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# Triglyceride-Glucose Index, Genetic Susceptibility, and Trajectory of Microvascular Multimorbidity in Type 2 Diabetes

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**Abstracts:**

**Background:** The role of the triglyceride-glucose (TyG) index in the progression of diabetic microvascular complication (DMC) multimorbidity remains unclear. Moreover, its interaction with genetic susceptibility to type 2 diabetes (T2D) has not been fully elucidated.

**Methods:** This study included T2D patients from the UK Biobank. Primary outcomes were the incidence of first DMC and DMC multimorbidity (including retinopathy, neuropathy, and nephropathy). Multivariable Cox regression and multistate models were used to assess associations between the TyG index and DMC progression. Interaction analyses examined the joint association of the TyG index and T2D genetic risk.

**Results:** A total of 19,512 T2D patients were included, with a median follow-up of 12.9 years. Among them, 5,875 (30.11%) developed a first DMC, and 1,314 (22.37%) progressed to multimorbidity. Each 1-SD increase in TyG was associated with a 19% increased risk of first DMC and a 38% higher risk of multimorbidity. Multistate models showed TyG was a significant predictor of progression from first DMC to multimorbidity (HR = 1.25; 95% CI: 1.15–1.37; $P < 0.001$), particularly among those with retinopathy (HR = 1.39) or nephropathy (HR = 1.14). A combined

association was observed between high TyG index and elevated genetic risk, demonstrating a stepwise increase in risk for DMC onset and progression.

**Conclusions:** In this large, population-based cohort of T2D patients, an elevated TyG index independently predicted both the onset and progression of DMC multimorbidity. This association was particularly evident in patients with retinopathy or nephropathy, with the highest risk observed among individuals with higher genetic risk, highlighting the potential utility of TyG for risk stratification and precision prevention strategies.

## Background

Diabetic microvascular complications (DMCs), including retinopathy, nephropathy, and neuropathy, contribute substantially to diabetes-related mortality and disability, accounting for 30–40% of global disease burden[1–3]. These complications frequently progress from single-organ involvement to multimorbidity as vascular damage accumulates[4,5], and individuals with multi-organ DMCs face a 2–6-fold increase in all-cause mortality[6]. Despite their clinical importance, the longitudinal progression patterns of DMC multimorbidity remain poorly understood, and reliable biomarkers to predict such trajectories are still lacking.

The triglyceride-glucose (TyG) index, a surrogate marker of insulin resistance (IR), integrates lipid and glucose metabolism and is readily measurable in clinical settings[7–10]. Prior studies have linked elevated TyG to individual DMC subtypes in cross-sectional and short-term longitudinal studies [11–14]. However, its role in predicting the transition from a single DMC to multimorbidity has not been systematically evaluated. Furthermore, both insulin resistance and genetic predisposition are known contributors to T2D pathophysiology and microvascular complications[15,16]. While polygenic risk scores (PRS) for T2D are increasingly used to stratify

genetic susceptibility, little is known about how TyG-related metabolic risk interacts with genetic risk to influence the trajectory of DMC progression.

To address these gaps, we leveraged data from the UK Biobank to map the longitudinal trajectories of DMC progression in patients with T2D, examine the association between the TyG index and both the onset and development of DMC multimorbidity, and explore whether this association is influenced by genetic susceptibility to T2D. Our findings aim to provide new insights into the interplay between metabolic and genetic risk factors in shaping the burden of diabetic microvascular disease.



## Methods

### *Participants*

The study utilized data from the UK Biobank, a nationwide prospective cohort that recruited over 500,000 volunteers aged 40–69 years across the UK since 2006. They conducted questionnaires through touch screens to collect baseline information. The UK Biobank study obtained written informed consent from all volunteers and ethical approval from the Northwest Multicenter Research Ethics Committee[17].

Participants with type 2 diabetes (T2D) were included in this study. Baseline diabetes mellitus was defined according to the following criteria: (1) a diagnosis history of diabetes by a physician; (2) baseline diabetes was determined through verbal interviews conducted by experienced healthcare professionals; (3) self-reported use of diabetes-related medications; (4) baseline glycated haemoglobin (HbA1c) concentration ≥ 48 mmol/mol; or (5) a random blood glucose concentration ≥ 7.0 mmol/L if measured ≥ 8 hours after the last meal, or ≥ 11.1 mmol/L if measured within 8 hours postprandially. T2D was defined as diabetes excluding type 1 diabetes (ICD-10 code E10), malnutrition-related diabetes (E12), other specified diabetes (E13), and unspecified diabetes (E14)[18].

Exclusion criteria were as follows: (1) presence of DMCs at baseline; (2) missing data required for the calculation of the TyG index; (3) missing genetic risk score data; (4) participants who were lost to follow-up or formally withdrew; and (5) lack of other relevant covariate data.

### *Definitions of TyG index*

The TyG index was calculated using fasting blood glucose (FBG) and triglyceride (TG) levels measured at baseline. The formulas used was: TyG index = Ln [TG (mg/dL) × FBG (mg/dL) /

2].

### *Outcomes*

The primary outcomes of interest were first DMC and DMC multimorbidity. Secondary outcomes included death and individual DMC subtypes, including diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. First DMC was defined as the initial occurrence of any DMC during follow-up. DMC multimorbidity was defined as the coexistence of two or more DMCs during follow-up. All DMCs were identified from hospital admission records using ICD-9 and ICD-10 codes from the World Health Organization (Table S1) [19]. Patients were followed until the onset of DMCs, death, or October 31, 2022, whichever occurred first.

### *Genetic Susceptibility of T2D*

We used polygenic risk scores (PRS) for type 2 diabetes (T2D) to assess the association between the TyG index and DMC multimorbidity across varying levels of genetic risk. The T2D PRS was obtained from the UK Biobank PRS release, which was generated using the PRS-CS Bayesian regression framework with LD information derived from the 1000 Genomes European reference panel[20]. The model was trained using the DIAMANTE consortium T2D GWAS summary statistics. PRS values were

computed by summing per-variant effect sizes weighted by allele dosage, and were subsequently standardized to have a mean of zero and unit variance within ancestry groups. Participants were categorized into low, intermediate, and high genetic risk groups according to PRS tertiles.

Genotyping, imputation, phasing, and quality control followed previously published methods[21]. Further details are available on the UK Biobank website (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=300).

***Covariates***

We collected a comprehensive set of baseline covariates. These included sociodemographic characteristics (age, sex, ethnicity, and townsend deprivation index [TDI]), lifestyle factors (smoking status, drinking status, physical inactivity, sleep status, and diet quality), and clinical parameters (hyperglycemia [HbA1c], diastolic blood pressure [DBP], systolic blood pressure [SBP], high density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], body mass index [BMI], diabetes duration and medication use).

Higher TDI scores indicated greater socioeconomic deprivation. Physical inactivity was assessed based on self-reported

types and frequency of activity over the past four weeks [22]. Participants were classified as physically inactive if they reported no or light activity once per week or less. Healthy sleep was defined as a sleep duration between 7 and 9 hours per day[23]. According to previous studies, dietary quality was assessed using a 10-component score aligned with cardiovascular health guidelines and comparable to the Mediterranean diet[24,25]. Components included intake of fruit, vegetables, whole grains, fish/shellfish, dairy, vegetable oils, refined grains, processed and unprocessed meats, and sugar-sweetened beverages. For each component, participants received 1 point if their intake met recommended levels.

***Statistics Analysis***

Baseline characteristics were compared across tertiles of the TyG index. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data, or median (interquartile range [IQR]) for skewed data. Group differences were assessed using one-way ANOVA for normally distributed variables, and the Kruskal-Wallis test for non-normally distributed variables. Categorical variables were expressed as frequencies (percentages), with between-group differences evaluated by the chi-square test.

We employed multivariable Cox proportional hazards models to examine the associations between the TyG index and the risk of first DMC, DMC multimorbidity, and each individual first DMC subtype (diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy). Covariates adjusted for in the models included age, sex, ethnicity, TDI, smoking and drinking status, LDL-C, HDL-C, systolic and diastolic blood pressure, diabetes duration, genetic risk score for T2D, dietary quality, sleep duration, physical activity, and medication use. To assess the dose-response relationship between the TyG index and outcomes, restricted cubic spline regression with four knots was employed. Further, subgroup analyses stratified by T2D polygenic risk scores were conducted to evaluate potential effect modification in the association between the TyG index and DMC multimorbidity. Interactions were assessed using likelihood ratio tests.

A multistate model was used to examine the role of the TyG index in the progression of DMCs, including transitions from no DMC to first DMC, DMC multimorbidity, and death[26]. For events occurring on the same day, standard methods were applied by assigning the preceding event 0.5 days before the subsequent one (e.g., first DMC 0.5 days before DMC multimorbidity)[26,28]. In

secondary analyses, six additional transitions based on diabetic retinopathy, neuropathy, and nephropathy were modeled to evaluate subtype-specific associations. Hazard ratios (HRs) were calculated for progression risks from baseline to each subtype of the first DMC.

To assess the robustness of the findings, two sensitivity analyses were performed. First, for participants who experienced state transitions on the same day, different event interval delays (6 months, 1 year, or 5 years) were applied, or these participants were excluded. Second, to minimize the potential impact of pre-existing conditions, individuals who developed outcome events within the first two years of follow-up were excluded. The analyses were then repeated accordingly. All sensitivity analyses were performed using fully adjusted models consistent with the covariates included in the primary analyses. All methods were performed in accordance with the STROBE guidelines, relevant institutional regulations, and the principles of the Declaration of Helsinki.



## Results

### *Baseline Characteristics*

A total of 19,512 patients were included in the study (Figure S1). The median age was 61 years, and 60.87% were male. The

median duration of diabetes was 5 years, with 56.38% having diabetes for more than 3 years. The median TyG index was 9.23. The mean HbA1c level was 6.71%, and 11.71% of patients used insulin.

Table 1 shows differences among participants with different TyG levels in demographics, lifestyle, metabolic indicators, and medication use. Compared with the lowest tertile, participants in the highest TyG tertile were younger, more likely to be male and White, and had higher BMI, blood pressure, HbA1c, and LDL-C, but lower HDL-C. They also had longer diabetes duration, were less physically active, reported poorer sleep, and used more insulin, lipid-lowering, and antihypertensive medications.



### *TyG and DMC Multimorbidity Risk*

After a median follow-up of 12.9 years, 5,875 participants developed at least one DMCs (Figure 1). Among patients with any DMCs, 1,314 developed DMC multimorbidity. Subtype-specific analyses of first DMC showed that the incidence rates were 2.55% for diabetic neuropathy (495/19,512), 14.72% for diabetic nephropathy (2,872/19,512), and 12.85% for diabetic retinopathy (2,508/19,512).

Adjusted survival curves and heatmap indicated a progressively higher cumulative incidence of first DMC and DMC multimorbidity across increasing TyG index levels (Figure S2). Restricted cubic spline analysis revealed a J-shaped dose–response relationship between the TyG index and the risk of DMCs (Figure S3). The Cox proportional hazards model showed that each 1-SD increase in the TyG index was associated with a 17% higher risk of first DMC (HR = 1.17; 95% CI: 1.13–1.21; P < 0.001) and a 35% higher risk of DMC multimorbidity (HR = 1.35; 95% CI: 1.26–1.46; P < 0.001) in the crude model (Table 2). These associations remained statistically significant after adjusting for lifestyle factors and relevant laboratory indicators. Further subtype analysis revealed that each SD increase in TyG was associated with a 16% higher risk of diabetic nephropathy, 20% higher risk of diabetic retinopathy, and 54% higher risk of diabetic neuropathy (Table 2).



### *TyG and Progression of DMC Multimorbidity*

We then applied a multi-state model to assess the effect of TyG on the risk of DMC multimorbidity progression and mortality over time (Table 3). A higher TyG index was associated with a 19% increased risk of developing first DMC from the initial state (HR =

1.19, 95% CI 1.14–1.24; P < 0.001), but showed no significant association with risk of death from the initial state. Among patients with first DMC, a higher TyG index was associated with a 25% increased risk of progression to DMC multimorbidity (HR = 1.25, 95% CI 1.15–1.37; P < 0.001) and a 10% increased risk of death (HR = 1.10, 95% CI 1.01–1.21; P = 0.034). However, TyG was not significantly associated with death risk among patients with DMC multimorbidity. Figure 2 illustrates the dose-response relationship between the TyG index and the risk of DMC multimorbidity.

Further subtype-specific multi-state analyses revealed distinct progression patterns from first DMC to multimorbidity. Patients initially diagnosed with diabetic retinopathy exhibited the highest progression risk (HR = 1.39, 95% CI 1.20–1.61; P < 0.001), followed by those with diabetic nephropathy (HR = 1.14, 95% CI 1.01–1.29; P = 0.041). Although the risk was elevated for diabetic neuropathy (HR = 1.16, 95% CI 0.89–1.52), it was not statistically significant (P = 0.277).

***Joint association of TyG and T2D genetic risk.***

As shown in Table S2, no statistically significant multiplicative interaction between the TyG index and the T2D polygenic risk

score was observed (P for interaction = 0.7). Figure 3 further illustrates the joint association of TyG and genetic risk, showing a stepwise increase in the risk of DMC outcomes with higher TyG levels and greater genetic susceptibility.

### *Sensitivity Analyses*

Sensitivity analyses confirmed the robustness of the main findings. The associations remained consistent when events occurring on the same day were either excluded or handled using different time intervals (e.g., 6 months, 1 year, or 5 years) (Table S3). Similar results were also observed after excluding participants who developed outcomes within the first two years of follow-up (Table S4, Table S5).



## Discussion

In this large, community-based national prospective cohort, a higher TyG index predicted the progression trajectory of DMC multimorbidity. Disease-specific transitions showed that TyG was significantly associated with the onset of retinopathy, nephropathy, and neuropathy, and further promoted progression from initial

retinopathy and nephropathy to DMC multimorbidity. Elevated TyG levels, together with higher T2D genetic risk, were associated with an increased risk of DMC multimorbidity progression.

Despite growing recognition by the American Diabetes Association[29], few studies have examined the progression, and mortality of DMC multimorbidity. A meta-analysis of 26 cross-sectional studies revealed strong correlations among microvascular complications: retinopathy was significantly associated with nephropathy (OR = 4.64) and neuropathy (OR = 2.22); nephropathy was linked to retinopathy (OR = 2.37); and neuropathy was associated with retinopathy (OR = 1.73). However, no significant correlation was observed between nephropathy and neuropathy[30]. Thus, the longitudinal patterns and risks of progression among these complications remain unclear. This study, based on a large cohort of patients with type 2 diabetes, is the first to clarify the progression risk of DMC multimorbidity. In our cohort, over 13 years of follow-up, 30.1% developed a first DMC—most commonly neuropathy—and 22.4% of them progressed to multimorbidity. Mortality was significantly higher among those with DMC multimorbidity (44.4%) than those with a single DMC (23.2%), consistent with previous reports[31,32]. Therefore, it is

necessary to identify predictors of its longitudinal progression.

Although previous studies have demonstrated significant associations between the TyG index and various subtypes of DMC (such as retinopathy, nephropathy, and neuropathy)[33–35]. systematic investigations into its role in the progression of DMC multimorbidity remain lacking. More importantly, lifestyle factors—such as physical activity and sleep—also play critical roles in cardiometabolic diseases, yet few studies have accounted for their confounding effects. In our study, even after adjusting for key lifestyle factors, the TyG index remained significantly associated with the onset of retinopathy, nephropathy, and neuropathy, and promoted progression from initial retinopathy and nephropathy to DMC multimorbidity.



The TyG index, as a surrogate marker of IR, reflects the combined effects of hyperglycemia and hypertriglyceridemia—two metabolic abnormalities that converge on several pathogenic pathways underlying diabetic microvascular complications. A strong correlation exists between DMCs subtypes, particularly diabetic nephropathy and retinopathy, with comparable pathogenic mechanisms[36,37].

Hyperglycemia drives microvascular injury through several

well-characterized mechanisms[38–40]. First, increased flux through the polyol pathway leads to sorbitol accumulation, NADPH depletion, and impaired synthesis of reduced glutathione, thereby compromising cellular antioxidant defenses. Second, enhanced formation of advanced glycation end products (AGEs) causes cross-linking of extracellular matrix proteins and vascular basement membrane thickening; AGEs also activate their receptor (RAGE), triggering downstream inflammatory cascades via nuclear factor-κB (NF-κB) signaling. Third, activation of protein kinase C (PKC) isoforms, particularly PKCβ and PKCδ, impairs endothelial nitric oxide synthase (eNOS) activity, increases vascular permeability, and promotes expression of vascular endothelial growth factor (VEGF). Fourth, increased hexosamine pathway activity modifies signaling proteins and transcription factors through O-GlcNAcylation. Importantly, mitochondrial overproduction of reactive oxygen species (ROS) serves as a unifying upstream trigger for these pathways, amplifying oxidative stress and cellular damage[40].

Elevated triglycerides, the other component of the TyG index, contribute to microvascular injury through lipotoxicity and exacerbation of insulin resistance. Hypertriglyceridemia promotes

endothelial dysfunction via lipid peroxidation, upregulation of vascular adhesion molecules, and enhanced platelet activation and aggregation[37]. Free fatty acids released from triglyceride-rich lipoproteins directly impair insulin signaling through activation of PKC and inhibitory phosphorylation of insulin receptor substrate-1 (IRS-1), perpetuating a vicious cycle of metabolic dysfunction[41]. These alterations collectively impair vasodilation, promote thrombosis, and diminish fibrinolysis, thereby elevating risks for both nephropathy and retinopathy[37,42].

In peripheral nerves, insulin resistance and hyperglycemia act synergistically to impair axonal function and Schwann cell integrity[43]. Schwann cells express insulin receptors, and impaired insulin signaling reduces neurotrophic support—including nerve growth factor (NGF) and neurotrophin-3 (NT-3)—while promoting mitochondrial dysfunction and oxidative damage. The polyol pathway is particularly active in peripheral nerves due to the high expression of aldose reductase and insulin-independent glucose uptake, making these tissues especially vulnerable to hyperglycemia-induced injury[44,45]. Notably, IR has been implicated in diabetic neuropathy pathogenesis for over a decade. The longitudinal Rochester Diabetic Neuropathy Study further

corroborates IR's role in neuropathy development[42].

Regarding mortality risk, our multistate analysis showed that the TyG index was not significantly associated with the transition from baseline to death (HR = 1.04, 95%CI 0.97–1.11; P = 0.241), whereas mortality risk was significantly elevated among patients who had already developed microvascular complications (HR = 1.10, 95%CI 1.01–1.21; P = 0.034). This finding positions microvascular complications as a mortality accelerator rather than an independent predictor of death.. Early mortality in patients without microvascular lesions may reflect competing risks from atherosclerotic cardiovascular disease or non-diabetic etiologies. Collectively, these mechanisms—including insulin resistance–related endothelial dysfunction, oxidative stress, chronic inflammation, and impaired microvascular perfusion—provide a biological rationale for the observed association between an elevated TyG index and the development and progression of diabetic microvascular complications.

In the present study, we explored whether genetic susceptibility to type 2 diabetes, assessed using a PRS, modified the association between the TyG index and the risk of diabetic microvascular complications. Although formal interaction analyses

did not reveal a statistically significant multiplicative interaction between the TyG index and PRS, individuals with higher genetic risk consistently exhibited higher absolute risks of both first-onset DMC and DMC multimorbidity across TyG categories. These findings suggest that PRS does not materially alter the relative effect of TyG, but rather serves as a complementary risk stratification tool, identifying individuals who may experience a greater overall burden of microvascular disease when exposed to adverse metabolic profiles. From a clinical perspective, the combined assessment of metabolic risk (TyG) and genetic susceptibility may therefore help to identify subgroups at particularly high risk, even in the absence of a formal statistical interaction.



This study has certain limitations to acknowledge. Participants from the UK Biobank in this cohort are generally healthier and have higher socioeconomic status than the national average. This may lead to underestimation of actual risks. Additionally, the population is predominantly of European ancestry, limiting worldwide generalizability. Future studies in multi-ethnic cohorts are needed to confirm these findings. Thirdly, DMCs were identified using ICD-coded hospital records, and some diagnostic

codes included may not be entirely specific to diabetes-related complications. Such non-specific coding may result in misclassification, which could lead to underestimation of risk estimates and attenuation of the observed associations with metabolic factors, thereby biasing the results toward the null.

## Conclusions

In this population-based T2D cohort, a higher TyG index was linked to the onset and progression of DMC multimorbidity, particularly via transitions from retinopathy and nephropathy. Elevated TyG levels, together with higher T2D genetic risk, were associated with an increased risk of DMC multimorbidity progression, supporting the potential utility of TyG for risk stratification in patients with type 2 diabetes.



## Supplemental Materials

Figure S1. Flow diagram of the study population selection

Figure S2. Adjusted survival curves for DMCs by TyG index

Figure S3. Dose-response association of TyG index with DMCs risk

Table S1. Definitions and sources of information for DMCs in the UK Biobank

Table S2. Subgroup analysis of the association between TyG index and DMC multimorbidity

Table S3. The association between the TyG index and the trajectory of DMC multimorbidity with different time intervals (0.5 years, 1 years, 5 years, or excluded directly)

Table S4. The association between TyG index and DMC multimorbidity: excluded the events in the previous two years

Table S5. The association between the TyG index and the trajectory of DMC multimorbidity: excluded the events in the previous two years



## List of abbreviations:

T2D

Type 2 diabetes

DMC

Diabetic microvascular complication

DMCs

Diabetic microvascular complications

TyG

Triglyceride-glucose

IR

Insulin resistance

FBG

Fasting blood glucose

TG

Triglyceride

PRS

Polygenic risk scores

SD

Standard deviation

HR

Hazard ratio

HbA1c

Hyperglycemia

BMI

Body mass index

HDL-C

High density lipoprotein cholesterol

TDI

Townsend deprivation index

LDL-C

Low-Density lipoprotein cholesterol

DBP

Diastolic blood pressure

SBP

Systolic blood pressure



## Declarations

### *Ethics approval and consent to participate*

This study was conducted using data from the UK Biobank under application number 540121. Ethical approval was obtained from the North West Multi-Centre Research Ethics Committee.

### *Consent for publication*

Not applicable.

### *Availability of data and materials*

The datasets generated and/or analyzed during the current study are available in the UK Biobank repository, [(https://www.ukbiobank.ac.uk/]

### *Competing interests*

No competing interests.



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### *Authors' contributions*

XY and MP conceived and designed the study. XY performed the data analysis and drafted the manuscript. XY, MP, XS, DY, FW and CH provided statistical and methodological support. GX and CH contributed to data interpretation and manuscript revision. All authors read and approved the final manuscript.

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## Figure legends

Figure 1. Progression trajectory of DMC multimorbidity

Figure 2. Dose-response association of TyG index with trajectory of DMC multimorbidity

Figure 3. Joint association of TyG index and type 2 diabetes polygenic risk score on first DMC and multimorbidity of DMC

**Table 1. Baseline characteristics of DMCs**

| | Overall (n = 19512) | Tertile 1 (n = 6427) | Tertile 2 (n = 6535) | Tertile 3 (n = 6550) | *P* value |
|---|---|---|---|---|---|
| **TyG index** | 9.23 [8.78, 9.71] | 8.59 [8.33, 8.78] | 9.22 [9.09, 9.37] | 9.94 [9.71, 10.28] | < 0.001 |
| **Age (years)** | 61.00 [55.00, 65.00] | 61.00 [55.00, 65.00] | 62.00 [56.00, 65.00] | 60.00 [54.00, 65.00] | < 0.001 |
| **Male** | 11876 (60.87) | 3656 (56.89) | 3869 (59.20) | 4351 (66.43) | < 0.001 |
| **White** | 17332 (88.83) | 5391 (83.88) | 5896 (90.22) | 6045 (92.29) | < 0.001 |
| **TDI** | -1.41 [-3.25, 1.81] | -1.27 [-3.21, 2.08] | -1.49 [-3.25, 1.66] | -1.46 [-3.30, 1.71] | < 0.001 |
| **BMI (kg/m$^2$)** | 30.66 [27.40, 34.63] | 29.27 [25.99, 33.26] | 31.11 [27.79, 35.08] | 31.48 [28.44, 35.23] | < 0.001 |
| **Smoking status** | | | | | < 0.001 |
| Never | 8807 (45.14) | 3107 (48.34) | 2906 (44.47) | 2794 (42.66) | |
| Previous | 8478 (43.45) | 2633 (40.97) | 2885 (44.15) | 2960 (45.19) | |
| Current | 2227 (11.41) | 687 (10.69) | 744 (11.38) | 796 (12.15) | |
| **Drinking status** | 16639 (85.28) | 5416 (84.27) | 5600 (85.69) | 5623 (85.85) | 0.020 |
| **Physical inactivity** | 3199 (16.40) | 931 (14.49) | 1073 (16.42) | 1195 (18.24) | < 0.001 |
| **Diet score** | 3.00 [2.00, 4.00] | 3.00 [2.00, 4.00] | 3.00 [2.00, 4.00] | 3.00 [2.00, 4.00] | < 0.001 |
| **Healthy sleep** | 11699 (59.96) | 3952 (61.49) | 3980 (60.90) | 3767 (57.51) | < |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | 0.001 |
| **SBP (mmHg)** | 140.50 [129.50, 152.50] | 138.50 [127.00, 150.50] | 141.00 [130.00, 153.00] | 142.50 [131.50, 154.00] | < 0.001 |
| **DBP (mmHg)** | 82.00 [75.50, 89.00] | 80.50 [74.00, 87.50] | 82.50 [76.00, 89.00] | 83.50 [77.00, 90.00] | < 0.001 |
| **Diabetes duration categories** | | | | | 0.017 |
| <3 years | 8510 (43.61) | 2810 (43.72) | 2810 (43.00) | 2890 (44.12) | |
| 3-5 years | 2711 (13.89) | 839 (13.05) | 982 (15.03) | 890 (13.59) | |
| ≥5 years | 8291 (42.49) | 2778 (43.22) | 2743 (41.97) | 2770 (42.29) | |
| **PRS of T2D** | 0.55 [-0.08, 1.17] | 0.49 [-0.16, 1.12] | 0.54 [-0.08, 1.17] | 0.63 [0.00, 1.21] | < 0.001 |
| **HbA1c (mmol/mol)** | 6.71 [6.14, 7.42] | 6.34 [5.78, 6.85] | 6.64 [6.17, 7.20] | 7.27 [6.64, 8.28] | < 0.001 |
| **HDL-C (mmol/L)** | 1.15 [0.98, 1.36] | 1.28 [1.08, 1.53] | 1.15 [0.99, 1.33] | 1.05 [0.91, 1.21] | < 0.001 |
| **LDL-C (mmol/L)** | 2.71 [2.25, 3.35] | 2.50 [2.08, 3.06] | 2.72 [2.28, 3.33] | 2.93 [2.42, 3.60] | < 0.001 |
| **Medication use** | | | | | |
| Insulin | 2284 (11.71) | 829 (12.90) | 689 (10.54) | 766 (11.69) | < 0.001 |
| Lipid-lowering drugs | 13087 (67.07) | 4245 (66.05) | 4531 (69.33) | 4311 (65.82) | < 0.001 |
| Antihypertensive drugs | 11298 (57.90) | 3592 (55.89) | 3932 (60.17) | 3774 (57.62) | < 0.001 |

**Abbreviations:** DMC: Diabetic microvascular complication; TyG: Triglyceride-glucose; T2D: Type 2 diabetes; PRS: Polygenic risk scores; HbA1c: Hyperglycemia; BMI: Body mass index; HDL-C: High density lipoprotein cholesterol; TDI: Townsend deprivation index; LDL-C: Low-density lipoprotein cholesterol; DBP: Diastolic blood pressure; SBP: Systolic blood pressure

**Table 2. The association between TyG index and DMC multimorbidity**

| | Crude model | | Adjusted model | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| **DMCs** | | | | |
| First DMC | 1.17 (1.13–1.21) | < 0.001 | 1.19 (1.14–1.24) | < 0.001 |
| DMC multimorbidity | 1.35 (1.26–1.46) | < 0.001 | 1.38 (1.27–1.51) | < 0.001 |
| **First DMC components** | | | | |
| Retinopathy | 1.12 (1.07–1.18) | < 0.001 | 1.20 (1.13–1.27) | < 0.001 |
| Nephropathy | 1.19 (1.13–1.25) | < 0.001 | 1.16 (1.10–1.23) | < 0.001 |
| Neuropathy | 1.55 (1.42–1.69) | < 0.001 | 1.54 (1.38–1.70) | < 0.001 |

**Abbreviations:** DMC: Diabetic microvascular complication; TyG: Triglyceride-glucose

The adjusted model included the following covariates: age, sex, ethnicity, Townsend deprivation index, smoking status, drinking status, body mass index, systolic and diastolic blood pressure, LDL-C, HDL-C, HbA1c, diabetes duration, physical activity, sleep duration, diet quality, medication use, and polygenic risk score for type 2 diabetes.

**Table 3. The association between the TyG index and the trajectory of DMC multimorbidity**

| Transition | HR (95% CI) | *P* value |
|---|---|---|
| **Model 1: T2D → First DMC → DMC multimorbidity → Death** | | |
| T2D → First DMC | 1.19 (1.14–1.24) | < 0.001 |
| First DMC → DMC multimorbidity | 1.25 (1.15–1.37) | < 0.001 |
| T2D → Death | 1.04 (0.97–1.11) | 0.241 |
| First DMC → Death | 1.10 (1.01–1.21) | 0.034 |
| DMC multimorbidity → Death | 1.06 (0.93–1.21) | 0.377 |
| **Model 2: T2D → First DMC subtypes (Retinopathy, Nephropathy, Neuropathy) → DMC multimorbidity** | | |
| T2D → Retinopathy | 1.18 (1.1–1.26) | < 0.001 |
| T2D → Nephropathy | 1.13 (1.06–1.2) | < 0.001 |
| T2D → Neuropathy | 1.41 (1.23–1.63) | < 0.001 |
| Retinopathy → DMC multimorbidity | 1.39 (1.2–1.61) | < 0.001 |
| Nephropathy → DMC multimorbidity | 1.14 (1.01–1.29) | 0.041 |
| Neuropathy → DMC multimorbidity | 1.16 (0.89–1.52) | 0.277 |

**Abbreviations:** DMC: Diabetic microvascular complication; TyG: Triglyceride-glucose; T2D: Type 2 diabetes

The adjusted model included the following covariates: age, sex, ethnicity, Townsend deprivation index, smoking status, drinking status, body mass index, systolic and diastolic blood pressure, LDL-C, HDL-C, HbA1c, diabetes duration, physical activity, sleep duration, diet quality, medication use, and polygenic risk score for type 2 diabetes.