Plant versus Animal-based Diets and Insulin Resistance, Prediabetes and Type 2 Diabetes: the Rotterdam Study

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ABSTRACT

Background

Vegan or vegetarian diets have been suggested to reduce risk of type 2 diabetes (T2D). However, not much is known on whether variation in the degree of having a plant-based versus animal-based diet may be beneficial for the prevention of T2D. We aimed to investigate whether level of adherence to a diet high in plant-based foods and low in animal-based foods is associated with insulin resistance, prediabetes, and T2D.

Methods

Our analysis included 6,798 participants (mean age 62.7 years, SD 7.8) from the Rotterdam Study, a prospective population-based cohort in the Netherlands. Dietary intake data were collected with food-frequency questionnaires at baseline of three Rotterdam Study sub-cohorts (RS-I-1: 1989-1993, RS-II-1: 2000-2001, RS-III-1: 2006-2008). We constructed a continuous plant-based dietary index (range 0-92) expressing adherence to a plant-based versus animal-based diet. Insulin resistance at baseline and follow-up was assessed using homeostatic model assessment of insulin resistance (HOMA-IR). Information on prediabetes and T2D were collected from general practitioners' records, pharmacies' databases, and follow-up examinations in our research center up to 2012. We used multivariable linear mixed models to examine associations of the index with longitudinal HOMA-IR and multivariable proportional hazards regression models to examine associations of the index with risk of prediabetes and T2D.

Results

We documented 928 cases of prediabetes and 642 cases of T2D, during a mean duration of follow-up of 5.7 and 7.3 years, respectively. After adjusting for sociodemographic and lifestyle factors, a higher score on the plant-based dietary index was associated with lower insulin resistance (per 10 units higher score: β -0.09, 95% CI -0.10; -0.08), lower prediabetes risk (HR 0.89, 95% CI 0.81; 0.98), and lower T2D risk (HR 0.82, 95% CI 0.73; 0.92). After additional adjustment for BMI, associations attenuated and remained statistically significant for longitudinal insulin resistance (β -0.05, 95% CI -0.06; -0.04) and T2D risk (HR 0.87, 95% CI 0.79; 0.99), but no longer for prediabetes risk (HR 0.93, 95% CI 0.85; 1.03).

Conclusions

A more plant-based and less animal-based diet may lower risk of insulin resistance, prediabetes and T2D. These findings strengthen recent dietary recommendations to adopt a more plant-based diet.

INTRODUCTION

Diet is an important modifiable lifestyle determinant in the development of type 2 diabetes (T2D).[1] Among dietary components, consumption of several plant-based foods such as root vegetables, green leafy vegetables, whole grains, nuts and peanut butter has been associated with a lower risk of T2D.[2–5] In contrast, consumption of several animal-based foods, including red meat, processed meat and eggs, has been associated with an increased risk of T2D.[4,6,7]

Although multiple food groups seem to influence the risk of T2D, humans generally do not consume single food items or food groups, and the role of diet in health may be better described by overall dietary patterns.[8] Previous studies have observed that vegan or vegetarian diets are associated with improved glycemic control and lower T2D risk.[9,10] However, these previous studies dichotomously classified participants, and only defined diets as vegetarian or vegan versus non-vegetarian diets. A dichotomous classification of vegans or vegetarians versus their non-vegetarian counterparts might not be an optimal approach in understanding the effect of a plant-based diet in Western countries, because it does not reflect dietary patterns of a large proportion of the population. From a public health perspective, it is interesting to know whether a more plant-based and less animal-based diet may also influence insulin resistance and risk of prediabetes and T2D beyond strict adherence to a vegetarian or vegan diet. To our knowledge, only one previous study, a large prospective cohort study in the US, examined associations between variations in the degree of adherence to plant-based versus animal-based diets with T2D risk and observed that a more plant-based diet was associated with a lower T2D risk.[11] Studies on the associations of such plant-based dietary patterns with T2D risk in other populations are needed. In addition, the association of such plant-based dietary patterns with intermediate risk factors for T2D, such as insulin resistance and prediabetes remain unknown.

Therefore, we aimed to investigate whether adherence to a more plant-based, and less animal-based diet is associated with insulin resistance, and risk of prediabetes and T2D in a Dutch middle-aged and older general population.

METHODS

Study population

This study was performed within three sub-cohorts of the Rotterdam Study, a prospective cohort study of adult aged 45 years and older living in the well-defined

district of Ommoord in Rotterdam, the Netherlands. A detailed description of the Rotterdam Study methodology has been provided elsewhere.[12] Briefly, recruitment of participants for the first sub-cohort (RS-I) started in the period of 1989-1993 among inhabitants aged ≥ 55 years (n = 7,983). In 2000-2001, the study was extended with a second sub-cohort (RS-II) of new individuals (n = 3,011) who had become 55 years of age or moved into the study area after 1990. In 2006-2008, a third sub-cohort (RS-III) was recruited with new individuals aged 45 years and older (n = 3,932). By the end of 2008, the overall study population contained 14,926 participants. Upon entering the study, participants underwent home interviews and a series of examinations in our research center every 3-5 years. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. The approval has been renewed every 5 years. All participants gave informed consent.

Population for current analyses

For the current study, we used data from all three sub-cohorts. Of the 14,926 participants, we excluded 5,225 participants without valid dietary data (no dietary data, unreliable dietary intake according to a trained nutritionist or an estimated energy intake of < 500 or > 5000 kcal/day[13]) at baseline (RS-I-1: starting 1989, RS-II-1: starting 2000, RS-III-1: starting 2006), and 2,903 participants without information on T2D status or with prevalent T2D at baseline, leaving 6,798 participants included as main population for analysis.

From this group of 6,798 participants, 6,514 participants had data on HOMA-IR before onset of T2D and were included in the longitudinal HOMA-IR analyses. For the analyses on prediabetes risk, we excluded those with prevalent prediabetes at baseline (n = 1,005) or without follow-up for prediabetes (n = 25), leaving 5,768 participants. In the analyses assessing risk of T2D, we excluded participants without follow-up of T2D (n = 28), leaving 6,770 participants. The flow-diagram of the included participants is presented in Figure 2.2.1.

Dietary assessment

Dietary intake was assessed at baseline in all three sub-cohorts using semi-quantitative food-frequency questionnaires (FFQ) as described in more detail elsewhere.[13] We used an FFQ with 170 food items to assess dietary intake at baseline of RS-I and RS-II; at baseline of RS-III, we used an FFQ with 389 food items.[14,15] The 170-item FFQ was validated in a subsample of the Rotterdam Study (n = 80) against fifteen 24-h food records and four 24h urinary urea excretion samples,[14] and the 389-item FFQ was previously validated in other Dutch population against measurement of biomarkers, against a

9-day dietary record, and against a 4 week dietary history.[16] In general, the validation studies demonstrated that the FFQs were able to adequately rank participants according to their intake.[13] Food intake data were converted to energy and nutrient intake based on Dutch Food Composition tables (NEVO).

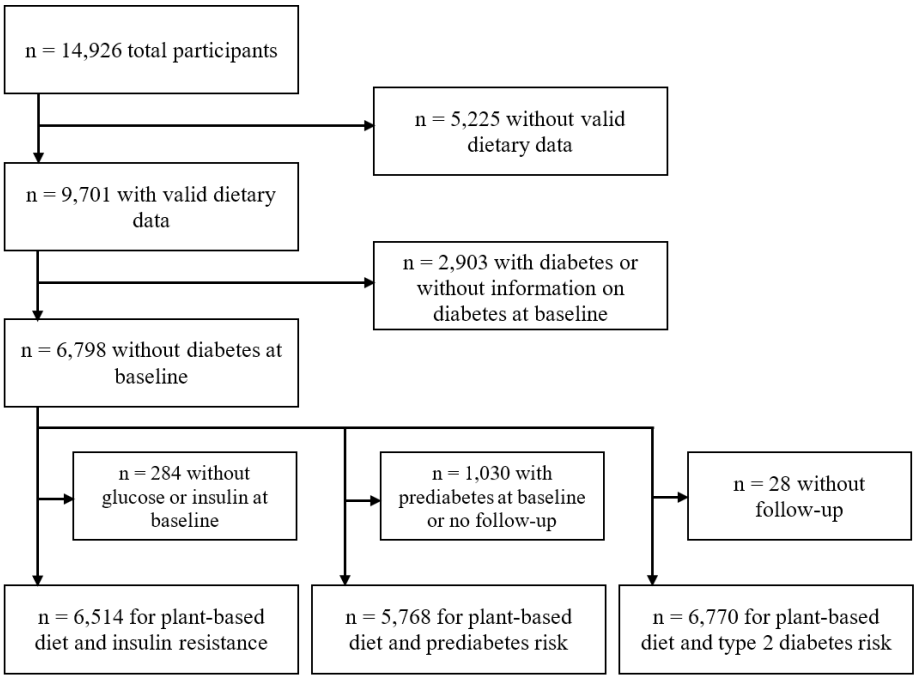

Figure 2.2.1. Selection of the study population.

Plant-based dietary index

We constructed an overall plant-based dietary index, which was a modified version of two previously created indices.[11,17] More specifically, our index is similar to the provegetarian food pattern of Martínez-Gonzáles et al.[17] and to the overall plant-based diet index of Satija et al.,[11] but was adapted to include slightly different types and numbers of food categories. First, the food items as measured by the FFQs were divided into 23 food categories (Supplemental Table 2.2.1), on the basis of the main food groups in the Dutch diet and the Dutch food-based dietary guidelines.[18,19] Twelve of the categories were plant-based and eleven were animal-based. Food items that were not clearly animal-based or plant-based, such as pizza, as well as dietary supplements, were not included in the food categories for the index. Dietary intake for each of the 23 food categories was calculated for each participant in grams per day. Subsequently, for each category, the intake was divided into cohort-specific quintiles. Each quintile

was assigned a value between 0 and 4. For the twelve plant-based food categories, consumption within the highest quintile was scored a 4, consumption within the second highest quintile was scored a 3, and so on, ending with consumption within the lowest quintile receiving a score of 0. The eleven animal-based food categories were scored in reverse: consumption within the highest quintile was scored a 0, consumption within the second highest quintile was scored a 1, ending with consumption within the lowest quintile receiving a score of 4. Furthermore, we ensured that all participants with null consumption were given the score belonging to the lowest quintile by re-scoring when necessary. Finally, these category quintile-scores were added up per participant to create their overall score on the plant-based dietary index. The resulting index yielded a score for each participant that measures adherence to a plant-based versus animal-based diet on a continuous scale, with a lowest possible score of 0 (low adherence to a plant-based diet) and a highest possible score of 92 (high adherence to a plant-based diet). Information on intake of each food category across quintiles of scores on the plant-based dietary index is shown in Supplemental Table 2.2.2.

Assessment of insulin resistance

Information on prediabetes and T2D was collected from general practitioners' records, pharmacies' databases, and follow-up examinations in our research center. Data on prediabetes and T2D in our analyses were collected until January 1, 2012. Prediabetes and T2D were identified according to WHO criteria: prediabetes was defined as a fasting blood glucose concentration of > 6.0 and < 7.0 mmol/L, or a non-fasting blood glucose concentration of > 7.7 mmol/L and < 11.1 mmol/L; T2D was defined as a fasting blood glucose concentration of ≥ 7.0 mmol/L, a non-fasting blood glucose concentration of ≥ 11.1 mmol/L (when fasting samples were unavailable), the use of blood glucose-lowering medication or dietary treatment, or registration of the diagnosis T2D. All possible cases of prediabetes and T2D were formally judged by two independently working study physicians or, in case of disagreement, by an endocrinologist.[20]

Assessment of covariates

Information on age, sex, smoking status, educational level, medication use, food supplement use and family history of diabetes was obtained from questionnaires at baseline. Information on physical activity was obtained using the adapted version of the Zutphen Physical Activity Questionnaire at RS-I-3 and RS-II-1 and using the LASA Physical Activity Questionnaire at RS-III-1. Physical activities were weighted according to intensity with Metabolic Equivalents of Task (MET), from the Compendium of Physical Activities version 2011. To account for differences between the two questionnaires, questionnaire-specific z-scores of MET-hours per week were calculated. At our

research center at baseline, body weight was measured using a digital scale and body height was measured using a stadiometer, while participants wore light clothing and no shoes, and BMI was calculated (kg/m^2). Information on hypertension, hypercholesterolemia, coronary heart disease (CHD), cancers, and stroke was obtained from general practitioners, pharmacies' databases, Nationwide Medical Register, or follow-up examinations in our research center.

Data analysis

To obtain a normal distribution for HOMA-IR, we applied a natural-log transformation. Non-linearity of associations of score on the plant-based dietary index with all outcomes were explored using three-knot natural cubic splines. As no indication for non-linear associations was found in the main model, all primary analyses were performed using models assuming linearity. We examined the association between score on the plant-based dietary index with longitudinal HOMA-IR using linear mixed models, with a random-effects structure including a random intercept and slope (for time of repeated measurements of HOMA-IR). We examined the association between score on the plant-based dietary index and risk of prediabetes and risk of T2D using proportional hazards regression. Hazard ratios (HRs) and regression coefficients (βs) are presented per 10 units higher score on the plant-based dietary index, along with the corresponding 95% confidence intervals (CIs). All analyses were performed in participants of the three sub-cohorts combined and in the three sub-cohorts separately.

All analyses were adjusted for energy intake, age, sex and RS sub-cohort in model. For the analyses of longitudinal HOMA-IR we additionally adjusted for the time of repeated measurements of HOMA-IR. In model 2, we additionally adjusted for smoking status, educational level, physical activity, food supplement use, and family history of diabetes. Baseline BMI was added in model 3 to examine its potential mediating effect. We examined effect modification by including interactions of the plant-based index with age, sex, or BMI for all outcomes in model 2.

Several sensitivity analyses were performed based on model 2. First, to check whether the associations were driven by any specific component of the plant-based dietary index, we repeated our main analyses by excluding each one of the 23 components from the plant-based dietary index one by one at a time, and additionally adjusting for the excluded component. Second, to check if the associations were mainly driven by plant-based beverages combined, we examined the associations by excluding all plant-based beverages combined (the categories coffee and tea, alcoholic beverages, and sugary beverages) from the plant-based dietary index at a time, and additionally adjusting for them. Third, we examined the associations by excluding less healthy

plant-based foods combined (the categories sweets, sugary beverages, potatoes and refined grains) from the plant-based dietary index at a time, and additionally adjusting for them. To further examine whether these less healthy plant foods contributed to the association of the plant-based dietary index, we created a less healthy plant foods score in which positive scores were given to these four types of less healthy plant-based food groups. In calculating this score, reverse scores were given to healthy plant food groups and animal food groups.[21] Fourth, to examine if potential associations of the plant-based dietary score with outcomes were independent of overall quality of the diet based on adherence to dietary guidelines, we examined the correlation between the plant-based dietary score and the dietary guidelines score, and we repeated analyses with additional adjustment for dietary guidelines score. Fifth, we additionally adjusted for hypertension and hypercholesterolemia. Sixth, we excluded the participants with chronic diseases at baseline, such as participants with coronary heart disease, cancers, or stroke, to exclude the possibility of a significant change of diet and lifestyle at follow-up. Last, we excluded the participants who developed prediabetes and T2D in the first 2 years of follow-up in the analyses for risk of prediabetes and T2D, respectively. Missing values in covariates (ranging from 0.3% to 3.9%) were accounted for using ten-fold multiple imputation. We used SPSS version 21 (IBM Corp., Armonk, NY, USA) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) to perform these analyses.

RESULTS

Baseline characteristics of the study population are shown in Table 2.2.1. In our population of 6,798 participants, baseline scores on the plant-based dietary index (with a theoretical range from 0 to 92) ranged from 24 to 75, with a mean ± SD score of 49.3 ± 7.1. Mean age of the study population was 62.0 ± 7.8 years and 41.3% of the participants were male. Mean BMI was 26.6 ± 3.9 kg/m^2. Characteristics were similar before and after multiple imputation (Supplemental Table 2.2.3). Supplemental Table 2.2.4 shows baseline characteristics of the participants not included in our analyses.

After adjustment for confounders in model 2, a higher score on the plant-based dietary index was associated with lower longitudinal HOMA-IR (per 10 units higher score on the index: β -0.09, 95% CI -0.10; -0.08) (Table 2.2.2). Additional adjustment for BMI in model 3 attenuated the association, but it remained statistically significant (β -0.05, 95% CI -0.06; -0.04).

Table 2.2.1. Baseline characteristics of study participants (n = 6,798)

Characteristic	Mean (SD), median (IQR), or %
Age (years)	62.0 (7.8)
Sex (% male)	41.3 %
BMI (kg/m^2)	26.6 (3.9)
Smoking (%)	
Never	32.2 %
Ever	45.1 %
Current	22.7 %
Physical activity[1] (MET-hours/week)	
RS-I and RS-II (Zutphen Questionnaire, n = 4,393)	86.7 (44.7)
RS-III (LASA Questionnaire, n = 2,194)	58.4 (55.8)
Hypertension (%)	42.3 %
Hypercholesterolemia (%)	45.4 %
Family history of diabetes (%)	10.8 %
Highest level of education (%)	
Primary	11.8 %
Lower	40.9 %
Intermediate	29.0 %
Higher	18.3 %
Current food supplement use (%)	16.5 %
Total energy intake (kcal/day)	2,134 (615)
Plant-based food category intake (grams/day)[2]	
Fruit	212.2 (115.5, 332.3)
Vegetables	209.1 (147.9, 286.87)
Whole grains	105.7 (61.3, 152.5)
Nuts	3.9 (0.0, 12.0)
Legumes	4.1 (0.0, 19.4)
Potatoes	99.7 (61.4, 148.2)
Vegetable oils	19.7 (9.2, 30.0)
Tea and coffee	758.9 (580.4, 1000)
Sugary beverages	46.3 (0.0, 139.6)
Refined grains	50.7 (23.9, 102.1)
Sweets	63.8 (37.1, 97.4)
Alcoholic beverages	56.4 (4.9, 159.8)
Animal-based food category intake (grams/day)[2]	
Low-fat milk	82.3 (0.0, 232.3)
Full-fat milk	0.0 (0.0, 0.0)
Low-fat yoghurt	56.1 (0.0, 164.6)
Full-fat yoghurt	0.0 (0.0, 4.9)

Table 2.2.1. Baseline characteristics of study participants (n = 6,798) (continued)

Characteristic	Mean (SD), median (IQR), or %
Cheese	30.8 (20.0, 47.1)
Unprocessed lean meat	10.7 (4.3, 18.1)
Fish	15.9 (3.9, 30.7)
Eggs	14.3 (7.1, 19.6)
Animal fat	0.0 (0.0, 0.9)
Desserts/dairy with sugars	14.1 (0.0, 54.6)
Processed meat/red meat	86.8 (60.4, 118.9)
Plant-based dietary index (score)	49.3 (7.1)

Plant-based dietary index: a higher score indicates a higher adherence to a plant-based diet (theoretical range from 0 to 92). Values shown are based on pooled results of imputed data. [1]Values shown for MET-hours are un-imputed; imputation was performed on z-scores of physical activity. [2]Variable expressed as median (IQR). Abbreviations: MET, metabolic equivalent of task; SD, standard deviation.

Table 2.2.2. Associations of the plant-based dietary index with longitudinal insulin resistance (HOMA-IR), risk of prediabetes, and risk of type 2 diabetes

	HOMA-IR	Prediabetes	Type 2 diabetes
	(n = 6,514)	(n = 5,768)	(n = 6,770)
	β (95% CI)	HR (95% CI)	HR (95% CI)
Model 1	-0.09 (-0.10; -0.08)***	0.88 (0.80; 0.97)**	0.82 (0.73; 0.92)***
Model 2	-0.09 (-0.10; -0.08)***	0.89 (0.81; 0.98)*	0.82 (0.73; 0.92)**
Model 3	-0.05 (-0.06; -0.04)***	0.93 (0.85; 1.03)	0.87 (0.79; 0.99)*

Effect estimates are regression coefficients (β) for ln HOMA-IR or hazard ratios (HRs) for incidence of prediabetes or type 2 diabetes with their 95%-confidence intervals (95% CIs), per 10 units higher score on the plant-based dietary index. Estimates are based on pooled results of imputed data. Model 1 is adjusted for energy intake, sex, age and RS sub-cohort (RS-I, RS-II, or RS-III); and only for the HOMA analyses additionally for the time measurements of longitudinal HOMA. Model 2 is additionally adjusted for education, smoking status, family history of diabetes, physical activity and food supplement use. Model 3 is additionally adjusted for BMI. *p < 0.05; ** p < 0.01; ***p < 0.001. Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; RS, Rotterdam Study.

During 43,773 person-years of follow-up among 5,768 participants (median follow-up 5.7 years), 928 participants developed prediabetes. After adjustment for confounders in model 2, a higher score on the plant-based dietary index was associated with a lower incidence of prediabetes (per 10 units higher score on the index: HR 0.89, 95% CI 0.81; 0.98). After additional adjustment for BMI in model 3 the association attenuated and was no longer statistically significant (HR 0.93, 95% CI 0.85; 1.03).

During 54,024 person-years of follow-up amongst 6,770 participants (median follow-up 7.3 years), 642 participants developed T2D. In model 2, a higher score on the plant-based dietary index was associated with a lower incidence of T2D (per 10 units higher score on the index: HR 0.82, 95% CI 0.73; 0.92). Additional adjustment for BMI in model 3 attenuated this association, but it remained statistically significant (HR 0.87, 95% CI 0.79; 0.99). The associations between the plant-based dietary index with longitudinal insulin resistance and risk of prediabetes and T2D were similar in three sub-cohorts (Supplemental Tables 2.2.5-2.2.7). Associations did not differ by age, sex or baseline BMI (p-values for all interaction terms were > 0.05).

Exclusion of each one of 23 foods from the index one by one at a time did not substantially change the estimates (Supplemental Table 2.2.8). Excluding all plant-based beverages combined at a time (coffee and tea, alcoholic beverages and sugary beverages) did not substantially change the estimates for insulin resistance (per 10 units higher score on the index: β -0.06, 95% CI -0.10; -0.03), risk of prediabetes (HR 0.93, 95% CI 0.84; 1.02) or risk of T2D (HR 0.85, 95% CI 0.80; 0.96). The estimates also remained similar after excluding these less healthy plant-based foods (sweets, sugary beverages, potatoes, and refined grains) combined at a time (per 10 units higher score on the index: insulin resistance: β -0.09, 95% CI -0.10; -0.07, prediabetes risk: HR 0.90, 95% CI 0.84; 0.98, T2D risk: HR 0.83, 95% CI 0.74; 0.94), but the less healthy plant foods score was not associated with insulin resistance, risk of prediabetes or type 2 diabetes. The Pearson's correlation coefficient between the plant-based dietary score with the dietary guidelines score was 0.16 ($p < 0.05$), and additionally controlling for the dietary guidelines score did not substantially affect the estimates. Additional adjustment for hypertension and hypercholesterolemia did not change effect estimates substantially. Estimates also remained similar after excluding participants with chronic diseases at baseline. Finally, excluding participants who developed T2D or prediabetes in the first 2 years of follow-up modestly attenuated the associations for risk of prediabetes (per 10 units higher score on the index, HR 0.91, 95% CI 0.83; 1.01) and risk of T2D (HR 0.82, 95% CI 0.73; 0.92).

DISCUSSION

In this large population-based cohort, we observed that a diet higher in plant-based foods and lower in animal-based foods was associated with lower insulin resistance as well as a lower risk of prediabetes and T2D, suggesting a protective role of a more plant-based as opposed to a more animal-based diet in the development to T2D, beyond strict adherence to a vegetarian or vegan diet.

The inverse association between plant-based diets and T2D risk is in agreement with previous research showing lower T2D risk for vegans or vegetarians compared to non-vegetarians.[10] Moreover, the associations we observed confirmed previous observations by Satija and colleagues in a US sample, which is the only other prospective study examining adherence to plant-based diets in a continuous graduation with risk of T2D[11]. We extend upon these previous findings by also showing associations between plant-based diets and earlier stages in the development of T2D (insulin resistance and prediabetes) in a European population.

Our results imply a beneficial effect of adherence to a diet higher in plant-based foods and lower in animal-based foods on the development of T2D, irrespective of general healthiness of the specific plant-based and animal-based foods. With these results, we provide a different view on what a healthy diet may entail. However, we acknowledge that our plant-based diet included positive scoring for some components that are not necessarily healthy choices for prevention of T2D, or a healthy diet in general. Sugary beverages, for example, have been associated with adverse effects for T2D in other studies.[22,23] To further clarify whether these less healthy plant foods contributed to the observed associations, we examined the associations between a less healthy plant-based diet score with insulin resistance and risks of prediabetes and T2D in sensitivity analyses, and observed null associations; suggesting beneficial associations were mainly driven by higher intake of healthy plant-based food groups and lower intake of animal-based food groups. This emphasizes that it is important to also consider the quality of plant-based foods consumed, which has important public health implications. Furthermore, the estimates for the plant-based dietary index remained similar after excluding these plant-based beverages combined, or after excluding the less healthy plant-based foods combined, meaning that our results were stable in diverse versions of plant-based diets and thus increasing our confidence in the validity of the findings. We also observed that excluding each one of 23 components one by one at a time resulted in similar associations as observed for the total plant-based index, indicating that the associations were not mainly explained by any one specific food group, which supports the importance of recognizing overall plant-based diet. Finally, we extended our analyses to examine if adherence to a plant-based diet was independent of adherence to current Dutch dietary guidelines. In line with results from the large prospective cohort study in the US which examined if adherence to a plant-based diet was independent of general healthy dietary patterns that have been linked to prevention of T2D, such as the Mediterranean diet, the alternative Healthy Eating Index (aHEI), and the Dietary approaches to stop hypertension (DASH) diet,[24–26] we observed that associations of the plant-based dietary index with outcomes remained

similar after additional adjustment for adherence to current Dutch dietary guidelines. This lends support to the novelty of the plant-based dietary index.

Taken together, a more plant-based, less animal-based diet may help prevent the development of T2D. Still more important, a more plant-based diet does not require a radical change in diet in terms of total elimination of meat or animal products but instead can be achieved in various ways, increasing the potential for population-wide health recommendations. For example, if a participant in our cohort would increase fruits intake from 95 grams per day to 200 grams per day, increase vegetables intake from 100 grams to 260 grams, and at the same time decrease red meat intake from 129 grams per day to 55 grams per day, this would improve the plant-based dietary index by 10 units, which may decrease risk of T2D by 13%, assuming other covariates remain stable.

Several mechanisms may underlie the observed associations. On the one hand, a plant-based diet usually contains more fiber, chlorogenic acids, certain types of amino acids, unsaturated fatty acids and antioxidants. For example, vegetables and fruits are the main sources of fiber, antioxidants, and chlorogenic acids; nuts are rich in poly-unsaturated fatty acids; soy and beans are main sources of plant protein; whole grains are rich in fiber and plant protein; and coffee and tea are rich in antioxidants and chlorogenic acid. These beneficial components may influence the development of T2D through affecting intermediate conditions in the pathogenesis of this disorder, such as obesity and inflammation. Fiber is known to lower gastric emptying and thereby glycemic responsiveness and might also have beneficial effects on inflammation and obesity.[27–30] Chlorogenic acids can improve inflammation, glucose tolerance and glucose levels, and improve increasing insulin secretion.[31] Soy protein contains high amounts of the amino acids arginine and glycine, which have been associated with a decrease in cholesterol levels.[32] High intake of unsaturated fatty acids has also been associated to lower inflammation and less obesity.[28,33] Phenol chlorogenic acid was reported to reduce insulin resistance.[34] On the other hand, a plant-based diet usually has less animal protein, saturated fatty acids, and heme iron. Animal protein is rich in branched-chain amino acids and aromatic amino acids and may impair glucose metabolism and increase T2D risk;[35–38] animal protein is also rich in heme iron, which has been suggested to increase risk of cardiometabolic disease.[39–41] Higher saturated fatty acids have been suggested to be associated with higher inflammation as well as higher risk of obesity and T2D.[33,42,43] Furthermore, other nutrients contained in processed red meat, such as sodium and nitrites, may also increase risk of cardio-metabolic disease.[41] More research is needed to explore whether the mechanisms underlying the observed associations also involve an effect of plant-based foods on gut

microbiome. Finally, these different mechanisms may influence each other because of interrelations between different food components. This also highlights the relevance of examining overall diets in addition to isolated food items, as this enables capturing the combined effects of the suggested pathways.

This study has several strengths. First, to our knowledge, we are the first to investigate the associations between plant-based diets and longitudinal insulin resistance and prediabetes, for which we had longitudinal data available with a long period of follow-up. Studying these early risk stages helps to minimize reverse causation in understanding how a plant-based diet influences the development of T2D. Second, we observed that the potential beneficial effect of a more plant-based diet was independent of less healthy plant-based foods, such as sweets, sugary beverages and refined grains, emphasizing the importance of considering the quality of plant-based foods consumed. We also observed associations of the plant-based dietary score independent of overall adherence to dietary guidelines, indicating that the plant-based diet score may reflect more than only a healthy dietary pattern as reflected by current dietary guidelines. Other strengths also included the population-based nature of the study, the detailed and thorough data collected on the outcomes and the assessment of the extent to which diets were plant-based and animal based, based upon overall dietary intake patterns of the general population.

Nevertheless, there are several limitations we should consider. First, the assessment of a plant-based diet with this index has its limitations as several, sometimes arbitrary, decisions had to be made. One such decision was, for example, to add up food items within categories based on the intake in grams per day. As a result, products that were high in water-content will have contributed less energy or nutrients compared to products containing less water in the same category. However, using grams per day reflects intake of foods as they are consumed and recommended.[19] Also, decisions had to be made for the categorization of foods and the number of categories. We chose categories reflecting those used in the Dutch dietary guidelines, which are based on similarities of the food items in (botanical) origin, nutrient composition, and nutrient density;[18] thereby reducing nutritional differences between food items within one category. Furthermore, in our main analyses, we treated all plant-based foods equally by giving all plant-based foods positive scores, and all animal-based foods equally by giving all animal-based foods reverse scores, irrespective of their nutrient-density or previous evidence for a role in T2D prevention and general health. For example, less healthy plant-based foods, such as sugary beverages and refined grains, were included as positive scores, although sugary beverages,[23] and refined grains[44] have been linked to higher T2D risk; by contrast, healthy animal-based foods, such as dairy

and fish, were included as reverse scores, although dairy[45] and fish[46] have been linked to lower T2D risk or mortality risk. This is because our study aimed to emphasize an overall plant-based diet accounting for the possibilities of increased plant-based foods consumption as well as decreased animal-based foods consumption, which could increase the potential for population-wide recommendation. However, in our sensitivity analyses, excluding any one of alcoholic beverages, sugary beverages, sweets, potatoes, refined grains, fish, and dairy did not substantially change our estimates. In addition to the choices we had to make in the construction of the index, this study has some other limitations. First, dietary data were derived from self-reported diet measured with FFQs, making measurement error likely. However, because we used relative scores (quintiles) of intake and the FFQs were shown in several validation studies to adequately rank subjects according to intake,[13–16] we do not expect this measurement error to have affected our results to a large extent. Second, we did not have dietary data for many of the participants of the original cohort, which might have resulted in sampling bias if associations of plant-based diets with T2D risk differed in those included and those not included in our current analyses. Third, we assumed that diets remained stable over time. However, the estimates were similar after excluding the participants who were likely to change their diet during follow-up, such as participants with CHD, stroke, or cancer at baseline. Lastly, our results may be generalizable only to people of similar age and ethnicity.

In conclusion, in this large population-based cohort, higher adherence to an overall plant-based diet is associated with lower longitudinal insulin resistance, and lower risk of prediabetes and T2D, indicating a protective role of diets high in plant-based foods and low in animal-based foods in the development to T2D beyond strict adherence to a vegetarian or vegan diet. These promising findings call for further exploration of overall plant-based dietary recommendations aimed at T2D prevention.

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Supplemental Table 2.2.1. Food categories used for the plant-based diet index and examples of food items included in each of the food categories

Plant-based food categories	
Fruits	Apple, banana, pear, orange, strawberry, grapes, other fruits
Vegetables	Cauliflower, broccoli, spinach, carrots, onion, lettuce, tomato, cabbage, cooked vegetables
Whole grains	Whole grain bread, dark bread, rye bread, whole grain breakfast oats, whole grain pasta, brown rice
Nuts	Peanuts, walnuts, other nuts, peanut butter
Legumes	Legumes, tofu, soybeans, other soy products
Potatoes	Potatoes, fries
Vegetable oils	Olive oil, vegetable oils used for cooking, and all margarines
Tea and coffee	Black tea, green tea, herbal tea, coffee
Sugary beverages	Carbonated beverages with sugar, non-carbonated beverages with sugar, orange juice, fruit juice
Refined grains	Cornflakes, white bread, croissants, raisin bread, white pasta, white rice
Sweets	Sugar, cookies, cake, chocolate, candy-bars, honey, sweets, chocolate toppings, other sweet toppings
Alcoholic beverages	Red wine, white wine, beer, liquor, Dutch-eggnog
Animal-based food categories	
Low-fat Yoghurt	Skimmed yoghurt, semi-skimmed yoghurt, skimmed quark, buttermilk
Full-fat Yoghurt	Full-fat yoghurt, semi-skimmed quark, full quark
Low-fat milk	Skimmed milk, semi-skimmed milk, skimmed coffee creamer, semi-skimmed coffee creamer
Full-fat milk	Full-fat milk, cream, coffee-cream
Cheese	Full fat cheese, low fat cheese, cheese fondue, other cheese
Fish	Salmon, tuna, trout, herring, mussels, other fish
Eggs	Boiled eggs, fried eggs
Animal fat	Butter on bread, butter used for cooking, lard
Desserts and sugary dairy	Custard, cream, ice cream, mousse, cream, chocolate milk, fruit yoghurt, yoghurt drinks
Unprocessed lean meat	Chicken
Processed and red meat	Beef, pork, meatballs, sate, bacon, liver, processed meats

Supplemental Table 2.2.2. Baseline intake of 23 food categories of participants (grams/day) in quintiles of the plant-based dietary index

Plant-based dietary index	score ≤ 43	43 < score ≤ 47	47 < score ≤ 51	51 < score ≤ 55	score > 55
	n = 1,417	n = 1,311	n = 1,559	n = 1,226	n = 1,285
Fruits	168.0 (83.4, 274.5)	197.4 (104.0, 320)	215.7 (115.2, 340.3)	226.7 (127.3, 351.9)	258.5 (161.1, 395.1)
Vegetables	181.6 (128.0, 252.9)	199.4 (143.9, 277.1)	205.2 (146.4, 283.3)	216.9 (156.4, 297.7)	241.3 (180.4, 331.4)
Whole grains	88.3 (46.6, 125.0)	99.5 (50.0, 140.6)	108.3 (63.0, 151.1)	114.7 (67.6, 160.0)	135.0 (80.0, 188.0)
Legumes	0.0 (0.0, 8.9)	0.0 (0.0, 16.9)	4.1 (0.0, 18.0)	7.8 (0.0, 24.0)	13.5 (0.0, 35.6)
Nuts	13.5 (0.0, 6.0)	2.1 (0.0, 8.8)	3.6 (0.0, 11.8)	5.6 (0.4, 14.1)	9.0 (2.7, 19.2)
Vegetable oils	12.0 (3.3, 21.4)	16.6 (7.2, 26.0)	20.6 (10.4, 30.0)	24.0 (13.3, 32.6)	27.7 (18.1, 38.5)
Tea and coffee	705.4 (500.0, 875.0)	750.0 (525.0, 937.5)	767.9 (597.1, 1000.0)	812.5 (625.0,1044.6)	900.0 (705.4, 1125.0)
Refined grains	37.7 (17.1, 76.8)	50.0 (22.7, 97.6)	50.6 (23.5, 101.3)	60.0 (30.4, 115.6)	61.2 (30.9, 122.2)
Potato	83.6 (45.9, 122.0)	88.2 (57.0, 131.0)	97.9 (61.7, 142.5)	108.3 (71.2, 163.1)	126.0 (85.5, 178.1)
Sweets	50.3 (26.6, 81.7)	57.2 (32.6, 87.5)	64.2 (38.2, 95.6)	71.3 (43.5, 105.2)	71.3 (43.5, 105.2)
Sugary beverages	15.0 (0.0, 89.6)	40.0 (0.0, 139.3)	42.9 (0.0, 139.6)	42.9 (0.0, 139.6)	59.8 (1.2, 152.6)
Alcoholic beverages	31.8 (2.5, 124.7)	47.7 (3.6, 155.3)	58.8 (4.9, 160.3)	65.4 (8.4, 167.9)	81.9 (14.2, 189.3)
Low-fat yoghurt	82.3 (5.4, 192.9)	64.1 (0.0, 166.1)	60.0 (0.0, 164.5)	53.6 (0.0, 162.0)	32.1 (0.0, 149.6)
Full-fat yoghurt	0.0 (0.0, 34.8)	0.0 (0.0, 13.4)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Low-fat milk	111.0 (1.9, 278.6)	100.8 (0.88, 263.6)	91.0 (0.0, 224.4)	59.0 (0.0, 224.4)	48.0 (0.0, 196.5)
Full-fat milk	0.0 (0.0, 7.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Cheese	32.9 (21.3, 47.1)	32.6 (20.3, 50.0)	30.3 (20.0, 46.6)	28.4 (18.2, 44.6)	29.9 (17.8, 47.0)
Fish	21.4 (7.1, 33.8)	18.9 (5.9, 33.0)	14.6 (4.2, 30.2)	14.4 (2.4, 28.6)	11.0 (0.0, 25.9)
Eggs	14.3 (8.9, 21.4)	14.3 (7.1, 21.4)	14.3 (7.1, 17.9)	14.3 (7.1, 17.1)	10.7 (7.1, 17.1)
Animal fat	0.7 (0.0, 12.0)	0.0 (0.0, 2.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Desserts / sugary dairy	21.4 (1.5, 63.9)	18.4 (0.4, 60.5)	14.9 (0.0, 59.6)	10.2 (0.0, 48.1)	6.4 (0.0, 35.8)
Unprocessed lean meat	14.3 (6.9, 21.4)	14.3 (7.1, 21.4)	11.4 (4.3, 18.6)	10.7 (4.3, 17.8)	7.6 (0.0, 14.9)
Processed/red meat	93.2 (65.4, 127.5)	89.3 (63.4, 127.5)	86.9 (60.0, 118.0)	85.5 (60.4, 117.9)	80.0 (52.5, 112.3)

Supplemental Table 2.2.3. Baseline characteristics of participants in original and multiple imputed dataset.

Characteristics	Original data (mean (SD) or %)	After imputation (mean (SD) or %)
Age (years)	62.0 (7.8)	NI
Missing (%)	-	-
Gender (% male)	41.3 %	NI
Missing (%)	-	-
BMI (kg/m^2)	26.6 (3.9)	26.6 (3.9)
Missing (%)	1.3%	-
Smoking (%)		
Never	32.2%	32.2%
Ever	45.1%	45.1%
Current	22.7%	22.7%
Missing (%)	0.5%	-
Physical activity[1] (MET-hours/week)		
RS-I / RS-II (Zutphen Questionnaire, n = 4,393)	86.7 (44.7)	86.7 (44.7)
RS-III (LASA Questionnaire, n = 2,194)	58.4 (55.8)	58.4 (55.8)
Missing (%)	3.9%	-
Hypertension (%)	42.3 %	42.3 %
Missing (%)	0.9 %	-
Hypercholesterolemia (%)	45.6 %	45.4 %
Missing (%)	1.6%	-
Family history of type 2 diabetes (%)	10.8 %	NI
Missing (%)	-	-
Education level (%)		
Primary	11.8%	11.8%
Lower	40.9%	40.9%
Intermediate	29.0%	29.0%
Higher	18.3%	18.3%
Missing (%)	0.6%	-
Current food supplement use (%)	16.5 %	16.5 %
Missing (%)	0.3%	-
Total energy intake (kcal/day)	2134 (615)	NI
Missing (%)	-	-
Food category intake[2] (grams/day)		
Fruits	212.2 (115.5, 332.3)	NI
Vegetables	209.1 (147.9, 286.9)	NI
Whole Grains	105.7 (61.3, 152.5)	NI
Nuts	3.9 (0.0, 12.0)	NI
Legumes	4.1 (0.0, 19.4)	NI

Supplemental Table 2.2.3. Baseline characteristics of participants in original and multiple imputed dataset. (continued)

Characteristics	Original data (mean (SD) or %)	After imputation (mean (SD) or %)
Potatoes	99.7 (61.4, 148.2)	NI
Vegetable oils	19.7 (9.2, 30.0)	NI
Tea and coffee	758.9 (580.4, 1000)	NI
Sugary beverages	46.3 (0.0, 139.6)	NI
Refined grains	50.7 (23.9, 102.1)	NI
Sweets	63.8 (37.1, 97.4)	NI
Alcoholic beverages	56.4 (4.9, 159.8)	NI
Low-fat milk	82.3 (0.0, 232.3)	NI
Full-fat milk	0.0 (0.0, 0.0)	NI
Low-fat yoghurt	56.1 (0.0, 164.6)	NI
Full-fat yoghurt	0.0 (0.0, 4.9)	NI
Cheese	30.8 (20, 47.1)	NI
Unprocessed lean meat	10.7 (4.3, 18.1)	NI
Fish	15.9 (3.9, 30.7)	NI
Eggs	14.3 (7.1, 19.6)	NI
Animal fat	0.0 (0.0, 0.9)	NI
Desserts / sugary diary	14.1 (0.0, 54.6)	NI
Processed / red meat	86.8 (60.4, 118.9)	NI
Plant-based dietary index (score)	49.3 (7.1)	NI

Plant-based dietary index: a higher score indicates a higher adherence to a plant-based diet (theoretical range from 0 to 92). [1]Values shown are un-imputed; imputation was performed on z-scores of physical activity. [2]Variables expressed as median (IQR) because of their skewed distributions. Abbreviations: MET, metabolic equivalent of task; NI, not imputed.

Supplemental Table 2.2.4. Non-response analyses.

	Participants without valid dietary data (n = 5,225)	**Participants with valid dietary data (n = 9,701)**	**P value**
	Mean (SD) or %	Mean (SD) or %	T-test or χ^2 test
Age (years)	64.9 (12.7)	62.0 (7.8)	P < 0.05
Sex (%)			
Female	59.0%	41.8%	P < 0.05
Male	38.8%	58.0%	
BMI (kg/m^2)	27.0 (4.4)	26.6 (3.9)	P < 0.05
Physical activity (MET-hours/week)			
RS-I and RS-II (Zutphen Questionnaire)	72.4 (42.5)	83.5 (44.6)	P < 0.05
RS-III (LASA Questionnaire)	65.3 (43.5)	59.3	
Education level (%)			
Primary	25.0%	11.8%	P > 0.05
Lower	37.2%	40.9%	
Intermediate	24.4%	29.0%	
Higher	13.3%	18.4%	
Smoking status (%)			
Never	35.0%	32.2%	P > 0.05
Ever	39.0%	45.1%	
Current	25.6%	22.7%	
Current food supplement use (%)			
Yes	16.9%	16.5%	P > 0.05
No	83.1%	83.2%	
Family history of diabetes (%)			
Yes	9.0%	10.8%	P > 0.05
No	39.8%	45.8%	
Unknown	51.3%	43.4%	

Supplemental Table 2.2.4. Non-response analyses. (continued)

	Participants not included in analyses (n = 8,128)	Included participants in analyses (n = 6,798)	P value
	Mean (SD) or %	Mean (SD) or %	T-test or χ^2 test
Age (years)	69.3 (11.4)	62.0 (7.8)	P < 0.05
Sex (%)			
Female	59.5%	57.0%	P > 0.05
Male	40.1%	41.3%	
BMI (kg/m^2)	27.1 (4.3)	26.6 (3.9)	P < 0.05
Physical activity (MET-hours/week)			
RS-I and RS-II (Zutphen Questionnaire)	72.1 (42.5)	86.7 (44.7)	P < 0.05
RS-III (LASA Questionnaire)	61.6 (79.9)	58.4 (55.8)	
Education level (%)			
Primary	23.6%	11.8%	P > 0.05
Lower	37.0%	40.9%	
Intermediate	23.6%	29.0%	
Higher	11.1%	18.3%	
Smoking status (%)			
Never	32.5%	32.2%	P > 0.05
Ever	38.4%	45.1%	
Current	24.3%	22.7%	
Current food supplement use (%)			
Yes	14.6%	16.5%	P < 0.05
No	84.6%	83.5%	
Family history of diabetes (%)			
Yes	13.9%	45.8%	P > 0.05
No	49.1%	10.8%	
Unknown	36.9%	43.4%	

T-tests were performed for continuous variables, and χ^2 tests were performed for categorical variables.

Supplemental Table 2.2.5. Associations of the plant-based dietary index with longitudinal insulin resistance (HOMA-IR) for the three sub-cohorts separately.

	β for HOMA-IR (95% CI)		
	RS-I (n = 2,892)	RS-II (n = 1,389)	RS-III (n = 2,233)
Model 1	-0.09 (-0.10; -0.08)***	-0.07 (-0.11; -0.03)***	-0.11 (-0.14; -0.07)***
Model 2	-0.09 (-0.10; -0.08)***	-0.06 (-0.10; -0.02)**	-0.10 (-0.13; -0.07)***
Model 3	-0.05 (-0.07; -0.03)*	-0.01 (-0.05; 0.02)	-0.06 (-0.09; -0.03)***

Effect estimates are βs for ln-transformed HOMA-IR per 10 units higher score on the plant-based dietary index and are based on pooled results of the imputed dataset. Model 1 is adjusted for energy intake, sex, age and time of repeated measurements of longitudinal insulin resistance. Model 2 is additionally adjusted for education, smoking status, family history of diabetes, physical activity and food supplement use. Model 3 is additionally adjusted for BMI (kg/m^2). *p < 0.05; **p < 0.01; ***p < 0.001. Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model assessment for insulin resistance; MET, metabolic equivalent of task; RS, Rotterdam-Study.

Supplemental Table 2.2.6. Associations of the plant-based dietary index with incidence of prediabetes for the three sub-cohorts separately.

	HR (95% CI) for prediabetes		
	RS-I (n = 2,492)	RS-II (n = 1,151)	RS-III (n = 2,125)
Model 1	0.93 (0.82; 1.05)	0.94 (0.78; 1.14)	0.65 (0.51; 0.84)***
Model 2	0.94 (0.83; 1.06)	0.94 (0.78; 1.14)	0.66 (0.52; 0.85)**
Model 3	0.96 (0.85; 1.09)	1.00 (0.83; 1.21)	0.70 (0.54; 0.90)**

Effect estimates are HRs (95% CIs) for incidence of prediabetes per 10 units higher score on the plant-based dietary index and are based on pooled results of the imputed dataset. Model 1 is adjusted for energy intake, sex and age. Model 2 is additionally adjusted for education, smoking status, family history of diabetes, physical activity and food supplement use. Model 3 is additionally adjusted for BMI (kg/m^2). *p < 0.05; **p < 0.01; ***p < 0.001. Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; RS, Rotterdam-Study.

Supplemental Table 2.2.7. Associations of the plant-based dietary index with incidence of type 2 diabetes for the three sub-cohorts separately.

	HR (95% CI) for type 2 diabetes		
	RS-I (n = 2,975)	RS-II (n = 1,411)	RS-III (n = 2,384)
Model 1	0.85 (0.73; 0.98)*	0.82 (0.65; 1.02)	0.74 (0.54; 1.02)
Model 2	0.86 (0.74; 1.00)*	0.86 (0.69; 1.07)	0.75 (0.54; 1.04)
Model 3	0.91 (0.78; 1.05)	0.93 (0.74; 1.16)	0.80 (0.58; 1.12)

Effect estimates are HRs (95% CIs) for incidence of type 2 diabetes per 10 units higher score on the plant-based dietary index and are based on pooled results of the imputed dataset. Model 1 is adjusted for energy intake, sex and age. Model 2 is additionally adjusted for education, smoking status, family history of diabetes, physical activity (z-score of MET-hours/week); and food supplement use (yes or no). Model 3 is additionally adjusted for BMI (kg/m2). *p<0.05; **p<0.01; ***p<0.001. Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; RS, Rotterdam-Study.

Supplemental Table 2.2.8. Associations of the plant-based dietary index with longitudinal insulin resistance (HOMA-IR), risk of prediabetes and type 2 diabetes (T2D) after excluding each one of 23 components one by one at a time, and additionally adjusting for the excluded one.

Plant-based dietary index with 22 components instead of 23 components	β (95% CI) for HOMA-IR	HR (95% CI) for prediabetes risk	HR (95% CI) for T2D risk
	n = 6,514	n = 5,768	n = 6,770
Excluding fruits	-0.08 (-0.10; -0.07) ***	0.89 (0.81; 0.98) *	0.82 (0.73; 0.92) **
Excluding vegetables	-0.09 (-0.10; -0.09) ***	0.89 (0.81; 0.98) *	0.81 (0.72; 0.92) **
Excluding whole grains	-0.09 (-0.10; -0.09) ***	0.89 (0.81; 0.98) *	0.81 (0.73; 0.92) **
Excluding nuts	-0.07 (-0.09; -0.06) ***	0.91 (0.81; 1.00)	0.84 (0.76; 0.95) **
Excluding legumes	-0.08 (-0.10; -0.07) ***	0.90 (0.82; 0.99) *	0.83 (0.74; 0.92) **
Excluding vegetable oils	-0.08 (-0.10; -0.07) ***	0.90 (0.82; 0.99) *	0.82 (0.73; 0.92) **
Excluding tea and coffee	-0.07 (-0.09; -0.06) ***	0.91 (0.83; 0.99) *	0.84 (0.75; 0.95) **
Excluding potatoes	-0.09 (-0.10; -0.09) ***	0.89 (0.81; 0.98) *	0.82 (0.73; 0.92) **
Excluding sugary beverages	-0.09 (-0.10; -0.08) ***	0.89 (0.81; 0.98) *	0.82 (0.72; 0.92) **
Excluding refined grains	-0.09 (-0.10; -0.08) ***	0.89 (0.81; 0.98) *	0.82 (0.73; 0.92) **
Excluding sweets	-0.08 (-0.10; -0.08) ***	0.90 (0.82; 0.99) *	0.81 (0.73; 0.92) **
Excluding alcoholic beverages	-0.08 (-0.10; -0.06) ***	0.89 (0.82; 0.98) *	0.83 (0.71; 0.95) **
Excluding red and processed meat	-0.07 (-0.08; -0.07) ***	0.93 (0.84; 0.99) *	0.84 (0.76; 0.95) **
Excluding unprocessed lean meat	-0.07(-0.08; -0.07) ***	0.90 (0.82; 0.99) *	0.84 (0.76; 0.95) **
Excluding fish	-0.08 (-0.10; -0.07) ***	0.90 (0.81; 0.99) *	0.84 (0.74; 0.94) **
Excluding eggs	-0.09 (-0.10; -0.08) ***	0.89 (0.80; 0.98) *	0.82 (0.73; 0.92) **
Excluding animal fat	-0.08 (-0.10; -0.08) ***	0.89 (0.79; 0.99) *	0.83 (0.70; 0.95) **
Excluding cheese	-0.08 (-0.10; -0.07) ***	0.91 (0.82; 0.99) *	0.84 (0.75; 0.94) **
Excluding low-fat milk	-0.08 (-0.10; -0.06) ***	0.86 (0.79; 0.95) *	0.81 (0.72; 0.92) **
Excluding full-fat milk	-0.08 (-0.10; -0.07) ***	0.90 (0.82; 0.99) *	0.83 (0.72; 0.93) **
Excluding low-fat yoghurt	-0.08 (-0.10; -0.07) ***	0.89 (0.81; 0.98) *	0.82 (0.74; 0.92) **
Excluding full-fat yoghurt	-0.09 (-0.10; -0.09) ***	0.86 (0.78; 0.94) *	0.80 (0.70; 0.90) **
Excluding desserts/dairy with sugars	-0.08 (-0.10; -0.08) ***	0.90 (0.81; 0.99) *	0.83 (0.71; 0.94) **

Effect estimates are regression coefficients (β) for ln HOMA-IR or hazard ratios (HRs) for incidence of prediabetes or type 2 diabetes with their 95%-confidence intervals (95%CIs), per 10 units higher score on the plant-based dietary index by excluding one of 23 foods at a time and additionally adjusting for the excluded food group. Estimates are adjusted for total energy, age, sex, RS subcohort, education, smoking status, family history diabetes, physical activity, and food supplement use (only for the HOMA analyses additionally for the time measurements of longitudinal HOMA), based on pooled results of imputed data. *p < 0.05; ** p < 0.01; ***p < 0.001