DOI: 10.26599/FSHW.2025.9250899

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Metabolomic Signatures Link Tea Consumption to Lower Incidence of Macrovascular and Microvascular Complications in Type 2 Diabetes: A Prospective Cohort Study

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ABSTRACT: Background: The association between tea consumption and complications of type 2 diabetes (T2D) remains inconsistent, with limited insights into underlying mechanisms. We aimed to identify tea-related metabolomic signatures and explore associations with risks of T2D complications. **Methods:** We included 26,472 T2D participants from the UK Biobank. Tea consumption was assessed via food frequency questionnaire. Using UK Biobank baseline plasma metabolomics data from 247,967 participants, we developed a tea-related metabolomic signature via elastic net regression. Cox regression models were used to evaluated associations among tea consumption, the metabolomic signature, and T2D complications. Mediation analyses were utilized to assess the contribution of different domains of tea-related metabolomic signatures in explaining the association between tea intake and T2D complications. **Results:** Compared with non-drinkers, moderate tea consumption (specifically 2-3 cups/day) was associated with the lowest risks of microvascular (HR=0.888, 95% CI: 0.823-0.958) and macrovascular complications (HR=0.921, 95% CI: 0.858-0.989). Tea-related metabolomic signature demonstrated a nonlinear association with both micro- and macrovascular complications. Participants in the third quartile of tea-related metabolomic signatures exhibited the lowest risks of diabetic nephropathy (HR=0.824, 95% CI: 0.704-0.964), diabetic retinopathy (HR=0.644, 95% CI: 0.564-0.736), diabetic neuropathy (HR=0.675, 95% CI: 0.530-0.859), cerebrovascular disease (HR=0.779, 95% CI: 0.644-0.942), and peripheral vascular disease (HR=0.580, 95% CI: 0.443-0.759). The glycolysis-related signature was identified as a key contributor in the mediation analyses. **Conclusions:** Moderate tea consumption of 2-3 cups per day is associated with the lowest risks of T2D complications, partially mediated by tea-related metabolomic signatures. These findings highlight novel insights and suggest potential dietary strategies for T2D management.

Key words: tea, metabolomic signatures, diabetic complications, type 2 diabetes.

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Received 8 September 2025
Received in revised from 25 October 2025
Accepted 20 November 2025

1. Introduction

Type 2 diabetes (T2D) is a significant public health concern, affecting 537 million individuals worldwide in 2021, with projected growth to 783 million by 2045[1]. T2D Patients have substantial risks of developing both macrovascular complications—including cardiovascular disease (CVD), cerebrovascular disease (CeVD), and peripheral vascular disease (PVD)—as well as microvascular complications such as diabetic nephropathy, retinopathy, and neuropathy[2]. The complications severely compromise the quality of life for T2D patients and impose a considerable societal burden[3]. Of note, diabetic nephropathy is the leading cause of end-stage renal disease (ESRD)[4], with retinopathy and neuropathy predominantly accounting for blindness and chronic pain[4]. Therefore, it is imperative to identify modifiable factors that may mitigate diabetic complication risks.

Tea is one of the most widely consumed beverages globally, and its widespread consumption may have significant public health implications[5]. The potential benefits of tea are largely attributed to its rich content of polyphenolic compounds, particularly catechins and theaflavins[5]. These bioactive components have been demonstrated to influence key metabolic pathways relevant to diabetic complications. Experimental studies suggest that tea polyphenols can enhance insulin sensitivity and improve glycemic control by activating the AMP-activated protein kinase (AMPK) pathway and modulating glucose transporter type 4 (GLUT4) translocation[6, 7]. Furthermore, they may ameliorate diabetic dyslipidemia by inhibiting enzymes involved in cholesterol and fatty acid synthesis, thereby reducing circulating levels of atherogenic lipids[8]. At a vascular level, the potent antioxidative and anti-inflammatory properties of these compounds are crucial for counteracting the oxidative stress and chronic inflammation that underlie the pathogenesis of both micro- and macrovascular complications[9]. However, population-based studies on the association between tea consumption and diabetic complications show inconsistent results. While some studies showed protective associations of tea consumption with microvascular complications[10-12], others failed to detect significant associations[13]. Moreover, the biological mechanisms underlying the relationship between tea intake and the risk of T2D complications are not yet fully elucidated.

In recent years, high-throughput metabolomics techniques have been increasingly used to assess individual responses to dietary intake, enabling the exploration of the overall impact of diet and other lifestyle factors on metabolic function and disease risk[14, 15]. Therefore, the approach offers a promising framework to investigate the metabolic mechanisms underlying the association between tea consumption and complications in T2D[16]. Although several observational studies and randomized controlled trials have identified metabolomic signatures associated with tea intake[17], less investigations have comprehensively examined the relationship between the tea-related metabolomic signatures and specific types of T2D complications[18].

In the present study, we aimed to investigate the association of tea consumption, and its corresponding metabolomic signatures with macrovascular and microvascular complications in T2D patients. By integrating metabolomics, the study could provide novel insights into the biological mechanisms linking tea-related metabolomic signatures to the risk of T2D complications.

2. Material and methods

2.1 Study population

The UK Biobank is a prospective cohort study that recruited over 500,000 participants aged 37-73 years between 2006 and 2010[19]. Ethical approval was obtained from the Northwest Multicentre Research Ethics Committee (reference: 21/NW/0157), and all participants provided written informed consent. The tea-related metabolomic signature was derived from 247,967 UK Biobank participants with complete baseline plasma metabolomics. The association analyses focused on 37,358 participants with baseline T2D. Baseline T2D cases were identified using the International Classification of Diseases Tenth revision (ICD-10) code E11, with the date of first occurrence compared to the baseline visit date to ascertain T2D status[2]. After excluding those with missing data on tea consumption (n=97), prior microvascular (n=1,233) or macrovascular (n=7,059) complications, or self-reported cancer (n=2,497), 26,472 participants were included in the analysis of tea consumption and T2D complications. Additionally, participants without baseline metabolomic signature data were further excluded in the tea-related metabolomic signature analysis. The detailed inclusion and exclusion process were shown in Figure 1.

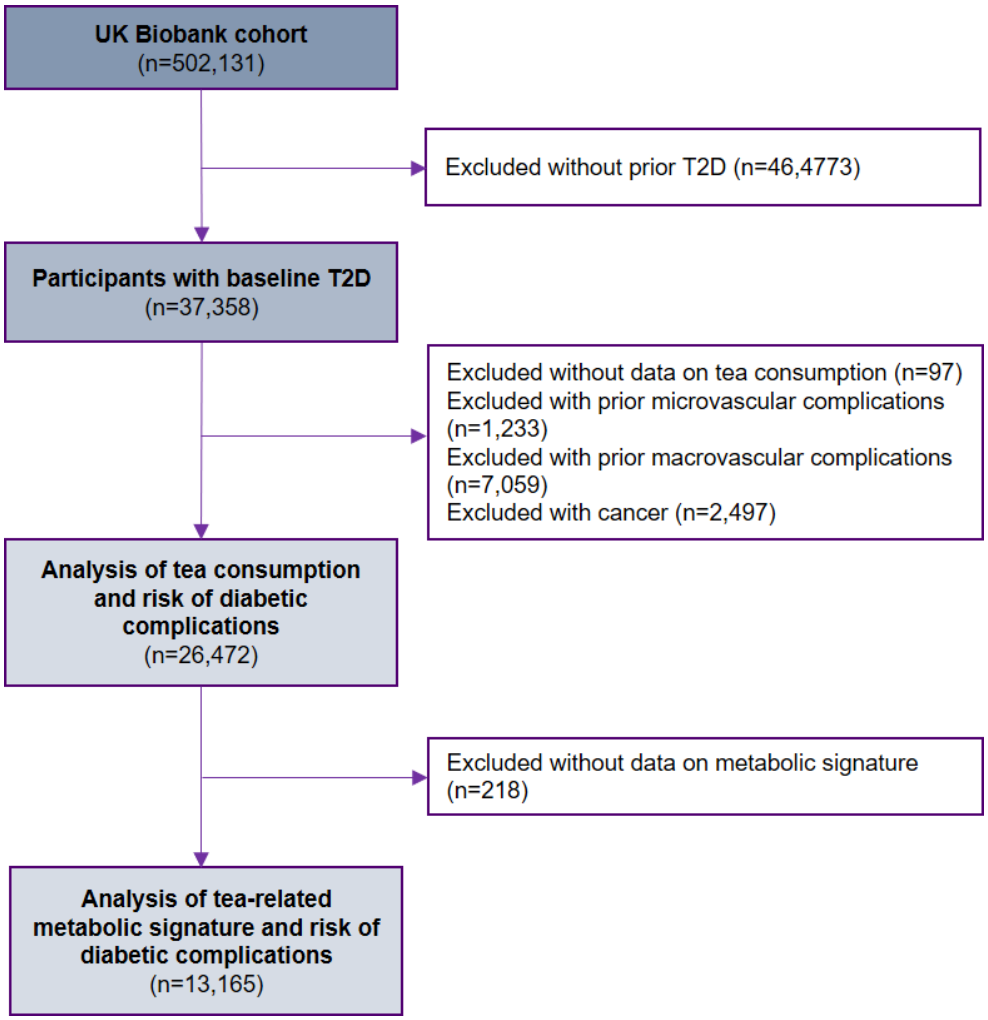

Figure 1. Flowchart for the exclusion of the study population in UK Biobank. T2D, type 2 diabetes.

We replicated the analyses regarding the association between tea consumption and diabetic complications in the Fangshan Family-based Ischemic Stroke Study in China (FISSIC), a family-based cohort

study in northern China. It was approved by the Peking University Institutional Review Board (reference: IRB00001052-13027). The FISSIC began recruiting participants in 2005 through a proband-initiated contact method, with more details described in previous studies[20, 21]. We ultimately included 2,110 participants with T2D at baseline. The elaborated exclusion process was shown in Supplementary Figure S1.

2.2 Assessment of tea consumption

Tea consumption over the past 12 months was assessed at baseline using a touch-screen food frequency questionnaire (FFQ) in UK Biobank[22]. Participants were asked 'How many cups of tea do you drink each day (including black and green tea)?' They selected either the number of cups, '<1', 'Do not know', 'Prefer not to answer', or a specific number per day. Previous studies have shown that most of the study participants did not change tea intake during the follow-up[5, 18]. In determining whether tea consumption was associated with T2D complications, we categorized tea intake into the following four categories: 0, 0-1, 2-3, ⩾4 cups/day. Tea consumption was considered as a continuous variable in characterizing the corresponding metabolomic signature. Tea intake in the FISSIC was also assessed at baseline using the FFQ. Participants reported their usual frequency of tea leaf consumption (including green, black, oolong, etc.) over the past 12 months by selecting one of five categories ('daily', '4-6 times/week', '1-3 times/week', 'several times/month', or 'rare/never') and indicating the average amount per occasion in grams. From these data, we calculated each participant's average daily tea intake (g/day). For the current analysis, participants were grouped into four categories: non-consumers (0 g/day) and three consumer tertiles based on daily intake among tea drinkers (0-1.37, 1.37-5.48, ⩾5.48 g/day).

2.3 Metabolomics profiling

The plasma from approximately 280,000 participants at baseline recruitment (2006-2010) and 16,000 participants at the repeat assessment (2012-2013) from the UK Biobank were measured using high-throughput nucleic magnetic resonance (NMR) spectroscopy on the Nightingale Health's metabolomic biomarker platform in Finland. For the current analysis, we exclusively used baseline plasma measurements to construct the tea-related metabolomic signature. A total of 251 metabolites, including 170 absolute levels and 81 ratio indexes, were identified, covering glycolysis-related metabolites, lipids, lipoproteins, fluid balance, ketone bodies, fatty acids, amino acids, and inflammation[23]. A *Z*-score standardization of each metabolite was performed prior to planned analyses.

2.4 Follow-up and outcome assessment

Participants were followed from the time of enrolment until either death, loss to follow-up, or April 1, 2024, whichever occurred first. Outcome data were derived from hospital admission records, including diagnostic information sourced from hospital event statistics for England, the Scottish Morbidity Record data, and the Patient Event Database for Wales. The primary outcomes included diabetic macrovascular complications (comprising CVD, CeVD, and PVD), as well as diabetic microvascular complications (including diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy). The conditions were

identified using codes from the International Classification of Diseases, Ninth revision (ICD-9) and Tenth revision (ICD-10). Detailed definitions can be found in *Supplementary Table S1*.

2.5 Covariates

A range of covariates were included in the analyses, such as age, sex, household income (Less than 18,000 £, 18,000 £ to 30,999 £, 31,000 £ to 51,999 £, 52,000 £ to 100,000 £), ethnicity, qualifications (college or university degree, other), Townsend deprivation index (TDI), body mass index (BMI) in kg/m^2, smoking status (never, previous, and current), alcohol consumption (never, previous, and current), physical activity level (METh/week), the dietary score (ranging from 0 to 4 points), the healthy sleep score (ranging from 0 to 5 points), coffee consumption (cups/day), systolic blood pressure (SBP), low density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR) based on creatinine levels, hemoglobin A1c (HbA1c), use of antidiabetic drugs, and the age of T2D diagnosis. The dietary score was derived from several dietary factors, including vegetable intake ($\geqslant$3 servings/day), fruit intake ($\geqslant$3 servings/day), fish consumption ($\geqslant$2 servings/week), and unprocessed red meat consumption ($\leqslant$2 servings/week)[5]. We generated the healthy sleep score based on five sleep factors (chronotype, sleep duration, insomnia, snoring, and excessive daytime sleepiness)[24].

2.6 Statistical analyses

2.6.1 Identifying the metabolomic signature reflecting tea consumption

Baseline metabolomics data from the UK Biobank were utilized to identify metabolites associated with tea consumption (*Supplementary Figure S2*). Multivariate linear regression was applied to examine the relationship between each metabolite and tea intake, with a significance threshold set at $P < 0.05/251$ (approximately 2E-4) after Bonferroni correction for multiple testing. To construct metabolomic signatures reflecting tea consumption, we employed the elastic net regression, a classification algorithm that combines the strengths of both Lasso and ridge regression. This approach effectively addresses multicollinearity and reduce the risk of overfitting[25]. The metabolomic signatures, which were calculated as weighted sums of the selected metabolites, were based on metabolites identified through the elastic net regression model.

2.6.2 Associations between tea consumption, metabolomic signatures and T2D complications

To assess the associations between tea consumption, metabolomic signatures, and the risk of T2D complications, we used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for the covariates listed above. The proportional hazards assumption was tested using Schoenfeld residuals. We also applied restricted cubic spline models with four knots to explore potential nonlinear dose-response relationships between tea consumption, metabolomic signatures, and the risk of developing T2D complications. We conducted a replication analysis of the association between tea consumption and T2D complications using data from the FISSIC cohort. Additionally, quantile-based g-computation was used to evaluate the contribution of different pathway components of the metabolomic signatures to the risk of T2D complications (*Supplementary Methods*).

2.6.3 Associations between tea consumption, metabolomic signatures and T2D complication comorbidity burden

To further characterize the relationship between tea consumption, metabolomic signatures, and diabetic complication comorbidity burden, we fitted zero-inflated negative binomial (ZINB) regression models[26]. We defined the comorbidity burden as the total number of concurrent diabetic complications (e.g., nephropathy, retinopathy, neuropathy, and cardiovascular events) observed over the follow-up period. The ZINB model accommodated the overdispersion and excess zeros inherent in our count outcome by combining a point mass at zero with a negative binomial distribution for counts greater than zero[27]. Incidence rate ratios (IRRs) and 95% CIs were estimated for tea consumption and the metabolomic signatures.

2.6.4 Subgroup analyses and sensitivity analyses

Multivariable Cox regression models stratified by age, sex, BMI, and eGFR, were also performed. Several sensitivity analyses were performed to assess the robustness of the findings: (i) excluding participants who developed T2D complications within one year of follow-up; (ii) including participants with cancer at baseline; (iii) treating all-cause mortality as a competing risk, followed by additional analyses using Fine-Gray sub-distribution hazards regression models; (iv) mutually adjusting for both tea consumption and metabolomic signature; (v) performing a complete case analysis to assess the influence of missing data; (vi) constructing generalized propensity scores (GPS) and applying inverse probability of treatment weighting (IPW) in the Cox regression models to balance confounders (*Supplementary Methods*) and quantifying the robustness of significant associations to unmeasured confounding using E-values[28]. We also conducted two additional analyses to test the robustness: applying weight trimming at the 1st and 99th percentiles, and directly adjusting for the GPS as a continuous covariate; (vii) excluding participants who reported not adding milk to tea to explore whether milk addition practice could impact our findings; and (viii) examining the associations by specific tea types (black tea, green tea, and herbal tea) to explore potential differential effects.

2.6.5 GWAS analysis for the metabolomic signature

A genome-wide association study (GWAS) was performed on the tea-related metabolomic signature. Variants with a minor allele frequency (MAF) <1% or Hardy-Weinberg equilibrium *P*-value < 1e-6 were excluded. Association analyses were conducted using the multiple regression function in PLINK2, adjusting for sex, age, and the first 10 principal components of ancestry. Statistical significance was defined as $P < 5E\text{-}8$.

Function annotation for the GWAS results was carried out using FUMA (*https://fuma.ctglab.nl/, version 1.6.1*). MAGMA analysis was then applied to evaluate individual genes and gene sets, with Bonferroni correction applied for multiple testing. A significance threshold of $P < 2.64E\text{-}6$ was used for genome-wide significance in gene analyses. Tissue-specific analysis was conducted using RNAseq data from the GTEx (version 8) dataset.

2.6.6 Mediation analyses

We conducted mediation analyses to assess the contribution of different components of tea-related metabolomic signatures in explaining the association between tea intake and diabetic complications. Specifically, we constructed two regression models: a generalized linear model with the mediator as the dependent variable and tea intake as the independent variable, and a Cox regression model with the T2D complications as the dependent variable and tea intake as the independent variable. The models were used to estimate the direct effect (DE) and indirect effect (IE). The confidence intervals were obtained using a resampling approach, drawing 1 million random samples from a multivariate normal distribution[29]. Similarly, we examined the potential mediating role of HbA1c in the association between metabolomic signatures and diabetic complications.

Analyses were conducted using R (version 4.2.3). Missing covariates values were imputed using multiple imputation with the "*mice*" package. All statistical tests were two-sided, and statistical significance was set at a *P*-value of < 0.05.

Additional details on the methods can be found in the Supplementary Methods section.

3. Results

3.1 Baseline characteristics of the participants

A total of 26,472 participants from the UK Biobank were included in the study, with a mean age of (58.37 ± 7.56) years, of whom 44.5% were females. Over a median follow-up of 14.45 years, 7,083 cases of macrovascular complications were recorded (including 5,827 CVD, 1,853 CeVD, and 997 PVD), along with 6,230 cases of microvascular complications (including 3,130 nephropathy, 3,586 retinopathy, and 1,113 neuropathy). Baseline characteristics across different tea consumption groups were summarized in Table 1. Participants with higher tea consumption tended to be younger, have lower BMI levels, engage in more physical activity levels, and exhibit healthier dietary patterns. Additionally, 2,110 individuals diagnosed with T2D at baseline from the FISSIC cohort were included, with a mean age of (58.45 ± 8.61) years, and 1,269 were females. Detailed baseline characteristics of participants in FISSIC study included in the current study were provided in *Table S2*.

Table 1. Baseline characteristics by tea consumption in UK Biobank.

Characteristic	Overall (n=26472)	0 (n=4464)	0-1 (n=3216)	2-3 (n=7977)	⩾4 (n=10815)	*P*
Age, mean (SD), y	58.37 (7.56)	57.46 (7.68)	57.51 (7.86)	58.57 (7.56)	58.87 (7.35)	<0.001
Female (%)	11773 (44.47)	2001 (44.83)	1404 (43.66)	3592 (45.03)	4776 (44.16)	0.472
College or university degree (%)	7491 (28.30)	1186 (26.57)	1137 (35.35)	2382 (29.86)	2786 (25.76)	<0.001
TDI*, mean (SD)	-0.62 (3.38)	-0.54 (3.36)	-0.35 (3.53)	-0.63 (3.41)	-0.73 (3.31)	<0.001
ethnicity (%)						
White	23027 (86.99)	3987 (89.31)	2645 (82.25)	6682 (83.77)	9713 (89.81)	
Asian	1024 (3.87)	204 (4.57)	200 (6.22)	293 (3.67)	327 (3.02)	
Black	385 (1.45)	47 (1.05)	46 (1.43)	174 (2.18)	118 (1.09)	
Other	2036 (7.69)	226 (5.06)	325 (10.11)	828 (10.38)	657 (6.07)	
Household income (annual, £), (%)						
Less than 18,000	7021 (26.52)	1194 (26.75)	755 (23.48)	2047 (25.66)	3025 (27.97)	
18,000 to 30,999	10802 (40.81)	1727 (38.69)	1290 (40.11)	3275 (41.06)	4510 (41.70)	
31,000 to 51,999	4775 (18.04)	872 (19.53)	590 (18.35)	1445 (18.11)	1868 (17.27)	
52,000 to 100,000	3149 (11.90)	541 (12.12)	459 (14.27)	968 (12.13)	1181 (10.92)	
Greater than 100,000	725 (2.74)	130 (2.91)	122 (3.79)	242 (3.03)	231 (2.14)	
BMI, mean (SD), kg/m^2	30.72 (5.91)	31.95 (6.28)	30.95 (6.08)	30.27 (5.77)	30.47 (5.72)	<0.001
Smoke (%)						
Never	13505 (51.02)	2202 (49.33)	1664 (51.74)	4339 (54.39)	5300 (49.01)	
Previous	10042 (37.93)	1692 (37.90)	1174 (36.50)	2927 (36.69)	4249 (39.29)	
Current	2925 (11.05)	570 (12.77)	378 (11.75)	711 (8.91)	1266 (11.71)	
Alcohol (%)						
Never	2230 (8.42)	325 (7.28)	283 (8.80)	863 (10.82)	759 (7.02)	
Previous	1581 (5.97)	352 (7.89)	157 (4.88)	374 (4.69)	698 (6.45)	
Current	22661 (85.60)	3787 (84.83)	2776 (86.32)	6740 (84.49)	9358 (86.53)	
Physical activity, mean (SD), METh/week	34.90 (36.81)	33.48 (36.28)	33.41 (36.90)	34.01 (34.57)	36.57 (38.51)	<0.001
Diet score, mean (SD)	2.18 (0.90)	2.11 (0.91)	2.12 (0.91)	2.17 (0.89)	2.23 (0.90)	<0.001
Sleep score, mean (SD)	2.55 (1.15)	2.51 (1.13)	2.53 (1.16)	2.58 (1.15)	2.55 (1.15)	0.010
Coffee consumption, mean (SD), cups/day	2.02 (2.20)	3.42 (2.79)	2.60 (2.22)	1.82 (1.72)	1.42 (1.92)	<0.001
SBP, mean (SD), mmHg	144.10 (18.29)	143.74 (17.75)	144.04 (18.41)	144.41 (18.41)	144.04 (18.38)	0.244
LDL cholesterol, mean (SD), mmol/L	3.03 (0.89)	3.04 (0.91)	3.01 (0.87)	3.04 (0.90)	3.01 (0.89)	0.086
eGFR, mean (SD), mL/min/1.73 m^2	91.55 (14.65)	92.99 (14.96)	92.73 (14.54)	91.67 (14.58)	90.52 (14.53)	<0.001
HbA1c, mean (SD), %	6.73 (1.30)	6.78 (1.29)	6.73 (1.27)	6.70 (1.31)	6.73 (1.30)	0.023
Age of T2D diagnosis, mean (SD), y	57.03 (7.98)	56.01 (8.15)	56.17 (8.21)	57.29 (7.89)	57.51 (7.85)	<0.001
Antidiabetic drugs (%)	3396 (12.83)	622 (13.93)	406 (12.62)	947 (11.87)	1421 (13.14)	0.006

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation; T2D, type 2 diabetes; TDI, Townsend deprivation index.*Positive values of the index indicate areas with high material deprivation, whereas those with negative values indicate relative affluence.

3.2 Identification of tea-consumption-related metabolomic signatures

We performed elastic net regression analyses on 251 metabolites to identify metabolomic signatures associated with tea consumption. 86.0% of the baseline metabolites, including triglycerides and fatty acids, were significantly correlated with tea intake (*Figure S3*). In particular, 44 metabolites spanning various metabolic categories—such as glycolysis, lipids, lipoproteins, fluid balance, ketone bodies, fatty acids, amino acids, and inflammation—were selected to calculate the tea-related metabolomic signature (*Figure S4*). The metabolomic signature was strongly associated with tea intake in both baseline and repeated measures (*Figure S5*). *Figure 2* presented associations of the 44 selected metabolites with tea intake and T2D complications. Notably, glycoprotein acetyls and creatinine made the largest contributions to the positive coefficients of the metabolomic signature, while triglycerides in large LDL were the primary factors influencing the negative coefficients.

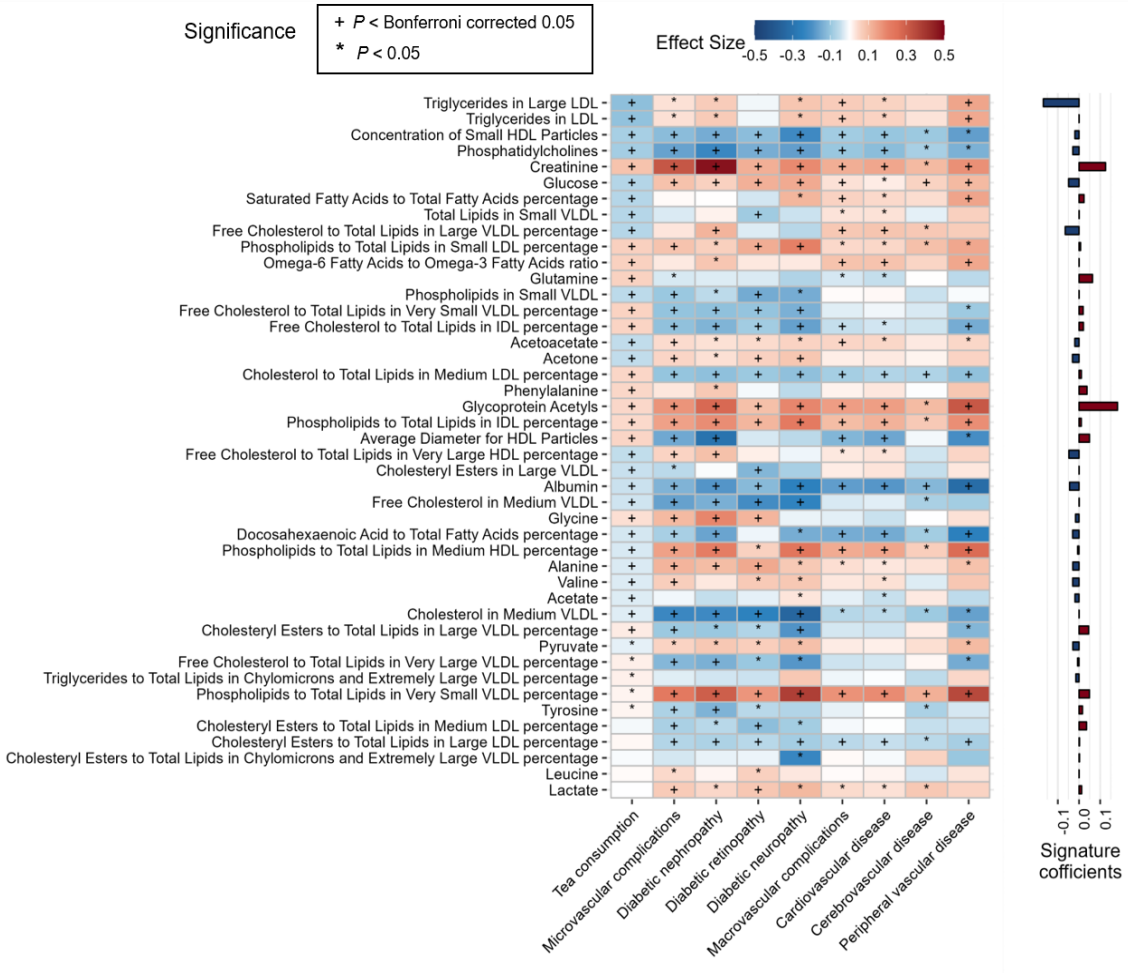

Figure 2. Associations of 44 metabolites constituting the metabolomic signature with tea consumption and diabetic complications risk. Shown from left to right are the association of metabolites with tea consumption and risk of T2D complications, as well as the coefficients (weights) of metabolites in the metabolomic signature. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

3.3 Association of tea consumption and metabolomic signature with incident T2D complications

Tea consumption was significantly associated with lower risks of both macrovascular and microvascular diabetic complications (*Table 2 and Figure S6*). We observed that consuming 2-3 cups of tea per day was

linked to an approximately 11% lower risk of microvascular complications (HR = 0.888, 95% CI: 0.823, 0.958) and a 8% lower risk of macrovascular complications (HR = 0.921, 95% CI: 0.858, 0.989) compared to non-tea consumers. The observed association was particularly pronounced for PVD. Nonlinear dose-response relationships were observed between tea consumption and PVD (*P* for nonlinear < 0.001), with the lowest risk associated with consuming 2-3 cups per day (*Figure S7*). We replicated the association analyses in the FISSIC cohort and similar trends were confirmed (*Figure S8-S9*). Consuming ⩾5.48 g of tea per day, equivalent to approximately 2-4 cups, was associated with a 23% lower risk of microvascular complications (HR = 0.776, 95% CI: 0.625, 0.964) compared to non-tea consumers.

In the analysis of metabolomic signatures, the tea-related metabolomic signature was inversely associated with the incidence of both diabetic microvascular and macrovascular complications (*Table 2 and Figure S10*). Compared to participants in the first quartile of metabolomic signatures, those in the third quartile had a significantly lower risk of diabetic microvascular complications (HR = 0.695, 95% CI: 0.626, 0.771). Specifically, the HRs were 0.824 (95% CI: 0.704, 0.964) for diabetic nephropathy, 0.644 (95% CI: 0.564, 0.736) for diabetic retinopathy and 0.675 (95% CI: 0.530, 0.859) for diabetic neuropathy. Compared with participants in the first quartile of the tea-related metabolomic signature, those in the third quartile experienced the strongest inverse association with macrovascular complications (HR = 0.868, 95% CI: 0.789-0.956). When broken down by specific macrovascular endpoints, the HRs were 0.779 (95% CI: 0.644-0.942) for cerebrovascular disease, and 0.580 (95% CI: 0.443-0.759) for peripheral vascular disease, respectively. Simultaneously, we observed nonlinear forms of dose-dependent associations (*Figure 3*).

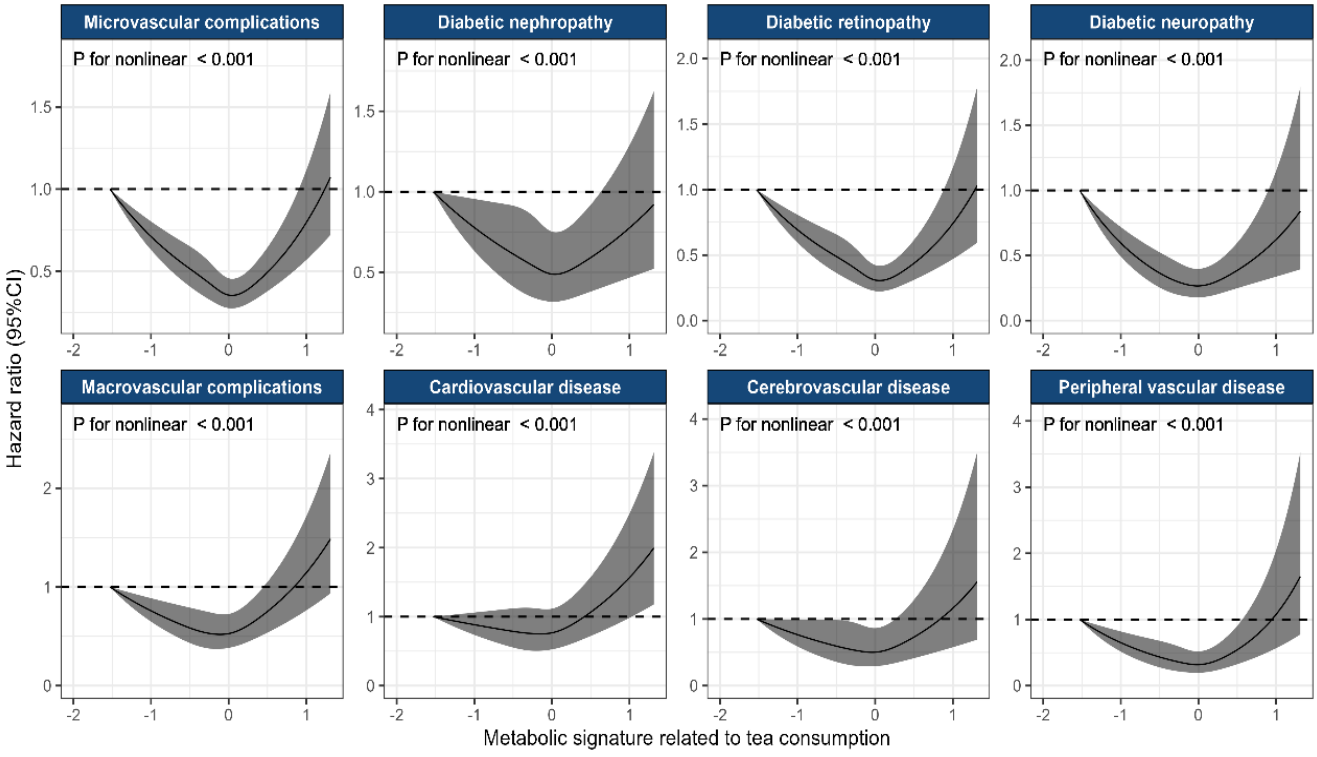

Figure 3. Dose-response relationships of tea-related metabolomic signature and diabetic complications in the UK Biobank. Multivariate models adjusted for age, sex, household income, ethnicity, education levels, TDI, BMI, smoking status, alcohol status, physical activity, diet score, healthy sleep score, coffee consumption, SBP, LDL-C, eGFR, HbA1c, use of antidiabetic drugs, and age of T2D diagnosis. CI, confidence interval; HR, hazard ratio.

Table 2. Associations of diabetic complications with tea consumption and metabolomic signature.

Outcomes	Tea consumption				Metabolomic signature			
	Cups / day	Case / total	HR (95%CI)	*P* value	Quantiles	Case / total	HR (95%CI)	*P* value
Microvascular complications	0	1095 / 4464	reference	reference	Q1	775 / 3292	reference	reference
	0.5-1	707 / 3216	0.896 (0.815, 0.986)	0.024	Q2	712 / 3291	0.801 (0.723, 0.887)	<0.001
	2-3	1823 / 7977	0.888 (0.823, 0.958)	0.002	Q3	708 / 3291	0.695 (0.626, 0.771)	<0.001
	⩾4	2605 / 10815	0.911 (0.848, 0.978)	0.010	Q4	983 / 3291	0.786 (0.709, 0.872)	<0.001
Diabetic nephropathy	0	542 / 4464	reference	reference	Q1	285 / 3292	reference	reference
	0.5-1	341 / 3216	0.896 (0.782, 1.027)	0.114	Q2	335 / 3291	0.938 (0.801, 1.100)	0.434
	2-3	918 / 7977	0.933 (0.838, 1.038)	0.203	Q3	372 / 3291	0.824 (0.704, 0.964)	0.016
	⩾4	1329 / 10815	0.923 (0.835, 1.021)	0.119	Q4	657 / 3291	0.904 (0.775, 1.054)	0.198
Diabetic retinopathy	0	612 / 4464	reference	reference	Q1	537 / 3292	reference	reference
	0.5-1	423 / 3216	0.943 (0.832, 1.068)	0.355	Q2	404 / 3291	0.699 (0.614, 0.796)	<0.001
	2-3	1028 / 7977	0.870 (0.786, 0.964)	0.007	Q3	394 / 3291	0.644 (0.564, 0.736)	<0.001
	⩾4	1523 / 10815	0.973 (0.885, 1.069)	0.568	Q4	462 / 3291	0.695 (0.607, 0.797)	<0.001
Diabetic neuropathy	0	216 / 4464	reference	reference	Q1	160 / 3292	reference	reference
	0.5-1	116 / 3216	0.773 (0.617, 0.970)	0.026	Q2	113 / 3291	0.688 (0.539, 0.876)	0.002
	2-3	318 / 7977	0.857 (0.719, 1.022)	0.085	Q3	120 / 3291	0.675 (0.530, 0.859)	0.001
	⩾4	463 / 10815	0.875 (0.744, 1.031)	0.110	Q4	169 / 3291	0.792 (0.624, 1.006)	0.056
Macrovascular complications	0	1240 / 4464	reference	reference	Q1	890 / 3292	reference	reference
	0.5-1	817 / 3216	0.911 (0.833, 0.995)	0.039	Q2	808 / 3291	0.879 (0.798, 0.967)	0.008
	2-3	2070 / 7977	0.921 (0.858, 0.989)	0.024	Q3	849 / 3291	0.868 (0.789, 0.956)	0.004
	⩾4	2956 / 10815	0.935 (0.875, 1.000)	0.051	Q4	1090 / 3291	1.039 (0.943, 1.145)	0.439
Cardiovascular disease	0	1008 / 4464	reference	reference	Q1	693 / 3292	reference	reference
	0.5-1	667 / 3216	0.925 (0.839, 1.021)	0.120	Q2	674 / 3291	0.947 (0.851, 1.053)	0.315
	2-3	1718 / 7977	0.962 (0.889, 1.041)	0.333	Q3	723 / 3291	0.957 (0.860, 1.065)	0.419
	⩾4	2434 / 10815	0.967 (0.898, 1.041)	0.371	Q4	921 / 3291	1.113 (0.999, 1.240)	0.051
Cerebrovascular disease	0	341 / 4464	reference	reference	Q1	238 / 3292	reference	reference
	0.5-1	216 / 3216	0.865 (0.728, 1.026)	0.096	Q2	187 / 3291	0.749 (0.618, 0.909)	0.003
	2-3	542 / 7977	0.833 (0.726, 0.955)	0.009	Q3	208 / 3291	0.779 (0.644, 0.942)	0.010
	⩾4	754 / 10815	0.827 (0.727, 0.940)	0.004	Q4	285 / 3291	0.964 (0.798, 1.163)	0.700
Peripheral vascular disease	0	217 / 4464	reference	reference	Q1	138 / 3292	reference	reference
	0.5-1	99 / 3216	0.656 (0.517, 0.833)	<0.001	Q2	91 / 3291	0.646 (0.495, 0.843)	0.001
	2-3	259 / 7977	0.691 (0.576, 0.830)	<0.001	Q3	91 / 3291	0.580 (0.443, 0.759)	<0.001
	⩾4	422 / 10815	0.754 (0.639, 0.890)	<0.001	Q4	170 / 3291	0.865 (0.674, 1.110)	0.254

CI, confidence interval; HR, hazard ratio.

Multivariate models adjusted for age, sex, household income, ethnicity, education levels, TDI, BMI, smoking status, alcohol status, physical activity, diet score, healthy sleep score, coffee consumption, SBP, LDL-C, eGFR, HbA1c, use of antidiabetic drugs, and age of T2D diagnosis. The microvascular complications included diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy, while the macrovascular complications included cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

3.4 Association of tea consumption and metabolomic signature with T2D complication comorbidity burden

In fully adjusted ZINB models, participants consuming 2-3 cups of tea per day experienced a significantly smaller comorbidity burden compared with non-drinkers (*Table 3*). The IRR for combined micro- and macrovascular complications was 0.918 (95% CI: 0.870-0.969). When examined separately, the IRRs were 0.928 (95% CI: 0.866-0.995) for microvascular complications and 0.914 (95% CI: 0.857-0.974) for macrovascular complications. Similarly, individuals in the third quartile of the tea-related metabolomic signature showed a substantially diminished comorbidity burden relative to those in the first quartile, with IRRs of 0.725 (95% CI: 0.660-0.797) for microvascular complications, 0.878 (95% CI: 0.804-0.958) for macrovascular complications, and 0.788 (95% CI: 0.733-0.848) for combined complications.

Table 3. Associations of tea consumption and metabolomic signature with diabetic complication comorbidity burden.

Outcomes	Tea consumption			Metabolomic signature		
	Cups / day	IRR (95%CI)	*P* value	Quantiles	IRR (95%CI)	*P* value
Microvascular complications	0	reference	reference	Q1	reference	reference
	0.5-1	0.920 (0.843-1.003)	0.060	Q2	0.785 (0.715-0.863)	<0.001
	2-3	0.928 (0.866-0.995)	0.035	Q3	0.725 (0.660-0.797)	<0.001
	⩾4	0.943 (0.883-1.006)	0.074	Q4	0.775 (0.705-0.852)	<0.001
Macrovascular complications	0	reference	reference	Q1	reference	reference
	0.5-1	0.896 (0.827-0.971)	0.007	Q2	0.871 (0.798-0.951)	0.002
	2-3	0.914 (0.857-0.974)	0.005	Q3	0.878 (0.804-0.958)	0.003
	⩾4	0.916 (0.863-0.973)	0.004	Q4	1.014 (0.929-1.106)	0.762
Microvascular & Macrovascular complications	0	reference	reference	Q1	reference	reference
	0.5-1	0.906 (0.847-0.969)	0.004	Q2	0.818 (0.761-0.880)	<0.001
	2-3	0.918 (0.870-0.969)	0.002	Q3	0.788 (0.733-0.848)	<0.001
	⩾4	0.927 (0.882-0.975)	0.003	Q4	0.883 (0.820-0.950)	<0.001

CI, confidence interval; IRR, incidence rate ratio.
Multivariate models adjusted for age, sex, household income, ethnicity, education levels, TDI, BMI, smoking status, alcohol status, physical activity, diet score, healthy sleep score, coffee consumption, SBP, LDL-C, eGFR, HbA1c, use of antidiabetic drugs, and age of T2D diagnosis. The microvascular complications included diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy, while the macrovascular complications included cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

3.5 Subgroup analyses and sensitivity analyses

Supplementary Tables S3-S6 present the associations of tea consumption and metabolomic signature with incident diabetic complications, stratified by age, sex, BMI, and eGFR, respectively, with findings largely consistent with those of the primary analysis. Notably, we observed that the strength of the association between tea intake or tea-related metabolomic signatures and a lower risk of T2D complications was weaker, or even reversed, in participants with eGFR<60 mL/min/1.73 m^2 compared to those with eGFR ⩾ 60 mL/min/1.73 m^2 (*Table S6*). The interaction effect of the tea-related metabolomic signatures and eGFR was statistically significant for all microvascular complications ($P < 0.001$ for total microvascular complications, diabetic retinopathy, and diabetic neuropathy, $P=0.008$ for diabetic nephropathy), as well as CeVD ($P=0.011$) and PVD ($P=0.025$).

The results remained robust across several sensitivity analyses, including the exclusion of participants who developed T2D complications within one year of follow-up (*Table S7*), inclusion of participants with cancer at baseline (*Table S8*), treating death as a competing risk (*Table S9*), simultaneous adjustment for both tea intake and metabolomic signatures (*Table S10*), complete case analysis (*Table S11*), and application of the GPS-based methods to control for confounders (*Table S12-S14*). The E-value analysis further indicated that unmeasured confounding was unlikely to fully explain the observed associations (*Table S12*). In our sensitivity analyses after excluding individuals who did not add milk to tea, we observed a persistent trend suggesting associations between tea consumption (and its related metabolomic signatures) and the lower risk of T2D complications (*Table S15*). Finally, the analysis based by tea types suggested that the observed protective associations were primarily driven by black tea consumption, which showed consistent inverse associations with multiple T2D complications, while the results for green tea and herbal tea were less consistent, potentially due to limited statistical power in these subgroups (*Table S17*). The consistency of results across these various approaches further supported the reliability of our findings.

3.6 The genetic determinants of the metabolomic signature

We performed a genome-wide association analysis to further interpret the identified tea-related metabolomic signature, leading to the discovery of 117 significant risk loci associated with the metabolomic signature (*Table S13 and Figure S11*). The gene-based association analysis using MAGMA identified 412 genes associated with metabolomic signatures (eg. *ALDH1A2* and *APOC4, Table S14 and Figure S12*), which were primarily involved in lipid metabolism, such as statin inhibition of cholesterol production, cholesterol metabolism, and the metabolism of lipoproteins such as LDL and HDL (*Table S15*). Additionally, the identified genes showed significant enrichment in liver tissue (*Figure S13*).

3.7 Mediation analyses

We conducted mediation analyses to evaluate the contribution of various components of metabolomic signature to the relationship between tea intake and T2D complications. It was found that the glycolysis-related and lipoprotein lipid-related components played a prominent mediating role (*Figure S14*). Estimation of the contribution of each component using a quantile-based g computation regression model showed that the lower risk of diabetic complications was significantly attributed to the glycolysis component (*Figure S15*). Furthermore, higher glycolysis-related component signatures were negatively associated with the risk of both microvascular and macrovascular diabetic complications (*Figure S16*). Given the potential mediating roles of long-term glycemic markers such as HbA1c in the association of tea-related metabolomic signature with T2D complications, we performed additional mediation analyses using HbA1c as mediators. Ultimately, the findings highlighted HbA1c as a key mediator for both microvascular and macrovascular complications (*Table S16*). Specifically, the indirect effects [HR (95% CI)] of HbA1c on diabetic nephropathy, and neuropathy were 0.954 (0.938, 0.971), and 0.956 (0.937, 0.973), with corresponding mediation percentages of 15.7%, and 5.6%, respectively. For macrovascular complications, the indirect

effects [HR (95% CI)] of HbA1c on CVD, CeVD and PVD were 0.979 (0.969, 0.988), 0.975 (0.960, 0.988) and 0.964 (0.943, 0.981), with mediation percentages of 4.7%, 6.6% and 5.4%, respectively.

4. Discussion

In the current large-scale prospective cohort study integrating metabolomics, we found that tea consumption and its associated metabolomic signature were significantly associated with lower risks of both macrovascular and microvascular complications in T2D patients. These findings provide novel insights supporting the potential protective role of tea consumption against T2D complications and offer mechanistic insights into the underlying metabolomic pathways.

Our results align with prior observational studies that suggest a protective relation of tea consumption with diabetic microvascular complications[11, 18], such as diabetic retinopathy[11]. A prospective cohort study from the China Kadoorie Biobank (CKB) indicated that tea consumption was inversely associated with the risk of diabetic retinopathy[11]. Similarly, another population-based study showed an inverse association between tea consumption and the risk of the disease progression in diabetes, though it did not analyze specific diabetic complications in detail[18]. The persistence of the inverse associations in the FISSIC cohort further highlights the robustness and external validity of our findings. Furthermore, we observed a negative association between the tea-related metabolomic signature and the occurrence of T2D complications. These findings imply that tea-related metabolomic alterations may at least partly explain the associations between habitual tea consumption and the lower risks of T2D complications.

From a public health perspective, the use of several representative metabolites related to tea consumption to construct the metabolomic signature offers valuable insights for both epidemiological research and practical application. By focusing on these key metabolites, we simplify the complex metabolic interactions in the human body, making the results more interpretable and directly translatable to population-level health interventions. As metabolites are often interrelated, applying dimensionality reduction methods, such as the one used in this study, allows for a more manageable analysis of extensive metabolomics data, enhancing the clarity and usefulness of findings for public health practices. The approach not only facilitates the identification of tea-related metabolomic biomarkers, but also provides a more actionable understanding of the metabolic pathways that may mediate the relationship between habitual tea consumption and the lower risks of T2D complications, thereby informing targeted health promotion strategies.

Several plausible mechanisms may underlie the associations between tea consumption and T2D complications observed. For instance, bioactive compounds in tea, such as catechins, theaflavins, and flavones, are known to exhibit antioxidative and anti-inflammatory properties, as well as their ability to improve insulin sensitivity and regulate lipid metabolism[9, 30]. Our metabolomic analyses provide further mechanistic insights by identifying specific pathways through which tea may exert its protective effects. Notably, mediation and quantile-based g-computation analyses highlighted the glycolysis-related and lipoprotein lipid-related signatures as key contributors. This suggests that the benefits of tea are partially mediated through improvements in glycemic control and lipid profiles. Specifically, within the lipoprotein

lipid pathway, tea consumption was associated with lower levels of atherogenic lipid particles such as triglycerides in large LDL and LDL overall. These metabolites are established risk factors for vascular damage, and their reduction could directly attenuate the atherosclerotic processes underlying macrovascular complications[8]. Concurrently, the glycolysis pathway implicated biomarkers like glucose, linking tea intake to enhanced glucose metabolism. Dysregulation of glycolysis has been implicated in the pathophysiology of diabetic complications, as excessive glucose flux through this pathway can lead to the accumulation of advanced glycation end-products (AGEs) and increased oxidative stress[31]. Our finding is consistent with experimental evidence that tea polyphenols can activate AMPK and improve glycemic control[6, 7]. The central role of glycolytic regulation is further corroborated by our finding that HbA1c, a long-term marker of glycemic stress, served as a significant mediator between the tea-related metabolomic signature and both micro- and macrovascular complications.

Tea polyphenols exert their protective effects primarily through modulating glucose metabolism and vascular integrity. Specifically, tea polyphenols inhibit glucose absorption[32], enhance insulin sensitivity[33], and stimulate insulin secretion[34], while lipolytic properties further amplify metabolic benefits[35]. Notably, gallic acid (GA), a key phenolic component found in tea, exemplifies the pleiotropic benefits of tea polyphenols. Recent experimental evidence demonstrates that GA can ameliorate chronic colitis by modulating the gut microbiota, enhancing the intestinal barrier, and suppressing the TLR4/NF-κB signaling pathway, thereby reducing systemic inflammation[36]. This is highly relevant to T2D complications, as a compromised gut barrier and chronic low-grade inflammation are key drivers of insulin resistance and vascular dysfunction in diabetes. By potentially normalizing glucose metabolism and mitigating systemic inflammation, tea consumption could thereby mitigate the downstream effects of hyperglycemia on vascular damage[37, 38]. Beyond polyphenols, caffeine in tea may contribute independently to vascular protection and neuroprotective benefits[39], thus negatively associated with the risk of T2D complications. A clinical–experimental study reported that moderate and high caffeine intake was associated with a 65% reduction in diabetic retinopathy risk[39]. Mendelian randomization indicates genetically higher plasma caffeine and coffee intake protect against retinopathy and nephropathy[40]. However, in the UK Biobank sample of 26,472 participants, only 181 (0.7%) provided any information on tea caffeine content, and of these, 160 reported consuming decaffeinated tea. The paucity of quantitative caffeine data limits our ability to disentangle the relative contributions of caffeine versus polyphenols. Future work should therefore incorporate direct assessments of caffeine intake or biomarkers[41] to clarify their independent and joint roles in modulating T2D complications.

Cultural variations in tea preparation, particularly milk addition, were systematically evaluated to ensure result generalizability. An analysis base on the UK Biobank noted that most participants who reported tea intake also added milk to their infusions[42]. In our current analysis based on 26,472 participants, 2,097 reported milk-adding information, with 2,082 (99.3%) of them reported adding milk to their tea. In sensitivity analyses restricted to participants who did not add milk, the inverse associations between tea intake and both microvascular and macrovascular comorbidity burden remained materially unchanged, underscoring the

robustness of our findings despite potential interference from milk proteins[43]. By contrast, in the FISSIC cohort—reflecting traditional Chinese tea habits—virtually no participants added milk to tea, consistent with the cultural norm of drinking plain tea in China. Taken together, the persistence of protective associations in both a high-milk-use Western cohort and a nearly exclusively plain-tea Eastern cohort lends support to the generalizability of our findings on tea consumption and T2D complications, however, these results should be interpreted with caution, and future studies could directly quantify milk addition to disentangle milk's potential modulatory effects.

Furthermore, we conducted supplementary analyses to explore the associations by tea type. The inverse associations with T2D complications were most pronounced and consistent for black tea consumption, which was the predominant type consumed in the UK. In contrast, the associations for green tea and herbal tea were much weaker. This pattern could be attributed to several factors, including the higher statistical power for black tea analysis due to its prevalence, potential differences in the bioavailability and bioactivity of polyphenols (e.g., theaflavins in black tea versus catechins in green tea)[44, 45]. Unfortunately, detailed information on brewing methods (e.g., water temperature, steeping time) and tea concentration was not available in the cohorts, which represents an important limitation for precisely quantifying the intake of bioactive components. Future studies incorporating such detailed assessments are warranted to clarify the role of specific tea types and preparation practices.

The protective associations of tea consumption varied across diabetic complications, suggesting organ-specific biological mechanisms. We observed that the strength of the association was slightly greater for CeVD and PVD, compared to other complications like diabetic retinopathy or nephropathy. These findings suggest that the mechanisms underlying tea consumption and its protective effects may vary across different types of diabetic complications[46, 47]. Although both microvascular and macrovascular complications involve endothelial dysfunction, inflammation, and oxidative stress, the stronger association observed for CeVD and PVD could reflect more pronounced effects of tea on vascular health. The unique interaction between tea-related metabolites and these vascular mechanisms may partly explain the greater protective effect seen in these complications.

Hepatic metabolic regulation emerged as a central pathway mediating tea's systemic benefits, particularly in glucose and lipid homeostasis[48], which are key factors in the development of metabolic dysregulation in T2D. Previous studies have highlighted that alterations in hepatic metabolic processes, such as gluconeogenesis and glycolysis[49, 50], contribute significantly to systemic metabolic dysregulation. In our study, the gene-based analyses revealed that genes associated with tea-related metabolomic signature were primarily enriched in liver tissue, suggesting that tea consumption may offer protective benefits, at least partially, through modulation of hepatic metabolic functions. Tea polyphenols may help restore liver metabolic balance by improving glucose and lipid homeostasis[51, 52], which, in turn, can improve overall metabolic health and reduce the risk of diabetic complications.

Our findings support tea consumption as an accessible dietary intervention, though implementation requires personalized consideration of metabolic status. While the tea-related metabolomic signatures highlighted the importance of metabolomic health, particularly liver function and glycemic control, in mediating the protective effects of tea. However, these benefits may vary across individuals depending on their conditions. For instance, the weaker associations observed in individuals with advanced renal dysfunction (eGFR <60 mL/min/1.73 m^2) suggest that organ-specific metabolic impairments may attenuate the benefits of tea consumption. The finding emphasizes the importance of tailoring dietary recommendations according to the individual's metabolic and clinical profile.

The current study has several strengths, including the use of large-scale prospective cohorts, rigorous adjustments for potential confounders, and the integration of metabolomics, and mediation analyses to uncover underlying mechanisms. The integration of metabolomics enabled the identification of tea-related metabolomic signatures, offering novel insights into the biochemical pathways involved. The mediation analyses helped to clarify the extent to which tea-related metabolomic signatures contribute to the observed associations, shedding light on the biological mechanisms underlying the protective effects of tea consumption against diabetic complications. Additionally, the novelty of this study lies in its exploration of the metabolomic signatures associated with tea consumption and their direct connection to diabetic complications, which has not been extensively studied before. A series of sensitivity analyses, including competing risk models and propensity score methods, further support the reliability of the results.

Nevertheless, several limitations should be acknowledged. First, self-reported tea consumption data in both the UK Biobank and FISSIC cohorts might raise the possibility of misclassification. As with all dietary questionnaires, the data are susceptible to recall bias and social expectation bias, where participants may inaccurately recall their intake or report socially desirable answers. Although the FFQs used in both cohorts were validated for general dietary assessment, they were not specifically designed to capture detailed tea consumption patterns. Recalling intake over a 12-month period poses inherent challenges for quantifying episodic consumption behaviours. Besides, despite evidence suggesting stable tea intake habits over time[18], residual measurement error cannot be excluded. Such inaccuracies may arise from the self-reported nature of the data, difficulties in precise recall, or unaccounted variations in tea preparation and serving sizes, all of which could affect the precision of our exposure assessment. Second, our metabolomic analyses are limited by their basis in single baseline measurements and a focused panel of 251 metabolites. This precludes the assessment of metabolic changes over time and may have missed other pathways relevant to tea consumption and complications. Future research with longitudinal and broader metabolomic assessments is necessary to elucidate temporal relationships between tea consumption, metabolic pathways, and disease progression. Third, despite adjusting for a wide range of covariates and employing robust methods like GPS-IPW, the possibility of residual confounding from unmeasured factors remains. Our E-value analyses suggest that explaining away the observed associations would require unmeasured confounders with substantial strength. Therefore, while these findings provide novel evidence of robust associations, they should be interpreted

cautiously, and future research is warranted to validate these relationships. Fourth, we lacked quantitative data on the specific bioactive components in tea (e.g., catechins, theaflavins, caffeine) and therefore could not determine their individual contributions. Future research employing direct biochemical assessments is warranted to pinpoint the key active compounds. Fifth, the statistical associations offer mechanistic clues, suggesting that the protective effect of tea may operate through the modulation of specific metabolism like glycolysis and lipoprotein. It is important to note, however, some statistical models (e.g. quantile-based g-computation) assumes linearity, which may not capture more complex, non-linear biological dynamics. Sixth, the participants in our study were primarily middle-aged and older adults. Therefore, the generalizability of our findings to younger populations and other ethnic groups requires further investigation. Finally, because tea intake in UK Biobank was recorded as cups per day and in FISSIC as grams of dry leaves, we were limited to examining each cohort independently rather than pooling results. Converting UKB's cups into grams using a 2 g/cup assumption may introduce exposure misclassification—brewing strength, leaf density, and scoop size can range from 1 to 3 g per cup. Future studies should collect both cup-based and dry-weight measures, or leverage objective biomarkers, to enable cross-cohort harmonization and combined analyses.

5. Conclusion

In summary, our study demonstrates that moderate tea consumption, particularly around 2-3 cups per day, is associated with a lower incidence of T2D complications based on two ethnically and culturally distinct cohorts. These associations are partially mediated by specific metabolic pathways, suggesting that tea-related metabolic alterations may contribute to the observed health benefits. These findings suggest that incorporating moderate tea intake into the diet could be a supportive dietary strategy for individuals with T2D. While promising, our results are observational and require confirmation in interventional trials. Future research should focus on establishing causality and elucidating the roles of specific tea constituents and preparation methods, for better prevention and management of T2D complications.

Availability of data and material

Data used in this study are available from the corresponding authors upon reasonable request.

Informed consent

The UK Biobank was approved by the Northwest Multicentre Research Ethics Committee (21/NW/0157). The FISSIC was approved by the Peking University Institutional Review Board (IRB00001052-13027). Written informed consent was obtained from all participants.

Consent for publication

The authors confirm that the work described has not been published elsewhere.

Conflict of interest

The authors have no conflict of interest for the publication of this study.

Funding

This research was supported by the National Natural Science Foundation of China (Grant No. 82204135, MYW), National Natural Science Foundation of China (Grant No. 82473716, TW), the Natural Science Foundation of Fujian Province, China (Grant No. 2021J01352, TW), the Beijing Municipal Natural Science Foundation (7232237, MYW), Peking University Talent Introduction Program Project (BMU2024YJ010, MYW), and the National Key Research and Development Program of China (2020YFC2002900, JH).

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