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Unveiling the Roles of Immune Function and Inflammation in the Associations Between Dietary Patterns and Incident Type 2 Diabetes

Guangrui Yang[a*], Xihao Du[a*], Jingxuan Wang[a], Xuanwei Jiang[a], Shuxiao Shi[a], Jie Shen[b], and Victor W. Zhong[a]

[a]Department of Epidemiology and Biostatistics, School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [b]Medical Records and Statistics Office, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

ABSTRACT

Objective: To investigate the associations between data-driven dietary patterns, immune function, and incident type 2 diabetes (T2D) and the mediating effects of immune function.

Methods: This study included 375,665 participants without diabetes at baseline in the UK Biobank study. Dietary patterns were derived through principal component analysis of food frequency questionnaire data. Immune function was assessed using 14 individual inflammatory markers and an integrated low-grade inflammation score (INFLA-score). Cox proportional hazard models were used to estimate the associations of dietary patterns or immune function with incident T2D. Linear regressions were used to estimate the associations of dietary patterns with immune function. Mediating effects of immune function were quantified.

Results: During a median 14.6-year follow-up, 13,932 participants developed T2D. Four dietary patterns were identified: prudent diet (high in whole grains, vegetables, fruits, fish), wheat/dairy/eggs restrictive diet (limiting these foods), meat-based diet (high in red/processed meat, salt), and full-cream dairy diet (preference for full cream milk or dairy products). The prudent diet was negatively ($HR_{Q4\ vs\ Q1}$, 0.69 [95% CI, 0.65–0.72]), while the wheat/dairy/eggs restrictive diet ($HR_{Q4\ vs\ Q1}$, 1.08 [95% CI, 1.03–1.13]), meat-based diet ($HR_{Q4\ vs\ Q1}$, 1.12 [95% CI, 1.06–1.17]), and full-cream dairy diet ($HR_{Q4\ vs\ Q1}$, 1.08 [95% CI, 1.03–1.12]) were positively associated with incident T2D (all p for trend ≤0.04). The prudent diet was negatively and the full-cream dairy diet was positively associated with most inflammatory markers. Most inflammatory markers, especially INFLA-score (HR, 1.18 [95% CI, 1.16–1.20]), were positively associated with incident T2D. INFLA-score mediated 13% of the association with incident T2D for the prudent diet and 34% for the full-cream dairy diet.

Conclusions: This study identified four distinct dietary patterns and a range of inflammatory markers associated with incident T2D. A notable proportion of the associations between dietary patterns and T2D was mediated by immune function.

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Dietary pattern; immune function; inflammation; type 2 diabetes

Introduction

According to the 2019 Global Burden of Diseases, 29.7% of disability-adjusted life-years of diabetes were attributable to dietary factors (1). Accumulating evidence suggests that poor diet quality, characterized by specific foods or nutrients, is a strong modifiable risk factor for type 2 diabetes (T2D) (2,3). For instance, higher consumption of refined grains, processed meat, or desserts is associated with a higher risk of T2D (4). Conversely, adherence to a high-quality diet rich in fresh fruits, vegetables, or nuts is associated with a lower risk of T2D (5,6). Improving diet quality is an important approach to reducing the risk of T2D (7).

The effects of individual foods or nutrients on T2D may not capture the synergistic impact of the overall diet, as foods are typically consumed in combination. Dietary patterns, deriving from the combination of foods commonly consumed, provide a more comprehensive approach to understanding the dietary influences on T2D (8). Current methods for deriving dietary patterns fall into hypothesis-driven and data-driven categories. The hypothesis-driven approach, which relies on prior knowledge, assesses population adherence to nutritional recommendations but is limited to predefined dietary components and may not fully reflect the diversity of actual dietary habits (9). Moreover, these patterns may be challenging for individuals to follow and do not account for variations in real-world diets. In contrast, the data-driven approach, based

CONTACT Victor W. Zhong wenze.zhong@shsmu.edu.cn School of Public Health, Shanghai Jiao Tong University School of Medicine, 415 East No. 1 Building, 227 South Chongqing Rd, Shanghai, 200025, China; Jie Shen slyysj2009@163.com Medical Records and Statistics Office, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 316 No. 15 Building, 600 Yi Shan Rd, Shanghai, 200233, China.
*These authors contributed equally to this work.
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on actual food intake, provides insights into participants' dietary behaviors and is more effective in identifying novel patterns and informing dietary guidelines (9,10). However, commonly derived data-driven patterns are often oversimplified as "Western" or "Prudent," and further research is needed to investigate the associations between other dietary patterns and incident T2D (8).

The mechanisms underlying the associations between dietary patterns and incident T2D remain unclear. Immune dysfunction, a key factor in the pathogenesis of T2D, leads to insulin resistance and impaired β-cell function and is often reflected in alterations in various inflammatory markers (11). These markers, including total and differential leukocytes and C-reactive protein (CRP), indicate the immune system state and have been associated with T2D risk (12). However, the roles of other important inflammatory markers, such as red cell distribution width (RDW) and platelet-to-lymphocyte ratio (PLR), in T2D development remain understudied in population-based prospective research. Furthermore, the collective impact of inflammatory markers, representing overall immune function, on T2D risk is not well understood. Additionally, while dietary patterns are known to influence both inflammation and T2D risk, the extent to which inflammatory markers mediate this relationship needs to be further investigated.

In this study, we conducted a prospective study using data from the UK Biobank to investigate the associations between dietary patterns, inflammation, and incident T2D. We also quantified the mediating effects of individual and composite inflammatory markers on the associations between dietary patterns and incident T2D.

Materials and methods

Study population

The participants of this study were from the UK Biobank study, an ongoing prospective cohort study that recruited over 500,000 individuals between 2006 and 2010, aged 37–73 years at baseline (13). All participants provided written informed consent. The UK Biobank study received ethical approval from the North West Multicenter Research Ethics Committee. At the time of recruitment, baseline blood measures were collected, and touch-screen questionnaires were administered to collect information on demographics, socioeconomics, diet, and health-related history and conditions. This research utilized data provided by patients and collected by the NHS as part of their care and support and was conducted using the UK Biobank Resource under application number 101169.

Ascertainment of the outcome and follow-up

The diagnosis of T2D during follow-up was ascertained based on the International Statistical Classification of Diseases and Related Health Problems, 10th (ICD10) edition, code E11 (14). Participants were followed from the date of attending assessment centers until the date of T2D diagnosis, loss to follow-up, death, or the end of the follow-up (October 31, 2022, for centers in England, August 31, 2022, for centers in Scottish, May 31, 2022, for centers in Wales), whichever was the earliest.

Dietary assessment

Participants completed a self-administered food frequency questionnaire (FFQ) at baseline, consisting of 29 questions assessing the amount, frequency, and type of various food items consumed over the past year. These items included cheese, bread, cereals, vegetables (cooked or raw), fruits (fresh or dried), beverages (tea, coffee, milk, or water), fish (oily or non-oily), poultry, meat (beef, mutton, pork, processed meat, or poultry), and elimination of specific food groups (eggs, dairy, wheat, or sugar). While the FFQ does not allow for the calculation of total energy, it has been shown to reliably estimate the intake of main food groups in the UK Biobank population (15).

Dietary patterns were derived using principal component analysis (PCA) applied to the 29 food items. The determination of the number of components to retain was guided by the Bayesian Information Criterion (BIC) Index under different assumed numbers of dietary patterns and empirical interpretability (16). Loadings were obtained through Promax rotation, and the rotated components were named based on the combination of their highest loadings.

Assessment of immune function

Various individual inflammatory markers, implicated to different extents in immune function, were employed to investigate the mediating effects of immune function in the associations between dietary patterns and incident T2D (17). These markers encompassed absolute counts of neutrophils, eosinophils, basophils, monocytes, lymphocytes, platelets, and leukocytes, as well as the level of CRP, RDW, and the percentage of lymphocytes, monocytes, and neutrophils to the total leukocyte count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). Implausible outliers of inflammatory markers (<quartile (Q) 1–3*interquartile (IQR) or > Q3 + 3*IQR) were excluded from all analyses (16).

An integrated low-grade inflammation score (INFLA-score), computed using CRP, NLR, leukocytes, and platelets count, was utilized to assess the collective effects of inflammatory markers (18). To compute the INFLA-score, for all four components, being in the highest deciles (7th to 10th) was given values from +1 to +4; being in the lowest deciles (1st to 4th) was given values from −4 to −1; being in the 5th or 6th decile was given a value of 0. The INFLA-score represented the arithmetic sum of these scores, ranging between −16 and +16, with a higher score indicating a higher level of low-grade inflammation.

Assessment of covariates

Covariates included demographic and socioeconomic characteristics (age, sex, ethnicity, Townsend deprivation index [TDI], employment status, and education), lifestyle factors (smoking status, drinking status, physical activity, and daily sleep duration), and clinical information (body mass index [BMI], prevalent cardiovascular disease [CVD], hyperlipidemia, hypertension, and family history of diabetes). These covariates were selected based on their well-reported associations with dietary patterns, immune function, and T2D risk, thereby having the potential to confound the associations

under investigation (16,19). Ethnicity was self-reported and classified as White or others. Education was categorized into a higher degree (college degree, university degree, or professional qualifications), any school degree (advanced levels, advanced subsidiary levels, ordinary levels, General Certificate of Secondary Education, Certificate of Secondary Education, or equivalent), vocational qualification (National Vocational Qualification, Higher National Diploma, Higher National Certificate, or equivalent), or none of the preceding groups. Smoking and drinking status were classified as never, former, or current. Physical activity was assessed using total metabolic equivalent task minutes (METs) per week.

Statistical analysis

Baseline characteristics of participants by incident T2D status were presented using numbers (percentages) for categorical variables and mean (standard deviation [*SD*]) for continuous variables. Three regression analyses were performed. Firstly, multivariable Cox proportional hazard models were employed to investigate the associations of dietary patterns with incident T2D. The association estimates were given by dividing a dietary pattern score into quartiles and based on one SD increment in the score. The medians of dietary pattern score quartiles were used as a continuous variable to test the linear trend. Secondly, multiple linear regression models were employed to assess the associations of dietary patterns with 15 inflammatory markers. Thirdly, multivariable Cox proportional hazards models were employed to investigate the associations of 15 inflammatory markers with incident T2D. All inflammatory markers were standardized before conducting regression by subtracting the mean and dividing by the SD. For Cox models, the proportional hazards assumption was tested using the Kolmogorov-type supremum test and no violation was found (20). Results were presented as hazard ratios (HRs) with their 95% confidence intervals (CIs). To control for potential confounding, a series of models were fitted progressively: (1) model 1 was adjusted for key demographic and socioeconomic factors including age, sex, ethnicity, TDI, employment status, and education; (2) model 2 was additionally adjusted for lifestyle factors including smoking status, drinking status, physical activity, daily sleep duration and its squared term, and BMI; (3) model 3 was further adjusted for clinical factors including history of CVD, hyperlipidemia, and hypertension, and family history of diabetes.

Mediation analyses were performed to estimate the mediating effects of immune function in the associations between dietary patterns and incident T2D. Direct and indirect effects of dietary patterns on incident T2D and mediated proportion by immune function were estimated with 5000 simulations of non-parametric bootstrapping by using R package *Lavaan*, adjusting for the model 3 covariates.

Sensitivity analyses were performed by excluding events documented during the first two years of follow-up from the analysis to avoid reverse causation.

Statistical analyses were conducted with R version 4.3.1. For the analyses involving 15 inflammatory markers, the Bonferroni procedure corrected $p < 0.05$ was used as the threshold to determine statistical significance. Otherwise, a conventionally two-sided $p < 0.05$ was used.

Results

After excluding participants with prevalent diabetes events and missing data at baseline, 375,665 participants were included (Figure S1). During a median follow-up of 14.6 years (IQR, 13.8–15.3), 13,932 participants developed T2D. Compared to participants without incident T2D, those who developed T2D were generally older, male, non-White, unemployed, and smokers, with higher TDI scores, lower education levels, less physical activity, shorter sleep durations, higher BMIs, and more comorbidities (Table 1). Participants without incident T2D tended to have lower levels of low-grade inflammation and adhere to a more prudent diet.

Associations of dietary patterns with incident T2D

Four dietary patterns were identified according to the plot of the BIC Index (Figure S2). Table S1 presents the factor

Table 1. Baseline Characteristics of Study Participants in the UK Biobank.

	Incident type 2 diabetes		
Characteristics	No ($n = 361,733$)	Yes ($n = 13,932$)	p
Age, mean (*SD*), years	56.1 (8.1)	59.0 (7.4)	<0.001
Male, *n* (%)	163,315 (45.1)	8016 (57.5)	<0.001
White race, *n* (%)	346,405 (95.8)	12,622 (90.6)	<0.001
Townsend deprivation index, mean (*SD*)	−1.5 (2.9)	−0.7 (3.3)	<0.001
Employed, *n* (%)	336,774 (93.1)	12,377 (88.7)	<0.001
Education level*, *n* (%)			<0.001
Higher degree	146,226 (40.4)	3894 (28.0)	
Any school degree	140,143 (38.7)	5034 (36.1)	
Vocational qualification	22,971 (6.4)	1242 (8.9)	
None of the preceding groups	52,393 (14.5)	3762 (27.0)	
Smoking status, *n* (%)			<0.001
Never	202,404 (56.0)	6271 (45.0)	
Previous	123,763 (34.2)	5649 (40.5)	
Current	35,566 (9.8)	2012 (14.4)	
Drinking status, *n* (%)			<0.001
Never	12,850 (3.6)	874 (6.3)	
Previous	10,735 (3.0)	733 (5.3)	
Current	338,148 (93.5)	12,325 (88.5)	
METs per week, mean (*SD*), min	1680.4 (2362.0)	1640.0 (2658.4)	<0.001
Daily sleep duration, mean (*SD*), h	7.2 (1.1)	7.1 (1.3)	<0.001
BMI, mean (*SD*), kg/m^2	26.9 (4.3)	30.9 (5.2)	<0.001
Health history and conditions, *n* (%)			
Cardiovascular disease	20,190 (5.6)	2272 (16.3)	<0.001
Hyperlipidemia	47,212 (13.1)	4491 (32.2)	<0.001
Hypertension	86,609 (23.9)	6753 (48.5)	<0.001
Family history of diabetes	47,896 (13.2)	3063 (22.0)	<0.001
INFLA-score, mean (*SD*)	−0.3 (6.3)	1.9 (6.3)	<0.001
Dietary patterns, mean (*SD*)†			
Prudent diet	0.01 (0.99)	−0.29 (1.02)	<0.001
W/d/e restrictive diet	−0.02 (0.99)	−0.03 (0.81)	<0.001
Meat-based diet	0.01 (0.99)	−0.02 (1.00)	<0.001
Full-cream dairy diet	0.01 (1.00)	−0.03 (0.99)	<0.001

Abbreviations: BMI = body mass index, INFLA score = low-grade chronic inflammation score, METs = metabolic equivalent task minutes, *SD* = standard deviation, W/d/e = wheat/dairy/eggs.

*Education was self-reported and grouped into four categories, higher degree (college or university degree, or professional qualifications), any school degree (advanced levels, advanced subsidiary levels, ordinary levels, General Certificate of Secondary Education, Certificate of Secondary Education, or equivalent), vocational qualification (National Vocational Qualification, Higher National Diploma, Higher National Certificate, or equivalent), or none of the preceding groups.

†Dietary pattern scores were standardized.

loadings of all food items in each dietary pattern. Figure 1 highlights the food items with an absolute factor loading >0.2 in each pattern. These patterns were labeled as follows based on foods with high loadings: the prudent diet, wheat/dairy/eggs restrictive diet, meat-based diet, and full-cream dairy diet. The prudent diet, characterized by high intakes of whole grains, vegetables, fruit, and fish, explained 7.4% of the variation. The wheat/dairy/eggs restrictive diet, indicating a tendency to limit these food items in the daily diet, explained 6.8% of the variation. The meat-based diet, marked by high intakes of red or processed meat and salt, explained 6.7% of the variation. The full-cream dairy diet, reflecting a preference for full-cream milk and dairy products, explained 6.6% of the variation. Together, these patterns accounted for 27.5% of the variation in food intake.

In the fully adjusted models, for each SD higher dietary pattern score, the prudent diet (HR, 0.87 [95% CI, 0.86–0.89]) was negatively associated with incident T2D, while the wheat/dairy/eggs restrictive diet (HR, 1.03 [95% CI, 1.02–1.05]), meat-based diet (HR, 1.04 [95% CI, 1.02–1.05]), and full-cream dairy diet (HR, 1.03 [95% CI, 1.01–1.04]) were positively associated with incident T2D (Table 2).

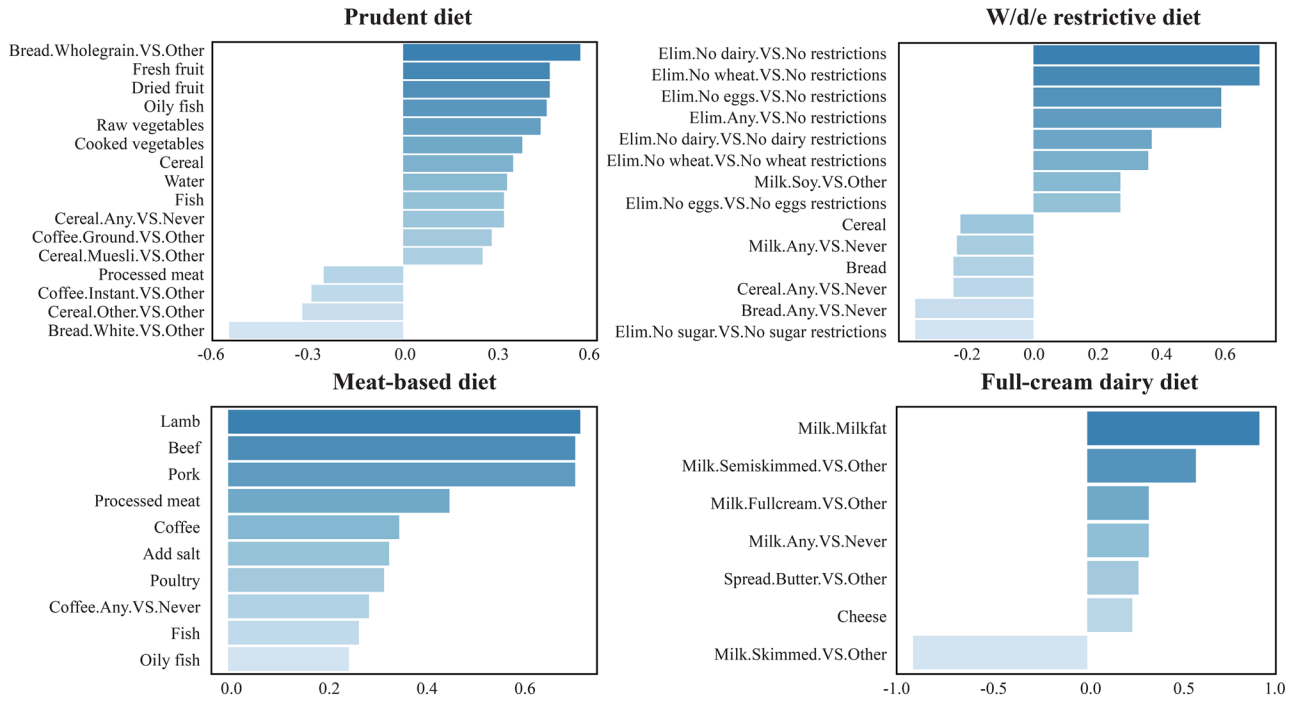

Figure 1. The food items with absolute factor loadings >0.2 in each dietary pattern. Results were from principal component analysis with Promax rotation. Abbreviations: Elim = elimination, W/d/e = wheat/dairy/eggs.

Table 2. Associations of Dietary Patterns with Incident Type 2 Diabetes*.

	Prudent diet†			Wheat/dairy/eggs restrictive diet†			Meat-based diet†			Full-cream dairy diet†		
	N_{case}/N_{total}	HR (95% CI)	p	N_{case}/N_{total}	HR (95% CI)	p	N_{case}/N_{total}	HR (95% CI)	p	N_{case}/N_{total}	HR (95% CI)	p
Per *SD*	13,932/375,665	0.87 (0.86–0.89)	<0.001	13,932/375,665	1.03 (1.02–1.05)	<0.001	13,932/375,665	1.04 (1.02–1.05)	<0.001	13,932/375,665	1.03 (1.01–1.04)	0.03
Quartiles												
Q1	4960/93,916	Reference		3070/93,916	Reference		3616/93,916	Reference		3437/93,916	Reference	
Q2	3649/93,916	0.87 (0.84–0.91)	<0.001	3477/93,916	1.06 (1.01–1.11)	0.03	3618/93,916	1.08 (1.03–1.14)	<0.001	3976/93,916	1.05 (1.01–1.11)	0.03
Q3	2990/93,916	0.80 (0.76–0.83)	<0.001	3569/93,916	1.05 (1.00–1.10)	0.07	3357/93,916	1.12 (1.07–1.18)	<0.001	3381/93,916	1.03 (0.99–1.09)	0.17
Q4	2353/93,916	0.69 (0.65–0.72)	<0.001	3816/93,916	1.08 (1.03–1.13)	0.002	3341/93,916	1.12 (1.06–1.17)	<0.001	3138/93,916	1.08 (1.03–1.12)	0.02
P for trend			<0.001			0.01			<0.001			0.04

Abbreviations: CI = confidence interval, HR = hazard ratio.

*Cox models were adjusted for age (continuous), sex (male/female), ethnicity (White or others), education (higher degree, any school degree, vocational qualification, none of the preceding groups), employment status (employed or not), Townsend deprivation index (continuous), smoking status (never, previous, or current), drinking status (never, previous, or current), metabolic equivalents task minutes per week (continuous), sleep duration hours per day (continuous), sleep duration hours per day squared (continuous), body mass index (continuous), cardiovascular diseases (yes/no), hyperlipidemia (yes/no), hypertension (yes/no), and family history of diabetes (yes/no).

†Dietary pattern scores were standardized.

Compared to individuals in the lowest quartile, those in the highest quartile of the prudent diet score had a 31% lower risk of T2D (HR, 0.69 [95% CI, 0.65–0.72]), whereas those in the highest quartile of the wheat/dairy/eggs restrictive diet score, the meat-based diet score, and the full-cream dairy diet score had an 8% (HR, 1.08 [95% CI, 1.03–1.13]), a 12% (HR, 1.12 [95% CI, 1.06–1.17]), and an 8% (HR, 1.08 [95% CI, 1.03–1.12]) higher risk of T2D, respectively (all p for trend ≤0.04). Partially adjusted results from model 1 and model 2 are shown in Table S2.

Associations of dietary patterns with immune function

Figure 2(A) and Table S3 show the standardized β coefficients from the linear regression analysis of each dietary pattern with the 15 inflammatory markers. Compared to the prudent

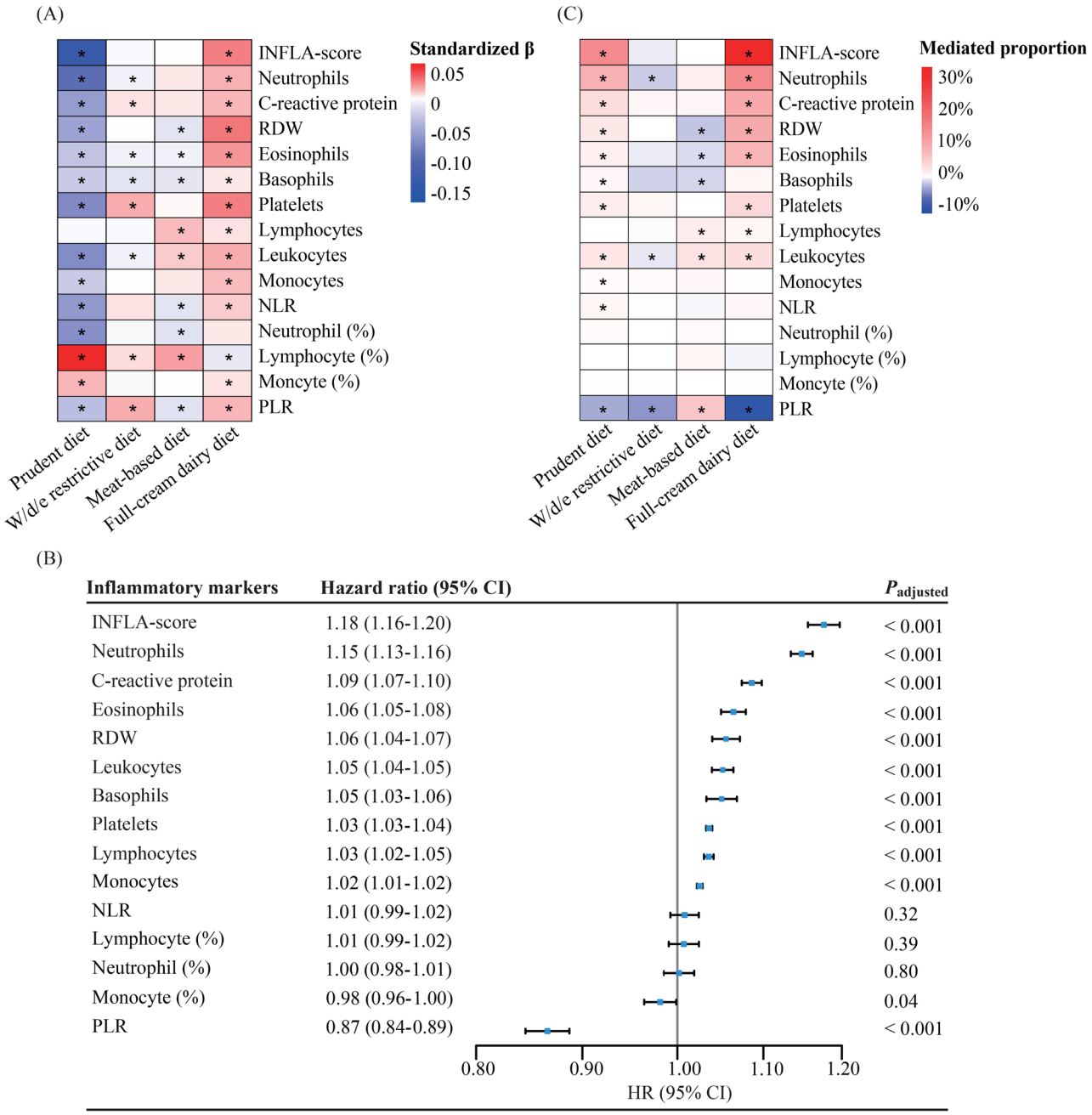

Figure 2. The association of dietary patterns with immune function and inflammatory markers with incident T2D, and the mediated proportion of inflammatory markers. (A) Associations of dietary patterns with inflammatory markers. (B) Associations of inflammatory markers with incident type 2 diabetes. $p_{adjusted}$: Bonferroni adjusted p-value. (C) Mediated proportions of inflammatory markers for the associations between dietary patterns and incident type 2 diabetes. All models were adjusted for age (continuous), sex (male/female), ethnicity (White or others), education (higher degree, any school degree, vocational qualification, none of the preceding groups), employment status (employed or not), Townsend deprivation index (continuous), smoking status (never, previous or current), drinking status (never, previous or current), metabolic equivalents task minutes per week (continuous), sleep duration hours per day (continuous), sleep duration hours per day squared (continuous), body mass index (continuous), cardiovascular diseases (yes/no), hyperlipidemia (yes/no), hypertension (yes/no), and family history of diabetes (yes/no). Dietary pattern scores and inflammatory markers were standardized. Abbreviations: NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, RDW = red blood cell distribution width, W/d/e = wheat/dairy/eggs. *Bonferroni adjusted $p < 0.05$.

diet and full-cream dairy diet, the associations of the wheat/dairy/eggs restrictive diet and meat-based diet with inflammatory markers were weaker and less consistent. The prudent diet was negatively associated with 12 inflammatory markers, with standardized β coefficients ranging from −0.02 for basophils and monocytes to −0.12 for the INFLA-score. The prudent diet also showed positive associations with 2 inflammatory markers, with standardized β coefficients of 0.01 for monocyte (%) and 0.07 for lymphocyte (%). The full-cream dairy diet exhibited positive associations with 13 inflammatory markers, with standardized β coefficients ranging from 0.003 for basophils to 0.03 for the INFLA-score. Lymphocyte (%) was negatively associated with the full-cream dairy diet, with a standardized β coefficient of −0.01.

Associations of immune function with incident T2D

Most inflammatory markers were positively associated with incident T2D (Figure 2(B)). Ranked by the strength of the associations per one SD increment in inflammatory markers, significant positive associations with T2D were observed for INFLA-score (HR, 1.18 [95% CI, 1.16–1.20]), neutrophils (HR, 1.15 [95% CI, 1.13–1.16]), CRP (HR, 1.09 [95% CI, 1.07–1.10]), eosinophils (HR, 1.06 [95% CI, 1.05–1.08]), RDW (HR, 1.06 [95% CI, 1.04–1.07]), leukocytes (HR, 1.05 [95% CI, 1.04–1.05]), basophils (HR, 1.05 [95% CI, 1.03–1.06]), platelets (HR, 1.03 [95% CI, 1.03–1.04]), lymphocytes (HR, 1.03 [95% CI, 1.02–1.05]), and monocytes (HR, 1.02 [95% CI, 1.01–1.02]). However, PLR (HR, 0.87 [95% CI, 0.84–0.89]) and monocytes (%) (HR, 0.98 [95%CI, 0.96–1.00], $p = 0.04$) were negatively associated with incident T2D.

Mediating effects of immune function

Figure 2(C) shows the mediated proportions of immune function for the associations between four dietary patterns and incident T2D. Consistent mediation effects were observed for the prudent diet and the full-cream dairy diet. Six individual inflammatory markers significantly mediated the associations of the prudent diet and full-cream dairy diet with incident T2D: neutrophils (mediated proportion: 7.8% for the prudent diet and 12.8% for the full-cream dairy diet), CRP (3.0 and 8.8%), RDW (1.8 and 8.6%), eosinophils (1.1 and 7.2%), platelets (1.3 and 3.4%), and leukocytes (2.1 and 2.8%). The INFLA-score had the highest mediated proportion, 13.0% for the prudent diet and 34.0% for the full-cream dairy diet. The mediating effects of most inflammatory markers in the associations of the wheat/dairy/eggs restrictive diet and meat-based diet with incident T2D were not significant. The direct and indirect effects of dietary patterns on incident T2D, along with the mediated proportion by inflammatory markers, are presented in Table S4.

Sensitivity analysis

The associations of dietary patterns or inflammatory markers with incident T2D remained significant after excluding participants with less than two years of follow-up (Tables S5 and S6).

Discussion

In this large prospective cohort study, four dietary patterns were identified in the UK population. The prudent diet was negatively associated with incident T2D, while the wheat/dairy/eggs restrictive diet, meat-based diet, and full-cream dairy diet were positively associated with incident T2D. Additionally, the prudent diet showed negative associations with immune dysfunction, whereas the full-cream dairy diet showed positive associations. Immune dysfunction was positively associated with incident T2D. Six individual inflammatory markers significantly mediated the associations of the prudent diet and full-cream dairy diet with incident T2D, with mediated proportions ranging from 1.1 to 12.8%. The integrated INFLA-score showed the strongest mediation effects, 13% for the prudent diet and 34% for the full-cream dairy diet.

Our study identified four dietary patterns that collectively accounted for 27.5% of the variation in food intake. This performance is comparable to or exceeds previous studies utilizing fully data-driven methods based on FFQ data (16, 21,22). These dietary patterns provide valuable insight into the prevailing dietary habits within the UK population, reflecting their typical eating behaviors and tendencies. While the characteristics of these patterns were consistent with previous findings, their associations with incident T2D were investigated for the first time, revealing differential results (16). The novel associations of these four dietary patterns with T2D are largely consistent with existing evidence related to the associations of relevant food groups, nutrients, and dietary patterns with metabolic diseases (2,4,23). The prudent diet resembles the "healthy/prudent" dietary pattern, negatively associated with obesity, insulin resistance, and incident T2D (24). The meat-based diet is similar to the "Western" dietary pattern, which has been positively associated with obesity and incident T2D (25). Whole grain intake was considered a protective factor, while refined grain intake may be a risk factor for T2D (26,27). The association between dairy consumption and T2D remains controversial, likely influenced by factors including varying fat content, processing levels, added ingredients, and the proportion of lactose intolerance within the study population (28–30). The association between moderate egg intake and T2D differed by geographic region, with no observed association in European populations (31). Although the associations of these foods with incident T2D differed depending on their processing levels and fat content, which were not distinguished in the wheat/dairy/eggs restrictive diet, our findings indicated that restricting all types of wheat, dairy, or eggs in the daily diet was associated with an increased risk of T2D. We also found that a preference for full-cream milk and dairy food was a risk factor for T2D, with a modest yet consistent positive association after adjusting for various covariates. This may be attributable to the high fat content and synergistic effects of dietary components within this pattern.

A major contribution of our study is the comprehensive mechanistic understanding it provides regarding the role of immune function in the associations between diet and T2D,

through analyzing 14 individual inflammatory markers and an integrated inflammation score. Consistent with prior research, the prudent diet displayed negative associations with most inflammatory markers, particularly the INFLA-score (16). The associations are likely attributable to the anti-inflammatory effects of antioxidant components found in fruits and vegetables, such as vitamins and flavonoids (32). Although previous studies have suggested that a high-fat diet may trigger early inflammatory responses in the liver and lead to systemic inflammation, the association between the full-cream dairy diet and inflammation remains unclear, with inconsistent findings from population-based studies (33,34). Our study provides prospective evidence supporting a positive association between the full-cream dairy diet and inflammation. Surprisingly, we did not observe significant associations between the meat-based diet and most inflammatory markers, contrary to previous findings that reported positive associations of red and processed meat with incident T2D (35). This discrepancy may be attributed to the potential anti-inflammatory effects of specific dietary components within our meat-based pattern, such as fish, particularly oily fish rich in omega-3 polyunsaturated fatty acids, and coffee, which may offset the pro-inflammatory effects of red and processed meat (36,37).

Various circulating inflammatory markers, with each playing different roles in immune function, were associated with incident T2D. Although the biological link between immune dysfunction and T2D is well-known, the specific roles of these inflammatory markers remain inadequately understood (12). Our study advances this understanding by investigating the associations of less frequently studied inflammatory markers, including platelets, RDW, and PLR, with incident T2D. Platelets and RDW, though less frequently studied previously, have been implicated in the pathophysiology of T2D. Platelets play key roles in regulating inflammatory responses, maintaining vascular integrity, and supporting regenerative processes, all of which are crucial in the T2D development (38). RDW, a measure of red blood cell distribution, has also been linked to inflammation and oxidative stress (39). Prior studies have found associations between these markers and metabolic dysfunction indicators, such as pancreatic β-cell dysfunction and abdominal obesity, underscoring their potential roles in the T2D development (40,41). Notably, our study, using a prospective design, identified a novel negative association between PLR and incident T2D, consistent with a cross-sectional study reporting lower PLR in individuals with prediabetes and diabetes compared to those with normoglycemia (42). Additionally, the INFLA-score, used to quantify the body's level of low-grade inflammation, was investigated for the first time regarding its association with incident T2D (18). The stronger association of the INFLA-score with incident T2D compared to individual inflammatory markers highlights the synergistic effects among the markers and its potential as a robust predictor of T2D. Moreover, our study corroborates the positive associations of well-established inflammatory markers, including CRP and total and differential leukocyte counts, with incident T2D, consistent with previous studies (43,44). Leukocytes and their subtypes can infiltrate adipose tissue and secrete proinflammatory cytokines such as IL-6, TNF-α, and IL-1β, which contribute to insulin resistance (45).

Our study revealed that up to 34% of the associations between dietary patterns and T2D could be explained by altered immune function, though the mediated proportions varied substantially across different dietary patterns and different inflammatory markers. Notably, the INFLA-score exhibited the strongest mediating effects in both the prudent and full-cream dairy diet-T2D relationships, underscoring the pivotal role of low-grade inflammation in T2D development. Interestingly, neutrophils displayed stronger mediating effects than other individual inflammatory markers including CRP, which is the most widely used surrogate marker for inflammation (46). This suggests that within the diet-inflammation-T2D pathway, changes in cellular-level inflammatory responses to dietary intake are a more crucial pathogenic mechanism compared to CRP, which reflects general inflammation levels (46,47). The mediated proportions of all inflammatory markers were stronger for the full-cream dairy diet than for the prudent diet, potentially due to the early inflammatory responses in the liver triggered by high-fat intake (33).

As the largest single prospective study linking dietary patterns, immune function, and incident T2D, our study offers several insights that may be valuable for future research. Firstly, the identification of four distinct dietary patterns in the UK population, including the novel wheat/dairy/eggs restrictive and full-cream dairy diet, underscores the importance of using data-driven approaches to capture population-specific dietary habits. Secondly, the varied associations between different inflammatory markers and T2D risk emphasize the importance of examining a comprehensive panel of immune markers rather than relying solely on traditional indicators like CRP. Thirdly, the substantial mediating effects of immune function highlight its crucial role in the diet-T2D relationship, which may help inform the design of immune mechanism-based dietary intervention studies.

However, our study has several limitations. Firstly, while the prospective design strengthens the evidence, it does not allow us to establish causal relationships between dietary patterns, inflammatory markers, and incident T2D. Secondly, reliance on self-reported data from FFQs may have introduced recall bias. The use of more objective dietary assessment tools, such as biomarkers of dietary intake, could help mitigate this issue in future research. Thirdly, although diet and immune data were collected at baseline, we assume a sequential relationship between them. A longitudinal design with repeated measures could help better understand their associations. Fourthly, we assumed that dietary patterns remained stable during follow-up. While dietary habits tend to be relatively stable in adulthood, they can change over time. Incorporating repeated dietary assessments in future research could help account for potential changes in dietary intake over the study period. Fifthly, residual confounding remains possible despite comprehensive adjustment for potential confounders and correction for multiple comparisons. Finally, as a volunteer cohort, participants may not be fully representative of the broader UK population,

potentially limiting the generalizability of findings beyond this context. Moreover, dietary differences between the UK and other regions may affect the applicability of the findings to non-UK populations. Specific dietary patterns identified in our study, such as the prudent and meat-based diet, have shown consistent associations with incident T2D reported from different populations (24,25,48). Nevertheless, extrapolating the results of our study to other populations, especially those who have different dietary habits, genetic backgrounds, and environmental exposures compared with the UK population, requires caution. Future research conducted in more diverse populations is encouraged to assess the consistency of these associations across different demographic and cultural settings.

In conclusion, four dietary patterns were identified in the UK population. The dietary patterns were significantly associated with incident T2D and immune function. Inflammation was positively associated with incident T2D and played a substantial mediating role in the associations of dietary patterns with incident T2D. Our findings are helpful for the development of immune mechanism-based dietary guidelines for the prevention and management of T2D.

Author contributions

GY and XD contributed equally to the paper as joint first authors. VWZ and JS are joint corresponding authors. VWZ, JS, GY, and XD designed the research. GY and XD performed statistical analyses. GY and VWZ drafted the manuscript. All authors interpreted data, critically reviewed and revised the manuscript, and read and approved the final version. VWZ is the guarantor of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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