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Original article

A healthful plant-based diet is associated with lower type 2 diabetes risk via improved metabolic state and organ function: A prospective cohort study☆

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ABSTRACT

Background: Plant-based diets are becoming increasingly popular due to favourable environmental footprints and have been associated with lower risk of type 2 diabetes mellitus (T2DM). Here, we investigated the potential mechanisms to explain the lower T2DM risk observed among individuals following plant-based diets.
Methods: Prospective data from the UK Biobank, a cohort study of participants aged 40 to 69 years at baseline, was evaluated. Associations between healthful and unhealthful plant-based indices (hPDI and uPDI) and T2DM risk were analysed by multivariable Cox regression models, followed by causal mediation analyses to investigate which cardiometabolic risk factors explained the observed associations.
Results: Of 113,097 study participants 2,628 developed T2DM over 12 years of follow-up. Participants with the highest hPDI scores (Quartile 4) had a 24 % lower T2DM risk compared to those with the lowest scores (Quartile 1) [Hazard Ratio (HR): 0.76, 95 % Confidence Interval (CI): 0.68–0.85]. This association was mediated by a lower BMI (proportion mediated: 28 %), lower waist circumference (28 %), and lower concentrations of HBA1c (11 %), triglycerides (9 %), alanine aminotransferase (5 %), gamma glutamyl transferase (4 %), C-reactive protein (4 %), insulin-like growth factor 1 (4 %), cystatin C (4 %) and urate (4 %). Higher uPDI scores were associated with a 37 % higher T2DM risk [HR: 1.37, 95 % CI:1.22- 1.53], with higher waist circumference (proportion mediated: 17 %), BMI (7 %), and higher concentrations of triglycerides (13 %) potentially playing mediating roles.
Conclusion: Healthful plant-based diets may protect against T2DM via lower body fatness, but also via normoglycaemia, lower basal inflammation as well as improved kidney and liver function.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CRP, C-reactive protein; GGT, Gamma glutamyl transferase; HbA1c, haemoglobin A1c; hPDI, healthful plant-based index; IGF-1, Insulin growth factor - 1; LDL, Low density lipoprotein; Lip A, Lipoprotein A; NAFLD, Non-alcoholic fatty liver disease; PDI, plant-based diet index; SD, standard deviation; T2DM, Type 2 Diabetes; uPDI, unhealthful plant-based diet index; UK, United Kingdom.

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Introduction

The global prevalence of diabetes was 6.1 % in 2021 with a projection to increase to over 10 % by 2050, with Type 2 Diabetes Mellitus (T2DM) accounting for approximately 95 % of cases [1–3]. In the UK alone, approximately 4.7 million individuals are living with T2DM, costing the National Health Service around £10 billion annually [4].

At least 75 % of all T2DM cases could be preventable by a healthy lifestyle [5]. Moreover, adopting a healthy lifestyle can reduce the risk of cause-specific and total diabetes mortality by up to 56 % [5]. In relation to diet, high consumption of fruits, vegetables, whole grains, dairy, and coffee have been associated with lower T2DM risk. By contrast, intakes of sugary drinks and red and processed meat have been associated with increased T2DM risk [6]. The above-mentioned findings on food groups and T2DM risk are in agreement with studies which suggest that vegan and vegetarian dietary patterns are associated with lower T2DM risk and better diabetes control [7,8]. Overall, plant-based diets are gaining popularity; in 2021, 13–15 % of Germans, Swiss and UK citizens stated that they were following a meat-free diet [9]. However, operationalizations of plant-based diets merely based on the exclusion of animal foods do not offer insights into the quality of the consumed plant-based foods. Therefore, the healthful and unhealthful Plant-Based Diet Indexes (hPDI and uPDI) have been established as measures of plant-based diet quality. Higher hPDI scores, reflecting a plant-based diet low in sweets, desserts, refined grains, potatoes, and sugary drinks, have been associated with a lower risk of T2DM, while an unfavourable plant-based dietary pattern characterized by high uPDI values has been associated with a higher risk [10].

The aim of the current study was to investigate the biological mechanisms that underlie the associations between the healthful and unhealthful PDI with T2DM risk using data from a large-scale prospective cohort study, the UK Biobank. Specifically, we hypothesized that obesity/glucose metabolism, inflammation, kidney function, liver function, hormonal and lipid pathways could be potential mediators, given that these factors have been shown to be associated with both plant-based diets [11–14] and T2DM risk [15–17] in previous studies.

Methods

Study population

The present analyses are based on data from the UK Biobank, a large-scale prospective study among over 500,000 volunteers between the age of 40 to 69. Recruitment occurred from 2006 to 2010 across centres in England, Scotland and Wales, and included a variety of comprehensive baseline assessments. A detailed description of the study protocol can be found elsewhere [18] .

The UK Biobank study obtained ethical approval from the Community Health Index Advisory Group for Scotland, the North West Multicentre Research Ethics Committee for the UK. Written informed consent was obtained from all participants.

Dietary assessment and plant based diet indices

Within the framework of the UK Biobank, the validated Oxford WebQ online questionnaire was used to assess information on dietary habits [19]. The Oxford WebQ captures dietary information on up to 206 different food types and 32 different beverages consumed within the previous 24 h. Participants completed their first 24-h dietary assessment in April 2009, followed by up to four further assessments until June 2012 (February/11 – April/11; June/11 - September /11; October/11 – December/11 and April/12 - June/12).

To analyse the quality of plant-based diets, the hPDI and uPDI were calculated. These indices were initially developed by Satija et al. who categorised 18 different food groups based on intakes [10]. Fruits, legumes, nuts, tea and coffee, vegetables, vegetable oils and whole grains were classified as healthy plant-based foods, whereas fruit juice, potatoes, refined grains, sugary drinks as well as sweets and desserts were classified as unhealthy plant-based foods. Animal-based foods used for the PDIs were classified by the following food groups: Meat, eggs, dairy products, animal fat, seafood or fish, and miscellaneous animal-based foods (Table 1). In this study, only 17 food groups were analysed, as there was no information on vegetable oil consumption [20]. Each of the remaining food groups were categorised into quartiles. Each food item was then ranked between 2 (low intake) to 5 points (high intake). One point was assigned if the food group was not consumed at all. For the hPDI calculation, healthy plant foods were scored positively and food groups classified as unhealthy (unhealthy plant-based foods or animal products) were scored negatively. To determine the uPDI, unhealthy plant foods scored positively, while healthy plant foods and animal foods scored negatively. Sex-specific quartiles of the final PDIs were used for statistical analyses.

Covariates assessment

During baseline recruitment, data on demographics, socioeconomic status and health status were obtained by a touchscreen questionnaire and verbal interviews with health care professionals at the study centres between 2006 and 2010. Furthermore, 24-hour dietary assessments (Oxford WebQ), physical measurements (anthropometry) and blood collection were carried out. The following covariates were collected at baseline (initial assessment visit) via self-reported touchscreen questionnaire: sex, ethnicity, region, age, education, Townsend deprivation index, physical activity, smoking status, alcohol intake, family history of diabetes and menopausal status. Data on prevalent hypercholesterolemia, prevalent hypertension, multimorbidity and polypharmacy were collected by touchscreen questionnaire and verbal interviews carried out at baseline. Physical measures including BMI, waist circumference and blood biomarkers (including glucose, haemoglobin A1c (HbA1c), insulin-like growth factor 1 (IGF-1), C-reactive protein (CRP), cystatin C, urate, creatinine, gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), low-density lipoprotein (LDL) direct cholesterol, lipoprotein A (Lip A) and triglycerides) were also collected at the initial assessment visit. Energy intake was first measured for participants upon completing the Oxford WebQ dietary assessment, issued between 2009 and 2012. Polygenetic risk scores (PRS) for T2DM were used as provided by the UK Biobank [21]. Further details on covariates and mediator variables, including their time of measurement can be found in **Table S1 (see supplementary materials associated with this article on line).**

Diabetes ascertainment

Incident T2DM cases were defined as primary type 2 diabetes mellitus according to the International Classification of Diseases 10th edition (ICD-10) (E11), using UK Biobank linked hospital inpatient data on admissions and diagnoses available until the 30th of September 2021 from the Hospital Episode Statistics for England, 31st of July 2021 for Scottish Morbidity Record, and 31st of March 2016 for the Patient Episode Database for Wales. Follow-up time for incident T2DM analyses was calculated from the date of recruitment until the date of hospitalization, death, or end of follow-up, whichever occurred first.

Statistical analyses

Baseline characteristics were summarised across hPDI and uPDI quartiles and expressed as means for continuous variables and percentages for categorical variables. To estimate the risk of T2DM across sex-specific hPDI and uPDI quartiles, Hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated by multivariable Cox proportional hazards regression analyses. To align with the measurement of mediating biomarkers and covariates used in this study, follow-up time

Table 1
Baseline characteristics across quartiles (Q) of the healthful plant-based diet score in the UK Biobank ($n = 113,097$).

Characteristics across hPDI	Participants, No. (%)* Q1	Q2	Q3	Q4
Number of participants	30,361 (26.8)	27,313 (24.2)	26,887 (23.8)	28,536 (25.2)
T2DM cases	928 (3.1)	626 (2.3)	563 (2.1)	511 (1.8)
Healthful plant-based diet index, mean (SD)	47.7 (3.3)	53.7 (1.5)	57.6 (1.5)	63.4 (3.3)
Sex-Female	16,310 (53.7)	15,472 (56.7)	15,536 (57.8)	16,537 (58.0)
Age at recruitment (years), mean (SD)	54.2 (8.1)	55.8 (7.8)	56.4 (7.6)	56.9 (7.4)
BMI(kg/m^2), mean (SD)	27.4 (4.8)	26.6 (4.3)	26.3 (4.2)	25.6 (4.0)
Waist circumference (cm), mean (SD)	90.5 (13.3)	88.2 (12.7)	87.1 (12.4)	85.5 (12.3)
Energy intake (kJ/day), mean (SD)	9106.2 (1820.7)	8527.1 (1800.4)	8230.4 (1797.2)	7991.7 (1807.2)
Physical activity (MET-h/wk), mean (SD)	29.4 (38.6)	30.4 (38.3)	31.8 (38.1)	34.4 (40.1)
Ethnicity				
Asian	1276 (4.2)	1202 (4.4)	1280 (4.8)	1545 (5.4)
Black	99 (0.3)	91 (0.3)	87 (0.3)	114 (0.4)
Multiple	894 (2.9)	755 (2.8)	699 (2.6)	815 (2.9)
White	27,828 (91.7)	25,032 (91.7)	24,589 (91.5)	25,769 (90.3)
Other†	174 (0.6)	134 (0.5)	159 (0.6)	188 (0.7)
Missing	90 (0.3)	100 (0.4)	73 (0.3)	105 (0.4)
Education				
Low	8428 (27.8)	7202 (26.4)	6749 (25.1)	6833 (24.0)
Medium	5400 (17.8)	4550 (16.7)	4058 (15.1)	4077 (14.3)
High	14,381 (47.4)	13,709 (50.2)	14,428 (53.7)	16,075 (56.3)
Missing	2152 (7.1)	1852 (6.8)	1652 (6.1)	1551 (5.4)
Smoking status				
Never	17,734 (58.4)	15,789 (57.8)	15,583 (58.0)	16,473 (57.7)
Previous	9896 (32.6)	9539 (34.9)	9516 (35.4)	10,484 (36.7)
Current	2684 (8.8)	1924 (7.0)	1731 (6.4)	1525 (5.4)
Missing	47 (0.2)	61 (0.2)	57 (0.2)	54 (0.2)
Alcohol intake (g/day), mean (SD)	18.3 (17.9)	17.4 (16.6)	16.8 (16.4)	15.6 (15.7)
Family history of diabetes	5048 (16.6)	4312 (15.8)	4195 (15.6)	4360 (15.3)
Hypertension	7070 (23.3)	6283 (23.0)	5979 (22.2)	6004 (21.0)
Hypercholesterolemia	3610 (11.9)	3368 (12.3)	3459 (12.9)	3542 (12.4)
Multimorbidity				
0 LTCs	11,914 (39.2)	10,918 (40.0)	10,668 (40.0)	11,618 (40.7)
1 LTC	10,060 (33.0)	8941 (32.7)	9060 (33.7)	9285 (32.6)
2 LTCs	5096 (16.8)	4600 (16.8)	4487 (16.7)	4670 (16.4)
≥3 LTCs	3291 (10.8)	2854 (10.5)	2662 (9.9)	2983 (10.4)
Polypharmacy				
0	9880 (32.5)	8983 (32.9)	8999 (33.5)	9713 (34.0)
1–3	14,674 (48.3)	13,120 (48.0)	12,763 (47.5)	13,464 (47.2)
4–6	4500 (14.8)	4068 (14.9)	3988 (14.8)	4114 (14.4)
7–9	999 (3.3)	870 (3.2)	871 (3.2)	978 (3.4)
≥10	308 (1.0)	271 (1.0)	264 (1.0)	266 (0.9)
Menopausal status				
Premenopausal	5718 (35.1)	4228 (27.3)	3887 (25.0)	3722 (22.5)
Postmenopausal	8078 (49.5)	9006 (58.2)	9421 (60.6)	10,537 (63.7)
PRS (T2D)				
Low	9844 (32.4)	8937 (32.7)	8815 (32.8)	9395 (32.9)
Medium	9851 (32.5)	9001 (33.0)	8785 (32.7)	9295 (32.6)
High	10,028 (33.0)	8823 (32.3)	8747 (32.5)	9224 (32.3)
Missing	638 (2.1)	552 (2.0)	540 (2.0)	622 (2.2)
Dietary intake (portion/day)‡				
Healthy plant food, mean (SD)				
Whole grains	1.5 (1.3)	2.0 (1.4)	2.3 (1.4)	2.8 (1.5)
Fruit	1.5 (1.2)	2.0 (1.4)	2.4 (1.6)	3.1 (1.7)
Vegetables	1.8 (1.4)	2.2 (1.6)	2.6 (1.8)	3.3 (2.1)
Nuts	0.1 (0.2)	0.1 (0.3)	0.2 (0.3)	0.3 (0.5)
Legumes	0.3 (0.3)	0.3 (0.4)	0.4 (0.4)	0.6 (0.6)
Tea and coffee	3.9 (1.6)	4.3 (1.6)	4.5 (1.6)	4.9 (1.7)
Unhealthy plant food, mean (SD)				
Refined grains	1.7 (1.2)	1.1 (1.0)	0.9 (0.9)	0.6 (0.7)
Potatoes	0.9 (0.6)	0.7 (0.5)	0.6 (0.5)	0.5 (0.5)
Sugary drinks	0.8 (1.0)	0.5 (0.8)	0.4 (0.6)	0.2 (0.5)
Fruit juices	0.6 (0.6)	0.5 (0.5)	0.4 (0.5)	0.3 (0.5)
Sweets and desserts	1.8 (1.3)	1.5 (1.2)	1.3 (1.1)	1.0 (1.0)
Animal fat	1.1 (1.1)	0.7 (1.0)	0.5 (0.9)	0.3 (0.7)
Dairy	1.2 (0.8)	1.1 (0.7)	1.1 (0.8)	1.0 (0.8)
Eggs	0.4 (0.5)	0.3 (0.4)	0.3 (0.4)	0.2 (0.4)
Fish or seafood	0.4 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)
Meat	1.5 (0.9)	1.2 (0.8)	1.1 (0.8)	0.8 (0.7)
Miscellaneous animal-based foods	0.2 (0.4)	0.1 (0.3)	0.1 (0.3)	0.0 (0.2)

Abbreviations: Q, quartile; hPDI, healthful plant-based diet index; BMI, body mass index; MET, metabolic equivalent task; PRS, polygenic risk score; T2DM, type 2 diabetes mellitus; SD, standard deviation.

* Relative frequencies (%) include missing values which may not equate to 100 %.

† Other includes any race or ethnic group not otherwise specified.

‡ Portion sizes were specified as a "serving" in the Oxford WebQ tool.

in Cox regression models on PDI scores and diabetes risk began at the date of recruitment rather than the date of the completion of the last dietary questionnaire. Thus, age at baseline was used as the underlying time scale in our main Cox regression models, while sensitivity analyses were carried out using age at last dietary assessment. Age at exit was set at last available follow-up date, date of diabetes diagnosis or death, whichever came first.

The following confounders were identified by literature review and used for multivariable adjustment: Sex (female, male), age (< 45 years, 45–, 50–, 55-, 60–, ≥ 65 years, BMI (≤ 18.5 kg/m^2, 18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥ 30 kg/m^2, or unknown/missing (0.1 %)), waist circumference (continuous scale, cm), ethnicity (Asian, Black, Multiple, White, Other, or unknown/missing (0.3 %)), region (10 regions), physical activity (METs hr/week in quintiles, or unknown/missing (1.8 %)), smoking status (never, previous, current, or unknown/missing (0.2 %)), level of education (Low: CSEs or equivalent, O levels/GCSEs or equivalent; Medium: A levels/AS levels or equivalent, NVQ or HND or HNC or equivalent; High: College or University degree, other professional qualifications e.g.: nursing, teaching; unknown/missing/prefer not to say (6.4 %)), energy intake (continuous scale, kJ/day), alcohol intake (< 1 g/day, 1–7 g/day, 8–15 g/day, 16+ g/day, or unknown/missing (16.3 %)), number of completed dietary assessments (continuous scale, ranging between 2 and 5), polypharmacy index (total number of self-reported medications taken at baseline; 0, 1–3, 4–6, 7–9, > 10), multimorbidity index (number of pre-existing long-term conditions; 0, 1, 2, or > 3), Townsend deprivation index (quintiles from low to

high deprivation index, or unknown/missing (0.1 %)), prevalent hypercholesterolemia (no, yes), prevalent hypertension (no, yes), family history of diabetes (no, yes), menopause status (no, yes, not sure (among women), and PRS (tertiles from low to high PRS for T2DM, or unknown/missing (2.1 %)). Further information on the covariates used in the study can be found in **Table S1 (see supplementary materials associated with this article on line**.

Sensitivity analyses were conducted to address potential reverse causality. In these analyses, participants with a T2DM diagnosis within or less than 2 years of follow-up (i.e., 2 years after completing their second 24 h dietary assessment) were excluded from the analyses. Further, primary analyses were repeated using age at last dietary assessment as the underlying time scale instead of age at recruitment. Stratified analyses were carried out to across key effect modifiers to assess heterogeneity in associations between the hPDI (continuous scale, 10-point increments) and T2DM. Key confounders included: smoking status (never, ever), sex (male, female), BMI (< 25, ≥ 25 kg/m^2), education (low: GSEs/O-Levels/GCSEs or equivalent, NVQ/HND/HNC/A-Levels/AS-Levels or equivalent; high: Other professional qualifications, College/university degree), ethnicity (white, non-white), drinking status (never, moderate, high) and polygenetic risk (T2DM) (PRS tertiles: low, intermediate, high). Likelihood ratio tests (LRT) were used to test for interactions between the hPDI and key covariates in relation to T2DM risk, comparing the fits of Cox proportional hazards regression models with and without the respective interaction terms. To assess potential nonlinearity of associations, cubic spline graphs were plotted with knots at percentiles (5th, 35th, 65th, and 95th).

Mediation analyses were carried out to examine whether the following markers of cardiometabolic risk (all on the continuous scale) may mediate associations between the hPDI, uPDI (1-point increments) and T2DM risk: BMI, waist circumference, Glucose, HBA1c, IGF-1, CRP, Cystatin C, Urate, Creatinine, GGT, ALT, AST, LDL direct Cholesterol, Lip A and triglycerides. To conduct this analysis the Stata paramed package [22,23] was used. This parametric regression approach estimates the total, direct, and indirect effects of the exposure: indirect associations (natural indirect effect [NIE]) of the mediator conditional on the exposure and covariates, and direct associations (natural direct effect [NDE]) of the outcome conditional on the exposure, mediator, and covariates. The model is based on four assumptions that need to be met in case of mediation: 1) The exposures (hPDI and uPDI) are associated with the endpoint (diabetes risk); 2) The mediators (see above) are associated with the exposures; 3) The mediators are associated with the endpoint; 4) The associations between exposures and endpoint are attenuated by adjustment for the mediators, but remain statistically significant [24,25]; The percentage proportion of the association between the hPDI, uPDI and T2DM mediated through one of the potential mediators of interest was calculated by dividing the log of the indirect effect HR by the sum of the log of the indirect effect HR and the log of the direct effect HR (log(NIE) / (log(NIE)+log(NDE)).

To test the reliability of the PDIs and potential mediators over time, intraclass coefficients (ICCs) and Spearman's rank correlation coefficients were calculated. Alike methods described previously [26], PDI scores were calculated from mean food intakes from the second and third vs the fourth and fifth Oxford WebQ dietary assessments for 22,329 participants with dietary data from each of these assessments. Spearman's rank correlation coefficients were calculated for mediator variables measured at baseline (initial assessment visit) vs the first repeat assessment visit. Mean (SD) duration (years) between baseline and first and last dietary assessments were 1.5 (1.3) and 2.7 (0.9), respectively and 3.7 (0.8) between baseline and first repeat biomarker sample collection.

All statistical analyses were performed using Stata, version 17.0 (StataCorp LLC). Statistical tests were considered as statistically significant at two-sided *P*-value of < 0.05. On completing the Schoenfeld residuals test, there was no indication of violation of the proportional hazards assumption.

RESULTS

Participants who had missing dietary data or covariate information ($n = 372{,}173$), implausible energy intakes ($>$ 17,573KJ or $\langle$ 3,347KJ for men and $\rangle$ 14,644KJ or $<$ 2,092KJ for women ($n = 3953$), prevalent diabetes (all types) ($n = 5009$), a diabetes diagnosis (all types) between baseline and the last dietary assessment ($n = 301$), were pregnant at baseline assessment (n = 46) or had prevalent cancer ($n = 5920$), or prevalent cardiovascular disease ($n = 1868$) were excluded, resulting in 113,097 individuals for the present analyses (**Figure S1; see supplementary materials associated with this article on line**).

Characteristics of the study population

Over an average (IQR) follow-up of 12 (1.6) years, 2628 out of 113,097 participants developed T2DM. Mean (SD) age at baseline was 55.8 (7.8) years, and 56.5% of the participants were female. Baseline characteristics of participants across quartiles of the hPDI and uPDI are presented in Table 1 and **Table S2 (see supplementary materials associated with this article on line)** respectively. BMI and waist circumference were lower in participants with higher hPDI scores (Table 1). Participants in the highest hPDI quartile were more likely to be older, have a lower BMI, have a higher education level and to be more physically active compared to the lowest quartile. Ethnicity and smoking status did not differ across hPDI quartiles. Participants in the highest uPDI quartile were more likely to be younger, have a higher BMI, be a current smoker and be less physically active compared to participants with lower uPDI scores.

The ICCs (range) for the reliability of the PDIs over time were 0.58 (34–83) and 0.55 (29–77) for hPDI and uPDI, respectively (**Table S3; see supplementary materials associated with this article on line**). For biomarkers used in mediation analyses, Spearman's coefficients for rank correlations over time ranged between 0.30 and 0.92 (**Table S4; see supplementary materials associated with this article on line**).

Associations between the PDIs and T2DM risk

In multivariable adjusted Cox regression models, participants in the highest hPDI quartile had a 24 % lower risk of T2DM compared to those in the lowest quartile [HR (95 % CI): 0.76 (0.68, 0.85), Table 2]. In contrast, participants in the highest uPDI quartile had a 37 % higher risk of T2DM [1.37 (1.22, 1.53), Table 2] compared to those in the lowest. Nominal non-linear associations were observed between hPDI and uPDI and incident T2DM ($P_{\text{non-linearity}} < 0.001$ for both, **Figure S2 (see supplementary materials associated with this article on line**). Although associations appeared linear for both hPDI and uPDI upon visual inspection, there was a slight trend of plateauing at the higher end of the distribution of the hPDI. Conversely, there was a slight trend for a stronger increase in diabetes risk with higher uPDI scores within the range of the highest uPDI quartile.

On the food group level, vegetables, as well as tea and coffee consumption, were inversely associated with T2DM risk, while positive associations were observed for the intakes of refined grains, potatoes, sugary drinks, and meat (**Table S5; see supplementary materials associated with this article on line**). On systematically removing each food group from the hPDI and uPDI, there was no indication that the observed associations were driven by one specific food group (**Tables S6** and **S7; see supplementary materials associated with this article on line**).

Sub-group and sensitivity analyses

Tests for statistical interaction did not indicate heterogeneity in associations between the PDIs and T2DM across strata of key covariates (smoking status, sex, BMI, education, ethnicity and drinking status) (Fig. 1 and **Table S8; see supplementary materials associated with**

Table 2
Hazard ratios (95 % confidence intervals) of type 2 diabetes across sex-specific quartiles (Q) of the healthful plant-based diet index (hPDI) and unhealthful plant-based diet index (uPDI) ($N = 113,097$).

hPDI	Q1	Q2	Q3	Q4	*P*-trend
hPDI, mean (SD)	47.7 (3.3)	53.7 (1.5)	57.6 (1.5)	63.4 (3.3)	
Cases/ total	928/ 30,361	626/27,313	563/26,887	511/28,536	
HR (95 % CI)*	1.00‡	0.71 (0.64–0.79)	0.64 (0.58–0.71)	0.54 (0.48-0.60)	< 0.001
HR (95 % CI)†	1.00‡	0.84 (0.76–0.93)	0.82 (0.73–0.91)	0.76 (0.68–0.85)	< 0.001
uPDI	Q1	Q2	Q3	Q4	*P*-trend
uPDI, mean (SD)	46.9 (3.0)	52.4 (1.5)	56.2 (1.5)	61.5 (2.8)	
Cases/ total	614/ 30,487	662/29,902	665/27,931	687/24,777	
HR (95 % CI)*	1.00‡	1.17 (1.04–1.30)	1.29 (1.16–1.44)	1.64 (1.47-1.84)	< 0.001
HR (95 % CI)†	1.00‡	1.15 (1.03–1.29)	1.24 (1.11–1.39)	1.37 (1.22-1.53)	< 0.001

Abbreviations: Q, quartile; hPDI, healthful plant-based diet index; uPDI, unhealthful plant-based diet index; BMI, Body Mass Index; PRS, polygenic risk score; HR, hazard ratio; CI, confidence interval.

* Hazard Ratios with 95 % Confidence Intervals (CI), adjusted for sex and education; stratified by age (5-year categories) and region.

† Hazard Ratios with 95 % Confidence Intervals (CI), adjusted for sex, BMI, waist circumference, ethnicity, physical activity, smoking status, alcohol intake, education, energy intake, polypharmacy index, multimorbidity index, townsend depriation index, family history of diabetes, prevalent hypercholesteroemia, prevalent hypertension, menopausal status, PRS (T2D), and number of completed dietary assessments; stratified by age (5-year categories) and region.

P-trend is for linear trend.

‡ Reference categories.

this article on line). Associations between hPDI (continuous scale, 10-point increments) and T2DM did not significantly differ across strata of T2DM risk (low, medium or high), showing no indication of heterogeneity ($p = 0.35$). Sensitivity analyses excluding cases that had occurred within two years after baseline did not materially change these associations (**Table S9; see supplementary materials associated with this article on line**). Replacing age at recruitment with age at last dietary assessment as the underlying time scale did not notably alter results (**Tables S10** and **S11; see supplementary materials associated with this article on line**).

Mediation analyses

These analyses indicated that BMI and waist circumference were the strongest mediators of the associations between hPDI and T2DM (proportion mediated: 28 % for both) followed by HBA1c (11 %), triglycerides (9 %) and ALT (5 %). Furthermore Urate, CRP, Cystatin C, GGT and IGF-1 showed a mediation effect of 4 % each (Table 3). Regarding uPDI and T2DM, only BMI, triglycerides and waist circumference showed statistically mediating effects, with proportions mediated of 7 %, 13 % and 17 % respectively (**Table S12; see supplementary materials associated with this article on line**).

Discussion

In this large UK-based study, a healthful plant-based diet was associated with a 24 % lower risk of T2DM, irrespective of genetic risk and other established T2DM risk factors. This association was in part mediated by lower body fatness, but also by better glucose metabolism, lower basal inflammation and better kidney and liver function. By contrast, adherence to an unhealthful plant-based diet was associated with a higher risk of T2DM, with greater body fatness and higher triglyceride levels constituting the only identified mediators. Overall, our results suggest that a healthful plant-based diet exerts anti-diabetic effects via common metabolic mechanisms, while obesity is a key mediator underlying greater T2DM risk among individuals following unhealthful plant-based diets.

To our knowledge, our study was the first to demonstrate that a healthful plant-based diet is associated with lower T2DM across individuals with low, medium and high genetic risk. Otherwise, our results are generally in agreement with those from three previous cohorts from the USA, France and Korea [10,27,28]. Satija et al. found a 45 % lower T2DM risk for US healthcare professionals with high hPDI scores, whereas a 16 % higher T2DM risk was observed with a higher uPDI [10]. Data from a French cohort showed that T2DM risk was significantly lower among individuals with higher hPDI scores (HR:0.88 [0.85–0.92]), although no association was observed for the uPDI [28]. Similarly, a 10-point increment in the hPDI score was associated with a 14 % lower risk of T2DM among Korean adults, whereas no association between uPDI and T2DM was observed [27]. We can only speculate why unlike in the other cohorts associations between the uPDI and T2DM were stronger in magnitude compared to those observed for the hPDI in our study. Possibly, the range of food intakes was wider for foods contributing to the uPDI in the UK Biobank leading to more contrast in the uPDI score, although dietary assessments across the cohorts cannot be easily compared.

Our mediation analyses showed that the inverse association between the hPDI and T2DM was in part attributable to lower BMI and waist circumference, as well as lower HbA1c values. These findings are plausible, given that energy intake is generally lower among people following a healthful plant-based diet, and that plant-based diets are associated with better insulin sensitivity [29]. In a cohort from France, BMI was also identified as a potential mediator of associations between hPDI and T2DM risk [28], with a much higher proportion mediated than in our study (52% vs. 28 %). This difference may be due to the fact that the French cohort only consisted of women with very low BMI values at baseline (average of 22.9 vs. 26.5 in our study).

Beyond obesity and glycaemia, we identified several further potential mediators. For example, our findings suggested that lower T2DM risk among people following a healthful plant-based diet was in part due to lower basal inflammation. While the mechanisms through which plant-based diets reduce inflammation are not well-understood, lower CRP levels observed among strict vegans and vegetarians compared to omnivores may be due to a more favourable composition of the gut microbiome [30]. Furthermore, diets rich in plant-based foods are characterized by higher intakes of bioactive substances such as flavonoids, other phenolic compounds, or carotenoids, which have potential anti-inflammatory and immune-modulatory functions [31].

Our study further showed that lower serum levels of liver enzymes mediated lower T2DM risk among people following a healthy plant-based diet. This is in line with recent studies showing that impaired liver function is an independent T2DM risk factor [32], and that higher consumption of plant-based foods may lower the risk for non-alcoholic fatty liver disease (NAFLD) [12]. In one cohort study, an unhealthy plant-based diet was associated with an increased risk of NAFLD at baseline, with a subsequent 2.95 times higher 10-year risk of T2DM among participants with NAFLD compared to individuals without NAFLD (47). On the molecular level healthy plant-based foods may alleviate NAFLD through their high content of bioactive compounds and phytochemicals. These substances may lead to lower oxidative stress, lower basal inflammation as well as a favourable autophagy regulation in the liver [33]. Furthermore, the consumption of plant foods rich in fibre and flavonoids may improve liver function via its impact on the composition and function of the gut microbiome [34].

Besides liver function, our findings suggest that a healthful plant-

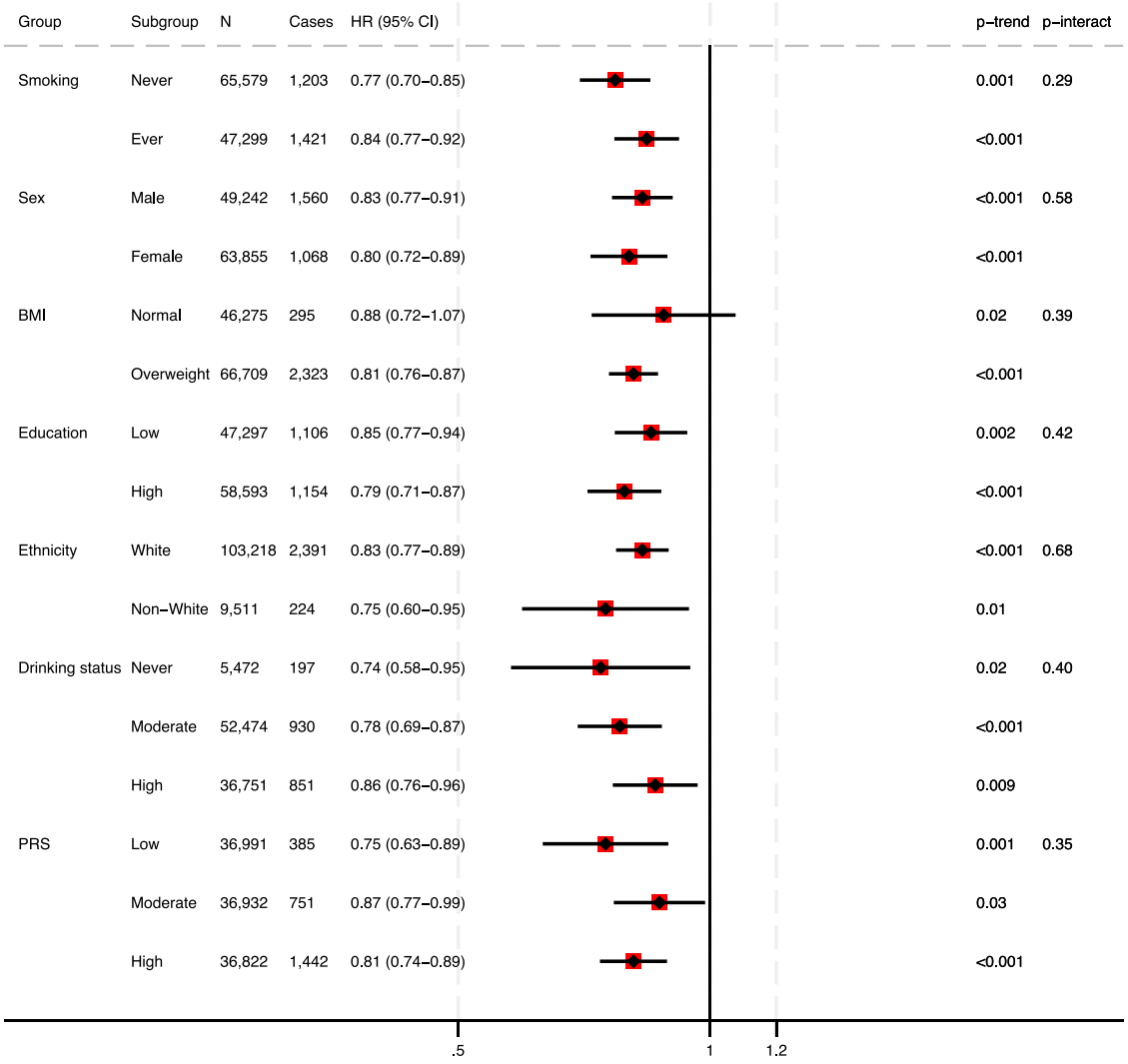

Fig. 1. Healthful plant-based diet score modelled as a continuous trend (10-point increments) and incident type 2 diabetes stratified by UK Biobank population subgroup

Hazard Ratios with 95 % Confidence Intervals for healthful plant-based diet score (10-point increments), adjusted for sex (excluding subgroup analysis), BMI (excluding subgroup analysis), waist circumference, ethnicity (excluding subgroup analysis), physical activity, smoking status (excluding subgroup analysis), alcohol intake (excluding subgroup analysis), education (excluding subgroup analysis), energy intake, polypharmacy index, multimorbidity index, Townsend deprivation index, prevalent hypercholesteroemia, prevalent hypertension, family history of diabetes, menopause status, PRS (T2D) (excluding subgroup analysis), and number of completed dietary assessments; stratified by age (5-year categories) and region.

Heterogeneity was tested by comparing two models – one without an interaction term between subgroup of interest and hPDI (categorical), with a model that included an interaction term. The likelihood ratio test was used to produce *P*-interaction values.

P-trend is for linear trend.

*Smoking status (never, ever), sex (male, female), BMI (<25, ≥25 kg/m^2), education (low: GSEs/O-Levels/GCSEs or equivalent, NVQ/HND/HNC/A-Levels/AS-Levels or equivalent; high: Other professional qualifications, College/university degree), ethnicity (white, non-white), drinking status (never (0 g/d), moderate (1-<16 g/d), high (≥16 g/d) and polygenic risk (T2DM) (PRS tertiles: low, intermediate, high)).

Abbreviations: hPDI, healthful plant-based diet index; PRS, polygenic risk; T2D, type 2 diabetes mellitus; HR, hazard ratios; CI, confidence intervals.

based diet beneficially affect kidney function. Impaired kidney function plays a role in early T2DM development, rather than solely being a consequence of T2DM [16]. Healthful plant-based diets may have positive effects on uraemic toxins and are recommended for people with chronic kidney disease [11]. They may lower dietary acid load, a risk factor for chronic kidney diseases and a slower glomerular filtration rate [35,36]. At the same time, healthy plant-based foods are rich in fibre and micronutrients, which are associated with a lower risk of proteinuria and microalbuminuria [37]. Our study further indicated that lower IGF-1 levels may mediate associations between high hPDI scores and T2DM. This finding is in line with studies to show both lower IGF-1 and lower T2DM risk among people following strict plant-based diets [14]. Both associations may be explained by a lower intake of animal foods rich in branched-chained amino acids, which may increase IGF-1 formation [38].

While our study is the first to investigate biomarkers of central metabolic pathways and organ function as potential mediators of health effects of plant-based diets, small metabolites were evaluated as potential mediators in a previous study from the USA [39]. In this study, lower levels of the branched-chained amino acid isoleucin mediated the inverse associations between hPDI and T2DM, which is consistent with our finding on IGF-1. The study further showed mediating effects of three triglyceride metabolites, which is consistent with the modest mediation via total triglycerides in our study, and which supports the notion that increased triglycerides contributes to insulin resistance [40].

Table 3
Mediation analysis between healthful plant-based diet score and type 2 diabetes.

	Healthful Plant-based Diet Index (1-point increments)							
	Participants, No.	Total effect (HR; 95 % CI)*	*P*-value	Direct effect (HR; 95 % CI)*	*P*-value	Natural indirect effect (HR; 95 % CI)*	*P*-value	Proportion mediated (Log (NIE) / (Log(NIE)+log (NDE))
Potential mediators†								
Obesity and sugar metabolism								
BMI	79,213	0.975 [0.967–0.983]	< 0.001	0.982 [0.973–0.991]	< 0.001	0.993 [0.993–0.994]	< 0.001	28 %
Waist circumference	79,213	0.975 [0.967–0.984]	< 0.001	0.982 [0.973–0.991]	< 0.001	0.993 [0.992–0.994]	< 0.001	28 %
Glucose	68,980	0.976 [0.967–0.986]	< 0.001	0.976 [0.967–0.986]	< 0.001	1.000 [0.999–1.000]	0.593	NA
HBA1c	75,147	0.975 [0.966–0.984]	< 0.001	0.977 [0.968–0.987]	< 0.001	0.997 [0.996–0.998]	< 0.001	11 %
IGF-1	75,076	0.977 [0.968–0.986]	< 0.001	0.978 [0.969–0.987]	< 0.001	0.999 [0.999–1.000]	< 0.001	4 %
Inflammatory biomarkers								
C-reactive protein	75,336	0.976 [0.968–0.985]	< 0.001	0.977 [0.968–0.986]	< 0.001	0.999 [0.999–0.999]	< 0.001	4 %
Kidney function								
Cystatin C	75,487	0.977 [0.969–0.986]	< 0.001	0.977 [0.969–0.986]	< 0.001	0.999 [0.999–1.000]	< 0.001	4 %
Urate	75,413	0.977 [0.968–0.986]	< 0.001	0.978 [0.969–0.987]	< 0.001	0.999 [0.998–0.999]	< 0.001	4 %
Creatinine	75,439	0.977 [0.968–0.986]	< 0.001	0.976 [0.967–0.985]	< 0.001	1.000 [1.000–1.001]	0.005	NA
Liver function								
Gamma glutamyl transferase (GGT)	75,443	0.977 [0.968–0.986]	< 0.001	0.978 [0.969–0.987]	< 0.001	0.999 [0.999–0.999]	< 0.001	4 %
Alanine aminotransferase (ALT)	75,464	0.977 [0.969–0.986]	< 0.001	0.979 [0.970–0.988]	< 0.001	0.999 [0.999–0.999]	< 0.001	5 %
Aspartate aminotransferase (AST)	75,234	0.976 [0.968–0.985]	< 0.001	0.976 [0.968–0.985]	< 0.001	1.000 [1.000–1.000]	0.207	NA
Lipid metabolism								
LDL-direct Cholesterol	76,358	0.977 [0.968–0.986]	< 0.001	0.977 [0.968–0.986]	< 0.001	1.000 [1.000–1.000]	0.984	NA
Lipoprotein A	60,799	0.971 [0.961–0.981]	< 0.001	0.971 [0.961–0.981]	< 0.001	1.000 [1.000–1.000]	0.493	NA
Triglycerides	75,430	0.977 [0.969–0.986]	< 0.001	0.979 [0.970–0.988]	< 0.001	0.998 [0.998–0.999]	< 0.001	9 %

Abbreviations: HR, hazard ratios; CI, confidence intervals; BMI, body mass index; PRS, polygenic risk; NIE, natural indirect effect; NDE, natural direct effect; T2D, type 2 diabetes.

* Hazard Ratios with 95 % Confidence Intervals (CI) for healthful plant-based diet score (1-point increments), adjusted for sex, BMI (excluding when considered as potential mediator), waist circumference (excluding when considered as potential mediator), ethnicity, physical activity, smoking status, alcohol intake, education, energy intake, polypharmacy index, multimorbidity index, Townsend deprivation index, prevalent hypercholesteroemia (excluding when lipids are considered as potential mediators), prevalent hypertension, family history of diabetes, menopause status, PRS (T2D), and number of completed dietary assessments; stratified by age (5-year categories) and region.

† Potential mediators are modelled on the continuous scale.

Limitations

One potential limitation of this study relates to the observational nature of the study design. Thus, residual or unmeasured confounding cannot be excluded. Nevertheless, we comprehensively adjusted for known T2DM risk factors, and our results are in line with findings from randomised controlled trials showing that plant-based diets improve insulin sensitivity/glycaemic control [29]. The PDI was operationalized based on two to five dietary assessments covering the past 24 h, which may not capture dietary intake over longer periods. However, we have previously shown that the reproducibility of the PDIs over time is very good, indicating that it reflects habitual diet despite the limited number of assessments [41]. Our mediation model was limited regarding temporality in that detailed dietary assessments in the UK Biobank were carried out slightly after the initial baseline visits, during which data on covariates and biomarkers used for our mediation analyses were obtained. Nevertheless, both dietary exposures and mediators, with the exception of glucose, showed good reliability over time indicating that our mediation model was valid. A second limitation of our mediation model is that mediated proportions can only be interpreted as crude estimates of magnitude, as our reliability analyses in a subset of UK Biobank participants with repeated biomarker measurements showed that the mediators used in the present study are likely differentially affected by regression dilution. In our Cox regression analyses, we set the age at entry at age at baseline, based on the assumption that the PDIs derived from the dietary assessments carried out slightly later in time reflected dietary intakes at baseline. However, setting the age at entry at the last available dietary assessment only very marginally affected our statistical estimates. Finally, the UK Biobank population is not representative of the adult UK general population. Generalisation of our findings may be limited in that the majority of study participants were white individuals with European ancestry. However, it has been stated that in terms of causality, representative populations are not needed at a sample size as large as in the UK Biobank.

Conclusion

This study suggests that a healthy plant-based diet is associated with a lower T2DM risk due to several mechanisms beyond beneficial effects on body fatness and blood glucose including improved renal and liver function, and lower basal inflammation. Our findings suggest that high quality plant-based diets, characterised by high consumption of fruits, vegetables, nuts, legumes, wholegrains, tea and coffee, are beneficial for T2DM prevention, in line with existing dietary recommendations to increase plant food consumption to reduce T2DM risk [42]. Given the well-documented co-benefits of healthful plant-based diets on planetary health, our data support the shift towards healthful plant-based diets to address the syndemic of climate change, undernutrition and obesity [43].

Authors' contributions

Design and concept: AT, CC, AC, TK; database development: AT, AJ, AC, ATR, TK; analysed and interpreted data: AT, CC, TK, AC; drafted manuscript: AT, CC, TK, AC; provided critical review of the manuscript: AJ, NB, ATR, SS, CH; guarantors of the work: AT, CC, AC and TK.

Data sharing

UK Biobank data can be requested by all bona fide researchers for approved projects, including replication, through https://www.ukbiobank.ac.uk/.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2023.101499.

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