assess the associations of TyG-BMI with all-cause mortality and MI. To conduct stratified analysis, participants were classified into four groups by SB (<6 h/d and ≥6 h/d) and moderate to vigorous physical activity (MVPA) (<150 min/wk and ≥150 min/wk). Additionally, the multiplicative interaction was assessed between TyG-BMI and SB & MVPA. Furthermore, to estimate their joint associations, participants were conjointly classified into twelve new groups by TyG-BMI (tertiles) and SB & MVPA (four groups).

Results During a median follow-up of 13.8 and 13.6 years, 21 335 deaths and 9 116 MI were observed, respectively. The dose-response relationship of TyG-BMI with all-cause mortality was U-shaped with a cut-off point at 225.09, whereas the relationship with MI was positive nonlinear with a cut-off point at 266.87. A synergistic effect on all-cause mortality was observed between TyG-BMI tertile 1 and ≥6 h/d SB & <150 min/wk MVPA (*P* for interaction < 0.001). When MVPA ≥ 150 min/wk combined with SB either <6 h/d or not, TyG-BMI tertile 2 showed no significant association with all-cause mortality risk, with HRs(95%CIs) of 0.98 (0.93–1.03) for <6 h/d SB and 1.00 (0.94–1.07) for ≥6 h/d SB. When one of the two healthy behaviors was present (i.e., either <6 h/d SB with <150 min/wk MVPA, or ≥150 min/

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wk MVPA with ≥ 6 h/d SB), its combination with TyG-BMI tertile 1 showed no significant association with MI risk, with HRs(95%CIs) of 1.07(0.95–1.20) and 1.09(0.94–1.25), respectively.

Conclusions TyG-BMI index and the combination of SB and PA were independently and jointly associated with risks of all-cause mortality and MI. Our findings highlight the importance of improving insulin resistance to reduce all-cause mortality risk, particularly in individuals with long-term SB and insufficient PA, who are more susceptible to the adverse effects of TyG-BMI index. In long-term sedentary individuals, meeting PA guidelines (≥ 150 min/wk of MVPA) effectively mitigated risks of all-cause mortality and MI associated with TyG-BMI index.

Keywords Triglyceride glucose-body mass index, Sedentary behavior, Physical activity, All-cause mortality, Myocardial infarction

Introduction

Myocardial infarction (MI) remains one of the major causes of mortality, imposing a substantial burden on society and individuals due to its acute onset, high mortality rate, poor prognosis, and high medical costs [1, 2]. Notably, metabolic disturbances, such as dyslipidemia, glucose intolerance, and obesity, have been identified as major risk factors for MI and related mortality [3, 4]. These factors further contribute to MI and mortality with its prevalence significantly increasing [5].

The triglyceride-glucose (TyG) index, derived from fasting triglycerides (TG) and fasting blood glucose (FBG), serves as a simple surrogate marker of insulin resistance (IR) that could comprehensively assess glycolipid metabolism [6]. More importantly, its combination with adiposity-related indices, such as the triglyceride glucose-body mass (TyG-BMI) index, has been manifested to perform better than TyG index at reflecting IR [7–14]. Previous studies have shown TyG-BMI index could assess risks of MI and mortality, but they mainly focused on population with certain disease such as diabetes, non-alcoholic fatty liver disease, acute myocardial infarction and atrial fibrillation [15–20].

In addition to metabolic disturbance, the American Heart Association and other leading organizations have emphasized sedentary behavior (SB) and physical activity (PA) as modifiable risk factors for cardiovascular disease (CVD) and all-cause mortality [1, 21–25]. SB and PA are interrelated and may coexist clinically, jointly affecting health outcomes [26–29], although long-term SB or insufficient PA was independently associated with increased risks of mortality and MI [4, 30–32]. Furthermore, individuals with long-term SB or insufficient PA are often accompanied by IR, glycolipid metabolism disorder and obesity [33–35]. However, it remains unclear whether TyG-BMI and the combination of SB and PA could synergistically affect all-cause mortality and MI, and whether reducing SB and promoting PA could offset the deleterious associations of TyG-BMI with all-cause mortality and MI.

This study aimed to investigate the interaction and joint associations of TyG-BMI and the combination of SB and PA with risks of all-cause mortality and MI among participants from the UK Biobank.

Methods

Study population

UK Biobank, a large-scale prospective cohort, recruited more than 500 000 participants aged 37 to 73 years from 22 assessment centers across England, Scotland, and Wales between 2007 and 2010. Participants completed a touch-screen questionnaire, had physical measurements taken, and provided biological samples, as described in detail elsewhere [36, 37]. UK Biobank was approved by the North West Multi-Centre Research Ethical Committee (REF: 11/NW/03820), and all participants provided written informed consent for the study [38].

Among the 502 356 participants, we excluded those with missing information on TG ($n = 33\,279$), FBG ($n = 72\,913$), BMI ($n = 3\,107$), sedentary time ($n = 10\,488$), PA ($n = 60\,330$) and covariates ($n = 42\,198$), as well as those with prevalent CVD (including angina pectoris, MI, heart failure and stroke) at baseline. Overall, 297 761 participants were included (Fig. 1). The diagnosis of prevalent CVD (ICD-9: 410–414, 428, 430–434, 436; ICD-10: I20-I25, I50, I60-I64) was obtained through self-reported disease history, medication history and linked hospital admissions data.

Outcome variable

All-cause mortality and incident MI were collected regularly through linked death register data and hospital admissions data. Date and cause of death were obtained from death register data to 31 December 2022. The hospital registry-based follow-up ended on October 31, 2022, in England; August 31, 2022, in Scotland; and May 31, 2022, in Wales [39]. MI was classified using ICD-10 codes (I21-I23, I24.1 and I25.2).

Exposure variable and covariates

The TyG-BMI index was calculated as ln [TG (mg/dl) × FBG (mg/dl)/2] × BMI [7]. BMI was calculated as weight (kg)/height $(m)^2$. The measurements of TG and FBG were analyzed via clinical chemistry (Beckman Coulter

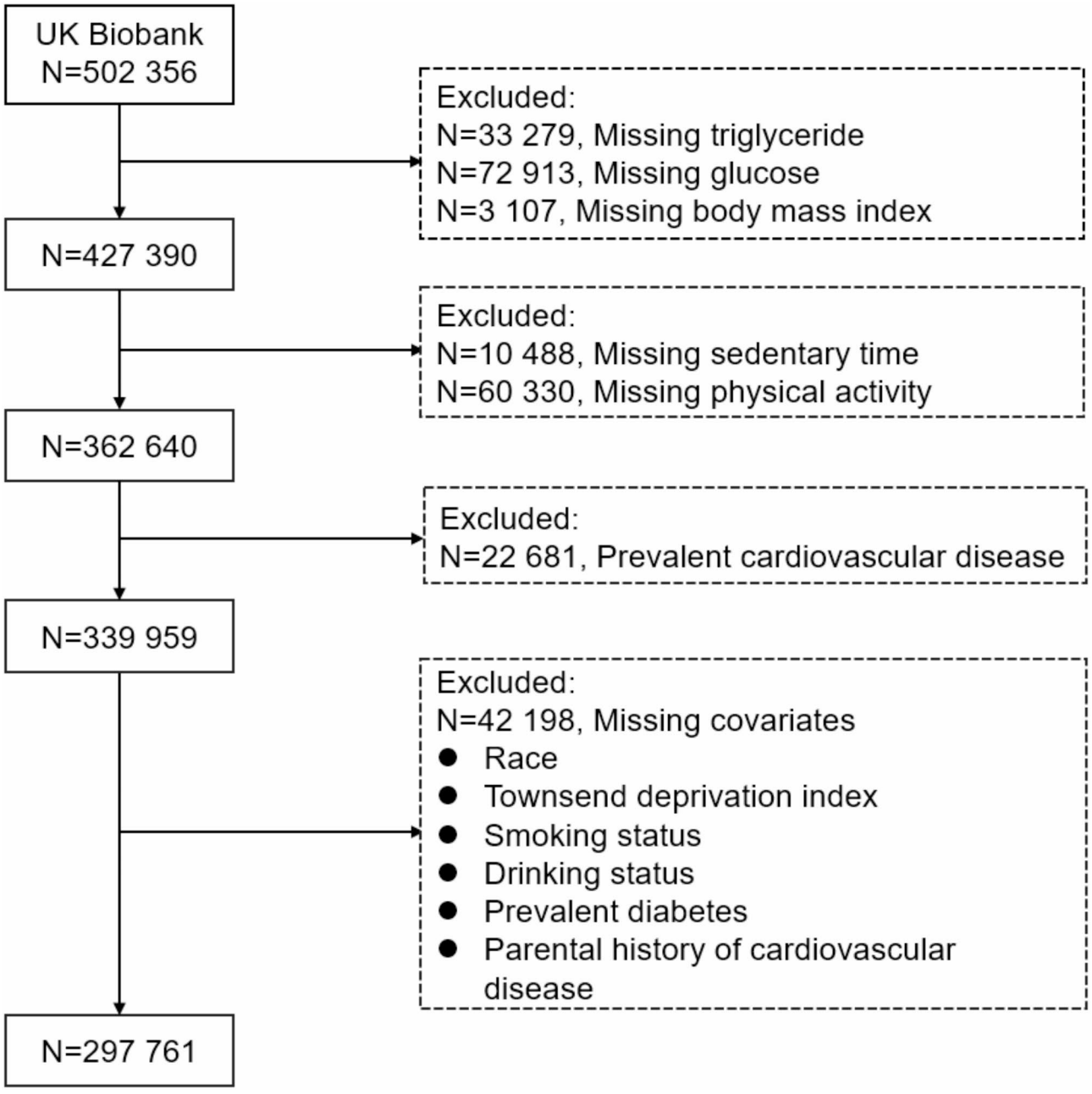

Fig. 1 Flowchart of participants screening

AU5800, LOCATION of device manufacturer). The coefficient of variation for concentration of TG was less than 3% and of FBG was less than 2%. Peripheral venous blood samples from all participants were collected at baseline, and collection procedures of the UK Biobank study were validated [36].

The daily sedentary time was calculated as the sum of self-reported time spent watching TV, driving and using a computer (non-occupational) over the last 4 weeks [40]. We classified SB into <6 h/d and ≥6 h/d, referring to two studies by Stamatakis and Patterson et al. [27, 41]. PA was self-reported and classified into <150 min/wk and ≥150 min/wk moderate to vigorous physical activity (MVPA) according to the guideline-recommended MVPA threshold [42]. Accelerometry devices cannot capture domain-specific activities and can be logistically challenging to implement in low-resource settings due to higher time and resource requirements [43]. In addition, self-reported MVPA has moderate validity ($r = 0.52$) for measuring MVPA among adults in the UK compared with accelerometer data [44]. Therefore, we used

self-reported SB and PA to explore the complex associations of SB & PA and TyG-BMI with health outcomes.

Other covariates included age, sex, race, education level, Townsend deprivation index, smoking status, drinking status, parental history of CVD, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes. Education level was classified into two categories: college or university degree, and others (including A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications). Townsend deprivation index was a score corresponding to the postcode of home dwelling based on the preceding national census data, and a negative value represented high socioeconomic status [45]. Smoking statuses were classified as current smoking or not. Drinking statuses were classified as moderate drinking and others. Moderate drinking was defined as consuming ≤ 8 g per day for women and ≤ 16 g per day for men, according to the dietary guidelines in the United Kingdom [46]. Systolic blood pressure and diastolic blood pressure were measured by using the Omron HEM-7015IT digital BP monitor or a manual sphygmomanometer. The diagnosis of prevalent hypertension (ICD-9 codes 401–405; ICD-10 codes I10-I13, I15, O10), prevalent hyperlipidemia (ICD-9 codes 272; ICD-10 codes E78) and prevalent diabetes (ICD-9 codes 250.00, 250.10, 250.20, 250.90; ICD-10 codes E11) was obtained through self-reported disease history, medication history and linked hospital admissions data.

Statistical analysis

All-cause mortality and MI were recorded and their incidence rate per 1000 person-years was calculated based on incidence and the total follow-up time. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of outcomes. Proportional hazards assumptions were tested by using likelihood ratio test comparing models with and without time-dependent exposure, and we found no significant deviation from the assumption. Testing for linear trends was done by assigning a median value to each group as a continuous variable. Additionally, the restricted cubic spline regression model was used to explore the dose-response association of TyG-BMI index with outcomes. We also classified participants into four groups by SB (<6 h/d and ≥ 6 h/d) and MVPA (<150 min/wk and ≥ 150 min/wk) to investigate associations of SB & MVPA with all-cause mortality and MI.

Furthermore, we conducted a stratified analysis by SB & MVPA groups to explore the associations of TyG-BMI index with all-cause mortality and MI. A product term of SB & MVPA (four groups) and TyG-BMI index (tertiles) was additionally included in the multivariable-adjusted model to assess the multiplicative interaction. The HR (95% CI) of the product term was the measure of interaction on the multiplicative scale. To assess the joint associations, we conjointly classified participants into twelve new groups by SB & MVPA (four groups) and TyG-BMI index (tertiles).

To test the robustness and potential variations in various subgroups, we repeated interaction and joint analyses stratified by age (< 65 and ≥ 65), sex (male and female), race (white and non-white) and education level (college or university degree, and others).

We conducted two sensitivity analyses. First, we excluded participants who had outcomes within the first two years of follow-up to reduce potential reverse causation. Second, we used multiple imputation to impute all missing covariates to test the influence of missing variables.

All analyses were performed using R statistical software version 4.3.2. A two-sided test with $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of study participants according to the tertiles of TyG-BMI index were shown in Table 1. Among the 297 761 participants, 161 567(54.3%) were females, the mean (SD) age at baseline was 56.0 (8.0) years, the mean (SD) BMI at baseline was 27.2 (4.6) kg/m^2, and the mean (SD) TyG-BMI index was 237.1 (48.4). The participants with higher TyG-BMI index were more likely to be males, less educated, most deprived, current smokers, moderate drinkers, and they were more likely to have more SB, less PA, parental history of CVD, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes. The baseline characteristics of study participants according to SB & PA groups were displayed in Supplemental Table 1. The participants with more SB and less PA were more likely to have a higher TyG-BMI index. The baseline characteristics of participants excluded and included in the analysis were displayed in Supplemental Table 2. The participants excluded were more likely to be older, female, less educated, most deprived, and they were more likely to have more SB, less PA and higher TyG-BMI. The baseline characteristics of study participants according to study outcomes were displayed in Supplemental Tables 3 and 4.

Independent association of TyG-BMI index or SB & MVPA with all-cause mortality and MI

Independent associations of TyG-BMI index with all-cause mortality and MI were shown in Table 2. During a median follow-up time of 13.8 years (mean 13.5 years, range 0.01–16.03 years, 4 029 301 person-years), 21 335 deaths were recorded. The mortality rates in TyG-BMI tertile 1 to 3 were 4.18(4.07–4.29), 5.13(5.01–5.25) and

Table 1 Baseline characteristics of participants according to TyG-BMI index tertiles

Variables	TyG-BMI tertile 1 (≤ 212.22)	TyG-BMI tertile 2 (212.22-251.15)	TyG-BMI tertile 3 (>251.15)	Total	*P* value
Number	99,254	99,253	99,254	297,761	< 0.001
Age (yrs)	54.8(8.2)	56.7(8.0)	56.5(7.8)	56.0(8.0)	< 0.001
Sex (%)					< 0.001
Male	31,902(32.1)	50,867(51.2)	53,425(53.8)	136,194(45.7)	
Female	67,352(67.9)	48,386(48.8)	45,829(46.2)	161,567(54.3)	
Race (%)					< 0.001
White	95,381(96.1)	95,111(95.8)	95,076(95.8)	285,568(95.9)	
Black	814(0.8)	1046(1.1)	1305(1.3)	3165(1.1)	
Asian	1786(1.8)	1973(2.0)	1643(1.7)	5402(1.8)	
Other	1273(1.3)	1123(1.1)	1230(1.2)	3626(1.2)	
Educational level (%)					< 0.001
College or university degree	57,122(57.6)	50,346(50.7)	44,962(45.3)	152,430(51.2)	
Others	42,132(42.4)	48,907(49.3)	54,292(54.7)	145,331(48.8)	
Townsend deprivation index (%)					< 0.001
Most deprived	16,179(16.3)	15,478(15.6)	19,716(19.9)	51,373(17.3)	
Intermediate deprived	60,711(61.2)	61,252(61.7)	60,189(60.6)	182,152(61.2)	
Least deprived	22,364(22.5)	22,523(22.7)	19,349(19.5)	64,236(21.6)	
BMI (kg/m^2)	22.9(1.9)	26.6(1.6)	32.0(4.0)	27.2(4.6)	< 0.001
SBP (mmHg)	131.6(18.4)	138.6(18.0)	142.2(17.5)	137.5(18.5)	< 0.001
DBP (mmHg)	78.4(9.6)	82.7(9.6)	86.0(9.6)	82.4(10.1)	< 0.001
Current smoking (%)					0.021
No	89,816(90.5)	89,683(90.4)	89,455(90.1)	268,954(90.3)	
Yes	9438(9.5)	9570(9.6)	9799(9.9)	28,807(9.7)	
Moderate drinking (%)					< 0.001
No	61,292(61.8)	59,322(59.8)	53,411(53.8)	174,025(58.4)	
Yes	37,962(38.2)	39,931(40.2)	45,843(46.2)	123,736(41.6)	
Sedentary behavior (%)					< 0.001
<6 h/d	81,428(82.0)	71,499(72.0)	60,793(61.2)	213,720(71.8)	
≥6 h/d	17,826(18.0)	27,754(28.0)	38,461(38.8)	84,041(28.2)	
Physical activity (%)					< 0.001
<150 min/wk MVPA	31,542(31.8)	35,091(35.4)	43,488(43.8)	110,121(37.0)	
≥150 min/wk MVPA	67,712(68.2)	64,162(64.6)	55,766(56.2)	187,640(63.0)	
Parental history of CVD (%)					< 0.001
No	45,176(45.5)	42,528(42.8)	40,356(40.7)	128,060(43.0)	
Yes	54,078(54.5)	56,725(57.2)	58,898(59.3)	169,701(57.0)	
Prevalent Hypertension (%)					< 0.001
No	63,930(64.4)	46,052(46.4)	30,941(31.2)	140,923(47.3)	
Yes	35,324(35.6)	53,201(53.6)	68,313(68.8)	156,838(52.7)	
Prevalent Hyperlipidemia (%)					< 0.001
No	92,184(92.9)	85,352(86.0)	77,158(77.7)	254,694(85.5)	
Yes	7070(7.1)	13,901(14.0)	22,096(22.3)	43,067(14.5)	
Prevalent Diabetes (%)					< 0.001
No	98,393(99.1)	96,818(97.5)	89,759(90.4)	284,970(95.7)	
Yes	861(0.9)	2435(2.5)	9495(9.6)	12,791(4.3)	
HDL-C (mmol/L)	1.7(0.4)	1.4(0.3)	1.3(0.3)	1.5(0.4)	< 0.001
LDL-C (mmol/L)	3.4(0.8)	3.7(0.8)	3.7(0.9)	3.6(0.9)	< 0.001
TG (mmol/L)	1.1(0.5)	1.7(0.7)	2.4(1.2)	1.7(1.0)	< 0.001
FPG (mmol/L)	4.8(0.7)	5.0(0.9)	5.4(1.6)	5.1(1.2)	< 0.001

Table 1 (continued)

Variables	TyG-BMI tertile 1 (≤ 212.22)	TyG-BMI tertile 2 (212.22-251.15)	TyG-BMI tertile 3 (>251.15)	Total	*P* value
HbA1c (mmol/mol)	34.2(4.1)	35.1(4.9)	37.6(8.2)	35.7(6.1)	< 0.001
TyG-BMI	189.2(16.4)	231.0(11.1)	291.0(37.4)	237.1(48.4)	< 0.001

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate to vigorous intensity physical activity; SBP, systolic blood pressure; TG, triglycerides; TyG-BMI, triglyceride glucose-body mass index

The differences among groups were analyzed using the Chi-squared test for categorical variables, expressed as absolute frequency (%). For continuous variables, one-way analysis of variance or Kruskal–Wallis test was used to analyze the differences among groups, expressed as mean (standard deviation)

Table 2 Independent association of TyG-BMI index with all-cause mortality and MI

	All-cause mortality				MI			
	Incidence/ person-years	Incidence rate/1000 person-year (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Incidence/ person-years	Incidence rate/1000 person-year (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
TyG-BMI (per SD)	21,335/4,029,301	5.29 (5.22–5.37)	1.22 (1.20–1.23)	1.07 (1.06–1.09)	9116/3,847,527	2.37 (2.32–2.42)	1.37 (1.35–1.40)	1.20 (1.18–1.23)
TyG-BMI (tertiles)								
Q 1	5648/1,350,625	4.18 (4.07–4.29)	1.00 (Reference)	1.00 (Reference)	1716/1,307,185	1.31 (1.25–1.38)	1.00 (Reference)	1.00 (Reference)
Q 2	6888/1,343,491	5.13 (5.01–5.25)	1.23 (1.19–1.27)	0.92 (0.89–0.95)	3100/1,283,011	2.42 (2.33–2.50)	1.85 (1.74–1.96)	1.29 (1.21–1.37)
Q 3	8799/1,335,184	6.59 (6.45–6.73)	1.58 (1.53–1.64)	1.07 (1.03–1.11)	4300/1,257,332	3.42 (3.32–3.52)	2.62 (2.48–2.77)	1.59 (1.50–1.69)
			P trend < 0.001	*P* trend < 0.001			*P* trend < 0.001	*P* trend < 0.001

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; SD, standard deviation; TyG-BMI, triglyceride glucose-body mass index

The multivariable-adjusted model was adjusted for age, sex, race, education level, Townsend deprivation index, sedentary behavior, physical activity, smoking status, drinking status, parental history of cardiovascular disease, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes

The SD of TyG-BMI is 48.41

6.59(6.45–6.73) per 1000 person-years, respectively. During a median follow-up time of 13.6 years (mean 12.9 years, range 0.003–15.87 years, 3 847 527 person-years), 9 116 MIs were recorded. The incidence rates of MI in TyG-BMI tertile 1 to 3 were 1.31(1.25–1.38), 2.42(2.33–2.50) and 3.42(3.32–3.52) per 1000 person-years, respectively. Each additional SD of TyG-BMI index was associated with 7% higher risk of all-cause mortality (HR, 1.07; 95%CI, 1.06–1.09) and 20% higher risk of MI (HR, 1.20; 95%CI, 1.18–1.23). Compared with TyG-BMI tertile 1, tertile 3 was associated with a higher risk of all-cause mortality (HR, 1.07; 95%CI, 1.03–1.11), whereas tertile 2 was associated with a lower risk (HR, 0.92; 95%CI, 0.89–0.95). For MI, higher TyG-BMI tertiles were associated with increased risks. The HRs(95% CIs) for tertile 2 and tertile 3 were 1.29(1.21–1.37) and 1.59(1.50–1.69), respectively (*P* for trend < 0.05) (Table 2). The multivariable restricted cubic spline regression model revealed a U-shaped dose-response relationship between TyG-BMI index and all-cause mortality, with a cut-off point at 225.09, whereas a positive nonlinear association with MI was observed, with a cut-off point at 266.87 (all overall *P*<0.001, all nonlinear *P*<0.001) (Fig. 2).

Independent associations of SB & MVPA with risks of all-cause mortality and MI were shown in Table 3. The mortality rates were 4.66(4.56–4.76) per 1000 person-years in <6 h/d SB & ≥150 min/wk MVPA group, 5.12(4.98–5.26) in <6 h/d SB & <150 min/wk MVPA group, 5.85(5.67–6.04) in ≥6 h/d SB & ≥150 min/wk MVPA group and 8.43(8.17,8.70) in ≥6 h/d SB & <150 min/wk MVPA group. The incidence rates of MI in four groups were 2.06(1.99–2.12), 2.09(2.00–2.18), 2.94(2.81–3.08) and 3.46(3.29–3.64) per 1000 person-years, respectively. Compared with <6 h/d SB & ≥150 min/wk MVPA, the remaining three groups were associated with higher risks of all-cause mortality and MI, and the highest risks of all-cause mortality (HR, 1.34; 95%CI, 1.28–1.39) and MI (HR, 1.29; 95%CI, 1.22–1.38) were both observed in ≥6 h/d SB & <150 min/wk MVPA group.

Interaction between SB & MVPA and TyG-BMI index on all-cause mortality and MI

Compared to TyG-BMI tertile 2, both TyG-BMI tertile 1 and TyG-BMI tertile 3 were associated with higher risk of all-cause mortality among participants of various SB & MVPA groups. Furthermore, the association was stronger

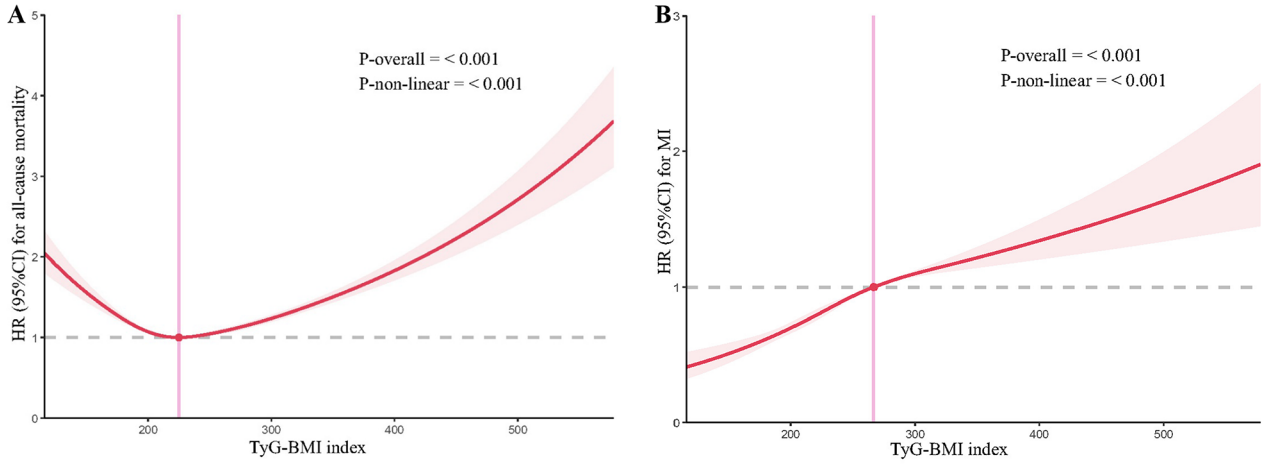

Fig. 2 MI, myocardial infarction; TyG-BMI, triglyceride glucose-body mass index. Each hazard ratio was computed with a TyG-BMI index level of A 225.09 and B 266.87 as the reference. The multivariable-adjusted model was adjusted for age, sex, race, education level, Townsend deprivation index, sedentary behavior, physical activity, smoking status, drinking status, parental history of cardiovascular disease, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes. The solid line and red area represent the estimated values and their corresponding 95% CIs, respectively

Table 3 Independent association of SB & MVPA with all-cause mortality and MI

	All-cause mortality				MI			
	Incidence/ person-years	Incidence rate/1000 person-year (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Incidence/ person-years	Incidence rate/1000 person-year (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
< 6 h/d SB & ≥150 min/wk MVPA	8748/1,876,712	4.66 (4.56–4.76)	1.00 (Reference)	1.00 (Reference)	3701/1,799,173	2.06 (1.99–2.12)	1.00 (Reference)	1.00 (Reference)
< 6 h/d SB & <150 min/wk MVPA	5247/1,025,608	5.12 (4.98–5.26)	1.10 (1.06–1.13)	1.16 (1.12–1.20)	2054/982,187	2.09 (2.00-2.18)	1.02 (0.96–1.07)	1.05 (1.00-1.11)
≥ 6 h/d SB & ≥150 min/wk MVPA	3894/665,164	5.85 (5.67–6.04)	1.26 (1.22–1.31)	1.06 (1.02–1.10)	1855/630,722	2.94 (2.81–3.08)	1.44 (1.36–1.52)	1.11 (1.05–1.17)
≥ 6 h/d SB & <150 min/wk MVPA	3446/461,818	8.43 (8.17–8.70)	1.61 (1.55–1.68)	1.34 (1.28–1.39)	1506/435,445	3.46 (3.29–3.64)	1.69 (1.59–1.79)	1.29 (1.22–1.38)

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; MVPA, moderate to vigorous intensity physical activity; SB, sedentary behavior

The multivariable-adjusted model was adjusted for age, sex, race, education level, Townsend deprivation index, smoking status, drinking status, parental history of cardiovascular disease, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes

among those with TyG-BMI tertile 1 and ≥6 h/d SB & <150 min/wk MVPA (Fig. 3). The HRs(95%CIs) for those with TyG-BMI tertile 1 were 1.03(0.98–1.08) in <6 h/d SB & ≥150 min/wk MVPA group, 1.12(1.04–1.20) in <6 h/d SB & <150 min/wk MVPA group, 1.10(1.01–1.21) in ≥6 h/d SB & ≥150 min/wk MVPA group, and 1.32(1.18–1.46) in ≥6 h/d SB & <150 min/wk MVPA group (HR for interaction, 1.31; 95%CI, 1.16–1.47; *P* for interaction <0.001) (Fig. 3 and Supplemental Table 5). However, the associations of TyG-BMI tertile 3 with all-cause mortality were not substantially different among participants of various SB & MVPA groups, with HRs(95% CIs) of 1.16(1.10–1.22), 1.18(1.10–1.26), 1.17(1.09–1.26), and 1.16(1.07–1.26), respectively (all *P* for interaction >0.05) (Fig. 3 and Supplemental Table 5). Compared to TyG-BMI tertile 1, both TyG-BMI tertile 2 and TyG-BMI tertile 3 were associated with higher risk of MI among individuals of various SB & MVPA groups, whereas the associations were weaker among those in ≥6/d SB & <150 min/wk MVPA group (Fig. 3). The HRs(95%CIs) for those with TyG-BMI tertile 2 were 1.35(1.23–1.49), 1.25(1.10–1.42), 1.23(1.08–1.40), and 1.15(1.01–1.32), respectively (HR for interaction in the ≥6 h/d SB & <150 min/wk MVPA group, 0.80; 95%CI, 0.66–0.97; *P* for interaction = 0.024) (Fig. 3 and Supplemental Table 6). Similarly, the HRs(95%CIs) for those with TyG-BMI tertile 3 were 1.69(1.54–1.85), 1.55(1.37–1.75), 1.57(1.38–1.77), and 1.26(1.09–1.44), respectively (HR for interaction in the ≥6 h/d SB & <150 min/wk MVPA

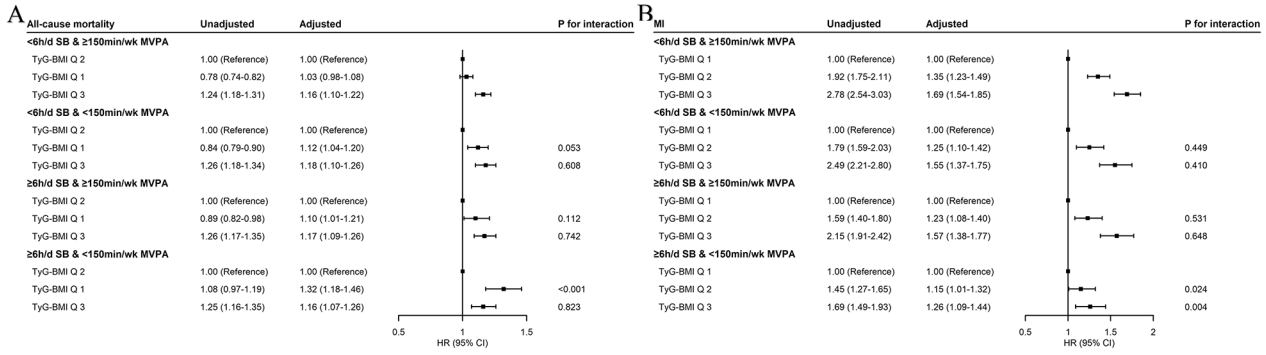

Fig. 3 CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; MVPA, moderate to vigorous intensity physical activity; SB, sedentary behavior; TyG-BMI, triglyceride glucose-body mass index. The P value for interaction was obtained including the product term of TyG-BMI index (tertiles) and SB & MVPA (four categories) in the multivariable-adjusted model. The multivariable-adjusted model was adjusted for age, sex, race, education level, Townsend deprivation index, smoking status, drinking status, parental history of cardiovascular disease, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes. The reference group was set as TyG-BMI Q 2 for all-cause mortality and TyG-BMI Q 1 for MI in each SB & MVPA group

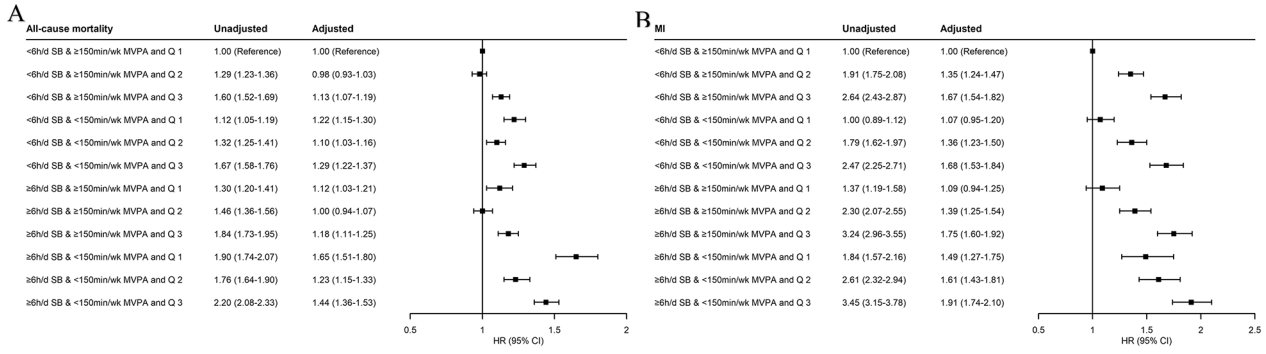

Fig. 4 CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; MVPA, moderate to vigorous intensity physical activity; SB, sedentary behavior; TyG-BMI, triglyceride glucose-body mass index. The multivariable-adjusted model was adjusted for age, sex, race, education level, Townsend deprivation index, smoking status, drinking status, parental history of cardiovascular disease, prevalent hypertension, prevalent hyperlipidemia and prevalent diabetes

group, 0.77; 95%CI, 0.64–0.92; *P* for interaction = 0.004) (Fig. 3 and Supplemental Table 6).

Joint associations of TyG-BMI and SB & MVPA with all-cause mortality and MI

Compared to the reference group (<6 h/d SB & ≥150 min/wk MVPA and TyG-BMI tertile 1), both TyG-BMI tertile 1 and TyG-BMI tertile 3 combined with SB & MVPA were associated with elevated all-cause mortality risk, regardless of SB & MVPA status (Fig. 4). The highest risk of all-cause mortality was observed in individuals with ≥6 h/d SB & <150 min/wk MVPA and TyG-BMI tertile 1 (HR, 1.65; 95%CI, 1.51–1.80). Notably, when sufficient PA was present (i.e., either <6 h/d SB & ≥150 min/wk MVPA, or ≥6 h/d SB & ≥150 min/wk MVPA), the combination with TyG-BMI tertile 2 showed no significant association with all-cause mortality risk, with HRs(95%CIs) of 0.98(0.93–1.03) and 1.00(0.94–1.07), respectively.

Compared to the reference group, both TyG-BMI tertile 2 and tertile 3 combined with SB & MVPA were associated with elevated MI risk, regardless of SB & MVPA status (Fig. 4). The highest risk of MI was observed in individuals with ≥6 h/d SB & <150 min/wk MVPA and TyG-BMI tertile 3 (HR, 1.91; 95%CI, 1.74–2.10). When two healthy behaviors were present (<6 h/d SB & ≥150 min/wk MVPA), the combination with TyG-BMI tertile 2 or tertile 3 remained associated with elevated MI risk, with HRs(95%CIs) of 1.35(1.24–1.47) and 1.67(1.54–1.82), respectively. When one of the two healthy behaviors was present (i.e., either <6 h/d SB & <150 min/wk MVPA, or ≥6 h/d SB & ≥150 min/wk MVPA), the combination with TyG-BMI tertile 1 showed no significant association with MI risk, with HRs(95%CIs) of 1.07(0.95–1.20) and 1.09(0.94–1.25), respectively.

Subgroup analysis and sensitivity analysis

Associations of TyG-BMI with all-cause mortality and MI in each SB & MVPA group were generally similar across age (<65 and ≥65), sex (male and female), and education level (college or university degree, and others) subgroups (Supplemental Tables 7–8, 10–11, 16–17). However, the associations of TyG-BMI with all-cause mortality across various SB & MVPA groups were different between white and non-white participants (Supplemental Table 13).

Specifically, among non-white participants, TyG-BMI tertile 1 was protectively associated with all-cause mortality compared to tertile 2 in other three SB & MVPA groups, but not in the <6 h/d SB & ≥150 min/wk MVPA group (Supplemental Table 13).

The joint associations of TyG-BMI and SB & MVPA with all-cause mortality were stronger in female and highly educated participants (*P* for interaction = 0.005 and 0.028, respectively, in the ≥6 h/d SB & <150 min/wk MVPA and TyG-BMI tertile 3 subgroup) (Supplemental Tables 12 and 18). For MI, the joint associations of TyG-BMI and SB & MVPA were stronger in younger adults (most *P* for interaction <0.05), and in female (*P* for interaction = 0.029 in the ≥6 h/d SB & <150 min/wk MVPA and TyG-BMI tertile 3 subgroup) (Supplemental Tables 9 and 12).

The results remained similar after we excluded participants who had mortality or MI within the first two years of follow-up or used multiple imputation to impute all missing covariates (Supplemental Tables 19–28).

Discussion

In this cohort study, TyG-BMI index and the combination of SB and MVPA were independently and jointly associated with risks of all-cause mortality and MI. The relationship of TyG-BMI index with all-cause mortality was U-shaped with a cut-off point at 225.09, whereas the relationship with MI was positive nonlinear with a cut-off point at 266.87. A synergistic effect was observed between TyG-BMI tertile 1 and ≥6 h/d SB & <150 min/wk MVPA on all-cause mortality, whereas no significant synergistic effect was observed on MI. Notably, whether or not SB was reduced, promoting PA could offset the deleterious association of TyG-BMI tertile 2 with all-cause mortality, whereas SB reduction alone without PA promotion failed to significantly attenuate that association. Both reducing SB and promoting PA demonstrated potential to counteract the deleterious effect of TyG-BMI tertile 1 on MI.

Our findings demonstrated a positive nonlinear relationship between TyG-BMI and MI risk with a cut-off point at 266.87, which is similar to the results of previous studies [47–49]. However, the dose-response association between TyG-BMI and all-cause mortality risk was U-shaped with a cut-off point at 225.09. Similar U-shaped associations have been observed among diabetes patients [15, 50, 51], US adults with osteoarthritis [52], critically ill patients with acute myocardial infarction [17] and patients with chronic kidney disease [53]. Notably, these cut-off points are inconsistent, suggesting that optimal intervention thresholds may vary across populations with distinct metabolic risk profiles. For instance, the TyG-BMI threshold identified in this study is lower than in the diabetic cohort [50], possibly because the baseline TyG-BMI is higher in diabetes resulting from increased IR and adiposity burden [54].

Certain possible mechanisms may explain this U-shaped association. On one hand, lower TyG-BMI index (< 225.09) may imply unstable state of cell membranes, hypoglycemia and frailty-related comorbidities [55–59]. On the other hand, elevated TyG-BMI (> 225.09) may exacerbate mortality through inflammatory responses, reactive oxidative stress, and IR-induced metabolic dysregulation, including glucose intolerance, dyslipidemia, and endothelial dysfunction [60–63]. In the pathogenesis of MI, IR reflected by the TyG-BMI index was confirmed as an important risk factor for coronary artery disease and remains a crucial driver of atherosclerosis [60–64].

Our findings also demonstrated that individuals with long-term SB and insufficient PA exhibit significantly elevated risks of all-cause mortality and MI. These findings are consistent with prior studies, which demonstrated that progressively longer sedentary durations and reduced PA are associated with elevated risk of all-cause mortality and CVD including MI [27–30]. Reducing sedentary time without some PA may be insufficient for reducing mortality risk [27]. Conversely, more PA effectively attenuated the association of sedentary time with mortality risk [26–30]. SB and PA may interact with metabolic pathways linked to the TyG-BMI index. For example, individuals with SB were often accompanied by IR, disordered glucose and lipids metabolism, and activated inflammation [33, 65, 66]. Insufficient PA is also closely associated with metabolic disorders, such as impaired glucose metabolism and obesity [34, 35]. However, it remains unclear whether the associations of TyG-BMI index with all-cause mortality and MI differ across individuals in different SB & PA groups, and whether there is a synergistic effect between TyG-BMI and the combination of SB and PA, highlighting a critical gap in understanding how modifiable behavioral and metabolic risk factors interact to affect clinical outcomes.

Our study identified the highest all-cause mortality risk in subjects with TyG-BMI tertile 1 and the combination of long-term SB and insufficient PA. It is worth mentioning that there was a synergistic effect between TyG-BMI tertile 1 and the combination of long-term SB and insufficient PA, which highlighted the necessity of improving IR, particularly among individuals with long-term SB and insufficient PA, who were more susceptible to the adverse effect of TyG-BMI. Previous studies reported that poor cardiorespiratory fitness exacerbates IR-related mortality [67], while increased PA may mitigate these risks through improvements in cardiorespiratory fitness [24, 68]. In terms of MI, the highest risk was seen among individuals of TyG-BMI tertile 3 combined with long-term SB and insufficient PA, whereas no significant synergistic effect

was observed. Surprisingly, the deleterious association of elevated TyG-BMI index with MI appears to be weaker among those with long-term SB and insufficient PA. This counterintuitive finding should be validated by large-scale randomized controlled trials in the future.

Furthermore, our study found that when sufficient PA (≥ 150 min/wk MVPA) was present, whether with ≥ 6 h/d SB or not, the combination of SB and PA with TyG-BMI tertile 2 showed no significant association with all-cause mortality, whereas SB reduction alone without PA promotion failed to significantly attenuate that association, underscoring the potential of PA to counteract the deleterious effects of TyG-BMI tertile 2 on all-cause mortality, in long-term sedentary populations. Additionally, when one of the two healthy behaviors was present (i.e., either <6 h/d SB & <150 min/wk MVPA, or ≥ 6 h/d SB & ≥150 min/wk MVPA), its combination with TyG-BMI tertile 1 showed no significant association with MI risk, which indicated that either SB reduction or PA promotion alone could offset the risk of MI among individuals with TyG-BMI tertile 1. When engaging in both < 6 h of SB and meeting PA guidelines, those with tertile 2 and tertile 3 of TyG-BMI still had a higher MI risk, suggesting even with low SB and high PA, metabolic abnormalities may still be important drivers of MI. TyG-BMI may be an important clinical biomarker worthy of frequent monitoring. To sum up, in long-term sedentary populations, PA promotion can effectively mitigate risks of all-cause mortality and MI associated with TyG-BMI index.

In subgroup analyses, stronger joint associations were observed in female, highly educated adults on all-cause mortality, and in younger, female adults on MI. Estrogen's role in modulating adiponectin and insulin sensitivity may explain heightened metabolic vulnerability among women [69]. Highly educated individuals are more likely to engage in sedentary occupations, such as white-collar jobs, which often lack opportunities for PA in the workplace [70, 71]. This occupational environment may exacerbate the synergistic effects of TyG-BMI, SB and PA, contributing to heightened health risks. The joint association seemed to be stronger in younger than in older adults. One potential reason might be that the elderly are more likely to have multiple comorbidities and be exposed to more risk factors for CVD, which to some extent undermined the joint effects of TyG-BMI, SB and PA on MI. However, these hypotheses require validation in the future.

Major strengths of this study are the large sample size from a well-established nationwide cohort in the UK, which allowed us to perform the interaction and joint analyses with sufficient statistical power. We also conducted sensitivity analyses to show the robustness of the findings. Importantly, our work highlights the need to integrate metabolic and lifestyle profiling for risk stratification and targeted interventions, which is a novel contribution. Limitations still existed in our study. First, we could not capture the SB & PA trajectories as well as TyG-BMI index changes, so the observed associations might be attenuated due to nondifferential misclassification bias. Future studies with repeated measurements are preferred. Second, SB and PA were self-reported and therefore likely prone to recall or social desirability bias. Third, the number of participants and events might be insufficient among the non-white subgroup and the results should be cautiously interpreted. Finally, although we adjusted for some potential confounding factors as much as possible, residual confounding was still possible and causal inference cannot be made because of the nature of observational studies.

Conclusions

Based on a large-scale prospective UK cohort, TyG-BMI index and the combination of SB and PA were found to be independently and jointly associated with risks of all-cause mortality and MI. A synergistic effect between TyG-BMI tertile 1 and long-term SB with insufficient PA on all-cause mortality highlights the importance of improving IR, particularly in individuals with long-term SB and insufficient PA, who are more susceptible to the adverse effects of TyG-BMI index. Meeting PA guidelines (≥ 150 min/wk of MVPA) effectively mitigated risks of all-cause mortality and MI associated with TyG-BMI index in long-term sedentary populations.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
FBG	Fasting blood glucose
HR	Hazard ratio
IR	Insulin resistance
ICD-9	International statistical classification of disease, 9th revision
ICD-10	International statistical classification of disease, 10th revision
MI	Myocardial infarction
MVPA	Moderate to vigorous intensity physical activity
PA	Physical activity
SB	Sedentary behavior
SD	Standard deviation
TG	Triglyceride
TyG	Triglyceride-glucose
TyG-BMI	Triglyceride glucose-body mass index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02652-5.

Supplementary Material 1

Acknowledgements

We are grateful to the UK Biobank participants.

Author contributions
Study conception: LT and QMK; study design: YZ, TCY, LT and QMK; data extraction and analyses: YZ and TCY; results presentation and interpretation: YZ and QMK; manuscript drafting and revising: YZ, TCY, QMK and LT; The work reported in the paper has been performed by the authors, unless clearly specified in the text. All authors read and approved the final manuscript.

Funding
This work was not supported.

Data availability
The UK Biobank data are available directly from UK Biobank upon submission of a data request proposal (www.ukbiobank.ac.uk/).

Declarations

Ethics approval and consent to participate
UK Biobank was approved by the North West Multi-Centre Research Ethical Committee (REF: 11/NW/03820), and all participants provided written informed consent for the study consent for publication.

Competing interests
The authors declare no competing interests.

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Received: 18 December 2024 / Accepted: 17 February 2025
Published online: 01 March 2025

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