



Review

Dietary habits contribute to define the risk of type 2 diabetes in humans



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SUMMARY

Background and aims: Type 2 diabetes (T2D) is a frequent disorder largely preventable. The aim of this review was to summarize information on the association between dietary habits and the risk of developing T2D.

Methods: We conducted a comprehensive literature search using the PubMed database from its inception to June, 2019. Articles were restricted to those written in English and concerning human subjects. Relevant manuscripts found in the list of references of the retrieved articles were also used in preparation for the review.

Results: Animal protein consumption increases the risk of T2D independently of body mass index. Intake of both unprocessed meat and processed meat is strongly and consistently associated with increased risk of developing T2D. In contrast, consumption of high-quality vegetable foods prevents the disease. High-quality plant foods include whole grains, nuts, legumes, fruits, and vegetables. Among less healthy plant-based foods are fruit juices, sweetened beverages, refined grains, potatoes, sweets, and desserts. Carbohydrate-restricted diets that encourage consumption of animal products promote T2D. Low intake of animal products is linked to high educational level so that well-informed individuals tend to consume diets with elevated content of vegetable food. According to the American Dietetic Association, “appropriately planned vegetarian diets including vegan diets are healthful, nutritionally adequate, and may provide health benefits in the prevention and treatment of certain diseases”.

Conclusions: restricting animal products while increasing healthy plant-based foods intake facilitates T2D prevention. To neutralize worldwide the burden of T2D and its devastating complications, animal products consumption should be limited or discontinued.

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1. Introduction

Type 2 diabetes (T2D) is a common metabolic disorder with severe systemic complications that can be mostly prevented by dietary modifications and physical exercise. In 1935, Himsworth and Marshall compared dietary habits of patients with T2D before the diagnosis of the disease to dietary habits of normal subjects, in a case–control study. The diet of patients with T2D prior to the

diagnosis of the disorder contained elevated amounts of animal products and reduced amounts of plant-based food compared to the diet of normal subjects [1]. Since then, multiple investigations provide evidence that consumption of both unprocessed meat and processed meat (sausages, salami, bacon, hotdogs, ham) raises the risk of developing T2D whereas elevated intake of high-quality vegetable foods contributes to the prevention of the disease [2–7]. High-quality plant-based foods include nuts, whole grains (rice, wheat, corn), legumes (beans, lentils, soy beans, peas, chickpeas, peanuts), vegetables, and fruits [8–10]. Less healthy plant-based foods include fruit juices, sweetened beverages, refined grains, potatoes, sweets, and desserts. Dietary habits with elevated content of animal products and low amount of high-quality plant-based food items increase the risk of developing T2D, independently of body mass index (BMI) [11–14]. Educational level is

Abbreviations: BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; HOMA-IR, homeostasis model assessment-insulin resistance; NHS, Nurses' Health Study; NIH, National Institutes of Health; T2D, type 2 diabetes.

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related positively to the intake of plant-based foods, so that well-informed subjects consume higher amount of vegetable protein compared to other individuals [15–17]. Age-standardized adult diabetes prevalence in 2014 was lowest in northwestern Europe in a pooled analysis of 751 population-based studies with 4.4 million participants. Between 1980 and 2014 there was little change in age-standardized diabetes prevalence in adult women in continental Western Europe although crude prevalence rose because of aging of the population [18]. However, the rate of T2D is currently escalating in places where the consumption of animal products is increasing, such as China [19,20].

The mechanisms underlying the detrimental effect of animal products and the protective effect of plant-based foods on the risk of developing T2D remain uncertain. The differential effect of animal versus vegetable food items on the development of insulin resistance may contribute to explain their opposite impact on T2D risk. In normal humans, animal protein activates prolonged glucagon secretion so that plasma glucagon remains elevated for at least four hours after the ingestion. Hyperglycemia attenuates the increase in plasma glucagon that follows animal protein intake [21,22]. In patients with diabetes, the response of plasma glucagon to animal protein ingestion is exaggerated and hyperglucagonemia occurs despite hyperglycemia [23,24]. Glucagon is a major hormone that opposes insulin action predominantly in the liver. Conditions such as glucagonoma and total pancreatectomy highlight the ability of glucagon to induce insulin resistance. Patients with glucagonoma experience uncontrolled glucagon secretion and insulin-dependent diabetes that disappear after the surgical resection of the tumor [25]. On the contrary, patients with total pancreatectomy lack pancreatic glucagon secretion and they experience striking insulin sensitivity with predisposition to life-threatening hypoglycemic episodes [26–29].

Longitudinal studies show that insulin resistance usually precedes T2D. Animal protein intake activates glucagon secretion that induces insulin resistance and predisposes to T2D, independently of BMI. Limiting the consumption of animal products while increasing plant-based food enhances insulin sensitivity and contributes to prevent T2D [30,31]. The beneficial effect of plant-based food compared to animal protein on insulin resistance has been documented in prospective studies [6,7,32], randomized clinical trials [33], and a systematic review [34]. Elevated intake of animal protein is independently associated with higher longitudinal insulin resistance while plant protein is not related to insulin resistance. The role of a plant-based diet on insulin resistance assessed by the homeostasis model assessment-insulin resistance (HOMA-IR) index was investigated in a randomized clinical trial. Participants were randomized to follow a plant-based diet or to maintain their usual omnivorous diet. The HOMA-IR values were reduced in the vegan group compared to the subjects who maintained their usual diet, suggesting that a plant-based diet is associated with improved insulin sensitivity [33]. The prospective association between protein intake from different sources and insulin resistance (HOMA-IR) was examined in three cohorts of the population-based Rotterdam Study among 6822 participants without diabetes at baseline. After adjusting for potential confounders, including waist circumference, higher animal protein intake was associated with higher longitudinal HOMA-IR. In contrast, total plant-based protein derived from nuts, legumes, grains, fruits, and vegetables was not associated with insulin resistance [6]. Similar results were obtained in four population-based cohort studies (three European cohorts and one Canadian cohort) included in the PREVIEW project. Higher plant-based protein intake was independently associated with lower incidences of prediabetes [7]. Further, a low-carbohydrate and high-animal protein diet promotes insulin resistance and greater risk of T2D. Carbohydrate-restricted diets aimed to lose weight tend to

encourage intake of animal products, but this kind of dietary pattern reduces insulin sensitivity. Dietary protein and fat should be obtained from foods other than animal products when consuming a low-carbohydrate diet. Nuts and whole grains are major sources of protein that have been related to lower T2D risk [35–38]. Consistently, weight loss fails to improve insulin resistance in the presence of a diet high in animal products [39,40]. Higher consumption of animal protein is associated also with an increased risk of gestational diabetes, a condition typically characterized by insulin resistance, suggesting that animal protein intake reduces insulin sensitivity among pregnant women [41–44]. In a prospective cohort study of 3063 pregnant women, multivariate analysis showed that the highest tertile of the vegetable pattern was associated with a decreased risk of gestational diabetes compared with the lowest tertile [41]. Protein intake before pregnancy and during the first and second trimesters of pregnancy was assessed in a prospective cohort of pregnant women to examine the association of dietary protein intake with the risk of gestational diabetes. Higher intake of animal protein was associated with higher risk of gestational diabetes whereas vegetable protein consumption was not related to gestational diabetes risk [42]. In a review aimed to evaluate the relationship between protein intake and insulin sensitivity during pregnancy, animal protein is associated with worsening insulin resistance while plant protein is related to improved insulin sensitivity [44]. The prospective association between animal versus plant-based foods and long-term risk of T2D was investigated among 4502 women with a history of gestational diabetes from the Nurses' Health Study (NHS)-2 cohort. A low-carbohydrate dietary pattern with high animal protein and fat intake is associated with higher risk of T2D whereas a low-carbohydrate dietary pattern with high vegetable protein and fat intake is not associated with T2D risk [43].

Insulin resistance by itself is a major cardiovascular risk factor both in the general population and in patients with diabetes. Accordingly, dietary habits with high animal protein content increase the risk of cardiovascular disease whereas the intake of healthy vegetable food decreases the risk of cardiovascular disease [45–47].

1. Dietary animal protein increases the risk of type 2 diabetes

Numerous prospective studies have consistently documented an association between animal protein consumption and elevated risk of developing T2D in humans (Table 1).

The first Seventh-day Adventist Study revealed the protective effect of a vegetarian diet on the incidence of diabetes in a prospective evaluation of 25,698 participants followed-up for 21 years. Multivariate analysis showed an association between meat consumption and incidence of diabetes that was not due to confounding by weight, other dietary factors or physical activity. Furthermore, Seventh-day Adventist vegetarians had a substantially lower risk of diabetes than nonvegetarians, suggesting that a vegetarian diet reduces the risk of developing diabetes [48].

Similar results were obtained by two new cohorts of Seventh-day Adventists, the Adventist Mortality Study and the Adventist Health Study in California, which examined the prospective association between meat intake and incidence of T2D. Multivariate logistic regression models showed that subjects who consume processed meat or unprocessed meat once or more per week were more likely to develop diabetes than those who consume no meat. Long-term adherence to a nonvegetarian diet (weekly meat intake) over a 17-year period was independently associated with a 74% increase in the risk of diabetes relative to a vegetarian diet [15].

In the Adventist Health Study-2, participants were grouped at baseline as vegan, lacto-ovo-vegetarian, pesco-vegetarian, semi-

Table 1
Prospective studies: animal protein intake increases the risk of type 2 diabetes (T2D).

	Study population	Follow-up/N	Main finding	Reference
Seventh-day Adventist Study	Seventh-day Adventists/US	21 years 25,698	The risk of T2D in Adventists (mostly vegetarians) is half than in the US population. Vegetarians have decreased risk of T2D than nonvegetarians	Snowdon, 1985
Adventist Mortality Study and Adventist Health Study	Seventh-day Adventists/US	17 years 8401	Subjects who consume any meat once or more per week are more likely to develop diabetes	Vang, 2008
Adventist Health Study-2	Seventh-day Adventists/US (17.3% Blacks)	96,592 2 years	The incidence of diabetes increases gradually among vegans, lacto-ovo-vegetarians, and nonvegetarians	Tonstad, 2013
Health Professionals Follow-up Study	Men/US	12 years 51,529	Meat (unprocessed and processed) and dairy products are associated with high risk of T2D	van Dam, 2002
Health Professionals Follow-up Study	Men/US	20 years 51,529	A low-carbohydrate, high-animal protein diet is associated with greater risk of T2D	de Koning, 2011
Nurses' Health Study-1	Women/US	14 years 41,518	There is a positive association between the Western dietary pattern and T2D. The major contributor is meat	Fung, 2004
Nurses' Health Study-2	Women/US	8 years 116,671	Diets high in meat, principally processed meats, increase the risk of developing T2D	Schulze, 2003
Women's Health Study	Women/US	8.8 years 37,309	Consumption of total meat and processed meat is associated with increased risk of T2D	Song, 2004
Women's Health Initiative study	Women/US	8.1 years 74,155	Animal protein consumption contributes to T2D risk regardless overweight/obesity	Tinker, 2011
Iowa Women's Health Study	Women/US	11 years 35,988	Intake of animal products (protein and fat) is associated increases T2D risk	Meyer, 2001
San Luis Valley Diabetes Study	Subjects with impaired glucose tolerance/US	22.6 months 134	Intake of animal products predicts T2D incidence in subjects with impaired glucose tolerance	Marshall, 1994
Multiethnic Cohort Trial	Multiethnic/US	14 years 74,970	Meat intake increases risk for diabetes irrespective of ethnicity and level of BMI	Steinbrecher, 2011
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study	Male smokers/Finland	12 years 29,133	Higher intake of processed meat is associated with increased risk of T2D	Mannisto, 2010
Malmö Diet and Cancer study	General population/Sweden	12 years 27,140	High intake of meat and poultry is associated with increased risk of T2D	Ericson, 2013
European Prospective Investigation into Cancer and Nutrition-InterAct	General population/Europe	11.7 years 340,234	There is a positive association between consumption of total and red meat and incident T2D	Bendinelli, 2013
The Rotterdam study	General population/The Netherlands	12.4 years 4366	Intake of red meat is positively associated with risk of T2D independently of BMI	van Woudenberg, 2012
French women study	Women/France	13.8 years 66,118	The risk of incident diabetes increases with higher consumption of processed red meat	Lajous, 2012
The Rotterdam Study	Three cohorts of subjects without T2D at baseline	7.1 years 9633	Higher intake of animal protein is associated with higher risk of T2D while plant protein is not related to risk of T2D.	Chen, 2019

vegetarian, and nonvegetarian (reference group) to investigate the relationship between several dietary habits and incidence of diabetes at follow-up. Vegetarian diets are associated with a substantial and independent reduction in diabetes incidence. Gradual adherence to a vegan diet offer increasingly greater protection against risk of T2D [49].

The Health Professionals Follow-up Study (HPFS) enrolled in 1986 51,529 US male health professionals. The association between two major dietary patterns and risk for T2D was prospectively analyzed. The "prudent" dietary pattern is characterized by higher consumption of vegetables, legumes, whole grains, fruits, and fish while the Western dietary pattern is characterized by higher consumption of red meat, processed meat, high-fat dairy products, French fries, and refined grains. During 12 years of follow-up, the Western dietary pattern was associated with an increased risk for T2D. The analysis of specific foods showed that unprocessed red meat, processed meat, and high-fat dairy products were associated with high risk of developing T2D [50].

These findings were confirmed at 20-year follow-up of the HPFS. A diet high in animal protein and animal fat and low in plant-based foods was associated with greater risk of T2D after adjustment for confounders, predominantly due to intake of red meat and processed meat. Most carbohydrate-restricted diets aimed to lose weight tend to encourage consumption of animal products. However, a low-carbohydrate, high-animal protein diet is associated with greater risk of T2D. Low-carbohydrate diets should obtain

protein and fat from foods other than red and processed meat. Nuts and whole grains are major sources of protein intake that have been related to a lower risk of T2D [35].

Similar results were observed for women in the NHS1 and NHS2. There was a positive association between the Western dietary pattern and T2D. When major contributors to diabetes risk were examined, positive associations with red and processed meats became evident. A diet high in red meat and processed meat was associated with an elevated risk of T2D [51].

In a pooled analysis from the HPFS, the NHS1 and the NHS2 cohorts, one serving/day increase of total red meat, processed meat, and unprocessed meat consumption is associated with an elevated risk of T2D. The association between meat intake and elevated risk of T2D remains significant after adjustment for BMI status [52].

The association between changes in red meat consumption during a 4-year period and subsequent 4-year risk of T2D in US adults was evaluated in the HPFS, the NHS1 and the NHS2 cohorts in an observational study. Multivariate-adjusted models showed that increasing red meat intake during a 4-year interval was associated with an elevated risk of T2D during the subsequent 4 years in each cohort. Accordingly, reduction in red meat intake was associated with lower incidence of diabetes during subsequent long-term follow-up. Limiting red meat consumption over time confers benefits for T2D prevention [53].

In order to evaluate the effect of dietary components on the incidence of T2D in the three US prospective cohort studies (HPFS,

NHS1 and NHS2), a dietary index was developed where plant foods received positive scores while animal foods (animal fats, dairy, eggs, fish, seafood, poultry, red meat) received negative scores. In pooled multivariable-adjusted analysis, this index was inversely associated with T2D incidence, indicating that reducing the intake of animal foods (especially red and processed meat) while increasing the intake of healthy plant foods is beneficial for diabetes prevention. Even a modest lowering in animal food consumption was associated with substantially lower T2D incidence [14].

Many other prospective studies conducted in diverse population groups consistently confirm that consumption of animal protein is associated with an increased risk of developing T2D independently of BMI and other diabetes risk factors. Among them are the Women's Health Study [54], Women's Health Initiative study [55], Iowa Women's Health Study [56], San Luis Valley Diabetes Study [57], Multiethnic Cohort Trial [58], Alpha-tocopherol, Beta-Carotene Cancer Prevention cohort study [59], Malmö Diet and Cancer cohort study [60], European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct Study [61], Rotterdam study [6,62], and a prospective study including French women [63].

Systematic reviews and meta-analyses confirm the association of animal protein intake and increased risk of T2D (Table 2). In a systematic review and meta-analysis of cohort studies aimed to evaluate the association of meat consumption and the risk of T2D, intake of red meat, processed meat, and subgroups of meats (hamburger, bacon, hot dogs and other processed meats) was associated with an increased risk of T2D [64]. Pooled data from three large prospective US cohort studies, the HPFS, the NHS1, and the NHS2 and an updated meta-analysis published in 2011 confirm that unprocessed meat and processed red meat intakes are both associated with an increased risk of T2D. Greater consumption of unprocessed and processed red meat is consistently associated with higher risk of T2D [52]. In a comprehensive literature review aimed to quantitatively assess the association between animal protein intake and T2D risk, the analysis of ten prospective cohorts revealed that a 5% of energy increment from animal protein intake was related to a 12% higher risk of T2D [4]. In a meta-analysis conducted to evaluate the association between dietary protein intake and the risk of T2D, analysis of 21 cohorts showed a high risk of T2D with elevated animal protein consumption while moderate intake of vegetable protein was associated with a reduced risk of T2D [5]. In a systematic review conducted to assess the effects of protein intake in healthy adults, the evidence is defined as suggestive regarding the relation of animal protein intake to increased risk of T2D [65]. In a systematic review aimed to examine the dose-response association of different measures of dietary acid load and risk of incident T2D, analyses from seven prospective cohorts show a linear association between animal protein-to-potassium ratio and risk of T2D [3].

2. Consumption of high-quality plant-based food items has a protective effect on the risk of type 2 diabetes

Multiple prospective studies find that intake of healthy vegetable food reduces the risk of incident T2D (Table 3).

The first longitudinal study that showed a protective effect of intake of legumes on diabetes incidence was published in 1991. The association between baseline intake of plant-based food items and 4-year incidence of diabetes was investigated among 175 subjects. A protective effect of the use of legumes on incident diabetes was found [66].

In the NHS1, the risk of incident T2D decreased with higher intakes of plant-based foods. Intake of vegetable fat was inversely associated with diabetes risk in multivariate analysis. Further,

replacing 5% energy from animal fat with energy from vegetable fat was associated with a 35% lower risk of T2D. Diets rich in vegetable sources of fat and protein reduce the risk of diabetes [67,68].

The association between intake of whole grain versus refined grain and the risk of T2D was prospectively examined in the NHS and the HPFS cohorts. On multivariate analysis, whole grain intake was inversely associated with the risk of T2D, suggesting that whole grain has a protective effect on T2D incidence compared to refined grain. Substituting whole grain for refined-grain products has a beneficial effect on diabetes prevention. Grains should be consumed in a minimally refined form to reduce the incidence of T2D [69,70].

The prospective association between magnesium intake and risk of T2D was evaluated in the NHS and the HPFS cohorts. The relative risk of T2D was lower comparing the highest with the lowest quintile of total magnesium intake, after adjusting for confounding variables, suggesting an inverse association between magnesium intake and diabetes risk. Increased consumption of major food sources of magnesium, such as whole grains and green leafy vegetables, protects from T2D [71].

The association of components of a plant-based diet with T2D risk was examined in three US prospective cohorts: the NHS1, the NHS2 and the HPFS. In pooled multivariable-adjusted analysis, a diet low in animal foods that emphasizes plant foods is associated with a reduction of about 20% in the risk of T2D, independently of BMI. Particularly healthy plant food items include whole grains, fruits, vegetables, nuts, legumes, vegetable oils, tea, and coffee. Consumption of a plant-based diet that emphasizes specifically healthy plant foods is associated with a larger decrease in diabetes risk (34%). Reduction of the intake of animal products while increasing the intake of healthy plant foods is beneficial for diabetes prevention [14].

Many other prospective studies confirm an association between intake of high-quality vegetable food items and reduced risk of T2D, including the Iowa Women's Health Study [72], Women's Health Study [73], Finnish Mobile Clinic Health Examination Survey [74], EPIC-Potsdam [75], Melbourne Collaborative Cohort Study [76], Shanghai Women's Health Study [77], Singapore Chinese Health Study [78], and Malmö Diet and Cancer trial [60].

Several systematic reviews and meta-analyses confirm the protective effect of vegetable food on the risk of developing T2D (Table 4). In 2004, a review examined accumulated evidence regarding the role of whole grain foods in the etiology of T2D, concluding that "epidemiological studies strongly support that high intake of whole grain foods protects against the development of T2D". People who consume 3 servings per day of whole grain foods are less likely to develop T2D than low consumers (<3 servings per week) with a risk reduction in the order of 20–30% [79]. In a meta-analysis that gathered information on the relation of intake of whole grain and risk of T2D from 6 prospective cohort studies, whole grain intake was inversely associated with risk of T2D after adjustment for potential confounders and BMI consistently across all 6 studies. Pooled data showed that a two-serving-per-day increment in whole grain intake was associated with a 21% decrease in risk of T2D, after adjustment for potential confounders and BMI [80]. In a meta-analysis that summarized information from prospective cohort studies on the association between fiber intake and risk of T2D, higher cereal fiber intake was inversely associated with diabetes risk, indicating that higher cereal fiber consumption decreases diabetes risk [75]. Pooled analyses with data from three US prospective cohort studies (HPFS, NHS1 and NHS2) and an updated meta-analysis document that nuts and whole grains are associated with lower risk of T2D compared with red meat [52]. Pooled results from four population-based prospective cohorts (three European and one

Table 2
Systematic reviews, meta-analyses, and pooled data from prospective studies: animal protein intake increases the risk of type 2 diabetes (T2D).

	Conclusion	Reference
Health Professionals Follow-up and Nurses' Health cohorts	Both unprocessed and processed red meat intake is positively associated with the risk of developing T2D across the three cohorts independently of BMI	Pan, 2011
Health Professionals Follow-up and Nurses' Health cohorts	Reduction in red meat intake is associated with lower incidence of diabetes during subsequent long-term follow-up. Limiting red meat consumption over time confers benefits for T2D prevention	Pan, 2013
Health Professionals Follow-up and Nurses' Health cohorts	Reducing the intake of animal foods while increasing consumption of healthy plant foods is beneficial for diabetes prevention	Satija, 2016
Systematic review and meta-analysis	Meat consumption increases the risk of T2D. Intake of red meat, processed meat, and subgroups of meats (hamburger, bacon, hot dogs and other processed meats) is associated with an increased risk of T2D	Aune, 2009
Pooled data from Health Professionals Follow-up and Nurses' Health cohorts and meta-analysis	Consumption of unprocessed and processed red meat is strongly and consistently associated with higher risk of T2D, independently of BMI	Pan, 2011
Systematic review	The evidence is defined as suggestive regarding the relation of animal protein intake to increased risk of T2D	Pedersen, 2013
Ten prospective cohorts	Consumption of animal protein is associated with an increased risk of T2D.	Zhao, 2019
Meta-analysis of 21 prospective cohorts	High animal protein intake is associated with an increased risk of T2D whereas moderate plant protein intake is associated with a decreased risk of T2D	Ye, 2019
Systematic review (seven prospective cohorts)	Adherence to a diet with high acid-forming potential (rich in animal protein and low in plant-based foods) might increase the risk of T2D	Jayedi, 2018

Table 3
Prospective studies: vegetable protein intake reduces the risk of type 2 diabetes (T2D).

	Study population	Follow-up/N	Main finding	Reference
Feskens et al.	Healthy subjects	4 years 175	The habitual intake of legumes is inversely related to the incidence of diabetes	Feskens, 1991
Nurses' Health Study	Women/US	6 years 84,360	The risk of incident T2D decreases with higher intakes of plant-based food items	Colditz, 1992
Nurses' Health Study	Women/US	6 years 65,173	Diets low in cereal fiber increase the risk of T2D in women	Salmeron, 1997
Nurses' Health Study	Women/US	10 years 75,521	Substituting whole grains for refined grains has a beneficial effect on diabetes prevention	Liu, 2000
Nurses' Health Study	Women/US	14 years 84,204	Intake of vegetable fat (polyunsaturated fatty acids) is inversely associated with T2D risk	Salmeron, 2001
Nurses' Health Study	Women/US	14 years 85,059	Replacing 5% energy from animal fat with energy from vegetable fat is associated with lower risk of T2D	Halton, 2008
Health Professionals Follow-up Study	Men/US	6 years 42,759	Diets high in cereal fiber reduce the risk of T2D in men	Salmeron, 1997
Health Professionals Follow-up Study	Men/US	12 years 51,529	Whole grains had a strong inverse association with the risk for T2D	van Dam, 2002
Health Professionals Follow-up Study	Men/US	12 years 42,504	A diet high in whole grains versus refined grains is associated with a reduced risk of T2D in men	Fung, 2002
Women's Health Study	Women/US	6 years 37,309	There is an inverse association between magnesium intake and risk of T2D	Song, 2004
Iowa Women's Health Study	Women/US	6 years 35,988	Intake of total grain, whole grain, total fiber, cereal fiber, and dietary magnesium is inversely associated with incidence of T2D	Meyer, 2000
Iowa Women's Health Study	Women/US	11 years 35,988	Substituting vegetable fat for animal fat reduces T2D risk	Meyer, 2001
Finnish Mobile Clinic Health Examination Survey	General population/Finland	23 years 4304	Consumption of plant-based foods is associated with reduced risk of diabetes independently of BMI	Montonen, 2005
EPIC-Potsdam Study	General population/Germany	9 years 27,548	Higher cereal fiber intake is inversely associated with diabetes risk	Schulze, 2007
Melbourne Collaborative Cohort Study	General population/Australia	4 years 36,787	Adherence to a diet high in salad and cooked vegetables is inversely associated with T2D	Hodge, 2007
Shanghai Women's Health study	Chinese women	4.6 years 74,493	Consumption of legumes mainly soybeans is inversely associated with the risk of T2D	Villegas, 2008
Shanghai Women's Health study	Chinese women	4.6 years 74,493	Vegetable intake is associated with decreased risk of T2D	Villegas, 2008
Singapore Chinese Health study	Chinese men and women	10 years 43,176	There is an inverse association between consumption of unsweetened soy food items and risk of T2D	Mueller, 2012
Malmö Diet and Cancer study	General population/Sweden	12 years 27,140	Increasing the intake of vegetable food at the expense of animal protein has a favorable effect on the risk of T2D	Ericson, 2013

Canadian) show that higher plant-based protein intake is associated with lower incidence of T2D, after adjustment for confounders including BMI and waist circumference [7]. In a systematic review conducted to assess the effects of protein intake in healthy adults, vegetable protein intake was associated with decreased risk of T2D in many studies [65].

3. Opposite effect of animal versus vegetable protein on the risk of type 2 diabetes

Several prospective studies have compared directly the effect of the source of protein (animal versus vegetable) in food items on the risk of developing T2D. Their findings corroborate the divergent

Table 4
Systematic reviews, meta-analyses, and pooled data from prospective studies: vegetable protein intake reduces the risk of type 2 diabetes (T2D).

	Conclusion	Reference
Health Professionals Follow-up and Nurses' Health cohorts	Increased consumption of major food sources of magnesium, such as whole grains and green leafy vegetables, protects from T2D	Lopez-Ridaura, 2004
Health Professionals Follow-up and Nurses' Health cohorts	Plant-based diets especially when rich in healthy plant foods are associated with substantially lower risk of developing T2D, independently of BMI	Satija, 2016
Venn and Mann Systematic review	Epidemiological studies strongly support that high intake of whole grain protects against the development of T2D	Venn, 2004
De-Munter et al. Meta-analysis	Whole grain intake is inversely associated with risk of T2D after adjustment for potential confounders and BMI consistently across all 6 studies	De-Munter, 2007
Schulze et al. Meta-analysis	Higher cereal fiber consumption decreases the risk of T2D	Schulze, 2007
Pooled data from Health Professionals Follow-up and Nurses' Health cohorts and meta-analysis	Nuts and whole grains are associated with lower risk of T2D compared with red meat	Pan, 2011
Pedersen et al. Systematic review	Vegetable protein intake is associated with decreased risk of T2D	Pedersen, 2013
Four population-based cohorts (PREVIEW project)	Higher vegetable protein intake is associated with a lower risk of T2D independently of BMI and waist circumference	Sluik, 2019

effect of animal and vegetable protein on T2D risk. Intake of animal protein such as red meat and processed meat increases the risk of T2D while intake of high-quality plant-based food such as whole grains, cereals, legumes, and nuts reduces T2D risk. Among them are the EPIC-Netherlands study [81], EPIC-InterAct study [17], Kuopio Ischemic Heart Disease Risk Factor Study [82], and the NHS and HPFS cohorts [52,83].

4. Substituting vegetable protein for animal protein in the diet reduces the risk of type 2 diabetes

Prospective studies consistently show that dietary modifications that increase the amount of vegetable protein at the expense of animal products reduce the risk of T2D, independently of BMI. The association between substituting vegetable protein for animal protein and T2D risk was evaluated in pooled data from three large prospective cohort studies, the HPFS, the NHS1, and the NHS2. In pooled multivariate models including BMI, substituting 5% of energy intake from vegetable protein for animal protein was associated with 23% reduced risk of T2D, suggesting a benefit of replacing animal protein with vegetable protein in regard to T2D risk [83]. Substitution of nuts and whole grains for red meat is associated with a lower risk of T2D. Compared with red meat, other dietary protein such as nuts and whole grains are associated with lower risk of T2D [52]. Other prospective studies confirm these findings, including the Malmö Diet and Cancer study [60], EPIC-Netherlands study [81], Kuopio Ischemic Heart Disease Risk Factor Study [82], and EPIC-Potsdam study [84].

5. Dietary patterns and the risk of T2D

Several prospective studies, such as the EPIC-Potsdam study, the EPIC-The Netherlands study, the Multi-Ethnic Study of Atherosclerosis, and the Multiethnic Cohort study, have analyzed the association between dietary patterns and the risk of T2D. They consistently show that dietary patterns characterized by high intake of animal products and refined grains and low intake of vegetable protein increase the risk of T2D. By contrast, dietary habits characterized by high consumption of healthy vegetable food and low intake of red meat, processed meat, soft drinks, desserts, and refined grains, decrease the incidence of T2D. Multiethnic cohorts show that the effect of diet composition on the risk of T2D is similar across ethnic groups [85–88]. In one study that examined the associations between protein intake and T2D in different dietary patterns using information from the China Health and Nutrition Survey 2009, plant protein intake was inversely associated with T2D risk while red meat was positively related to T2D risk [2].

6. Modification of dietary habits toward elevated consumption of animal products may contribute to explain the higher rate of type 2 diabetes associated with lifestyle changes in population groups that change their traditional way of life

The rate of T2D rises markedly in population groups that change their daily life reducing physical activity and replacing mostly vegetarian diets with Western-type diets, compared with genetically homogenous counterparts that do not change their standard of living. The newly acquired sedentary lifestyle and nutritional habits typically high in animal products are contributing factors to the development of insulin resistance and T2D. The rate of T2D escalates both in populations who change their way of life to Western-type life due to “modernization” and in migrant populations to Western countries that acquire Western-type habits on arrival. Despite genetic homogeneity, the rate of T2D soars in migrant groups to Western societies compared to their counterparts who remain in their original community settings [89,90].

The traditional diet of the Pima Indians of Arizona consisted largely of proteins from vegetable source and complex carbohydrates with an elevated amount of fiber. In 1959, an investigation on the dietary components of the traditional Pima Indian diet estimated that the protein intake was above the normal recommended average, but 84% of the protein originated from plant sources while only 16% of the protein was of animal origin [91–94]. Diabetes was virtually unknown among the Pimas around the early decades of the 20th century. In 1963, an arthritis survey conducted by the National Institutes of Health (NIH) found unexpectedly that many members of the Pima Indian community suffered T2D. Two years later the NIH initiated a longitudinal survey of diabetes in which Pimas from the Gila River Indian Community of Arizona have participated since 1965 [95]. In 1971, the prevalence of T2D among the Pimas of Arizona was very high (50% in those older than 35 years) while the prevalence of diabetes in Western Europe and the US ranged between 1 and 3%. Other Native American communities also showed high prevalence of the disease [96]. During the 20th century, the traditional Pima Indian diet high in vegetable protein changed to a Western-type diet typically high in animal products and refined carbohydrates and low in legumes and grains. The “Westernization” of dietary habits experienced by the US Pimas contributed to explain the remarkable increase in the rate of T2D during the 20th century [92,93,95].

Two genetically homogeneous groups of Pima Indians dwell separately in two places of America, the US Pimas in southern Arizona and the Mexican Pimas in Maycoba, Sonora. In the village of Maycoba also reside non-Pima Mexicans, a population group that is not genetically related to the Pimas. The Mexican Pimas and their

non-Pima neighbors consume a traditional Pima diet, high in vegetable protein, in contrast to the Western-type diet consumed by the US Pimas. In 1995, the prevalence of T2D among US Pimas, Mexican Pimas and non-Pima Mexicans was 38%, 6.9%, and 2.6%, respectively. The prevalence of the disease was uniformly low among the two Mexican communities (Pimas and non-Pimas) that consume a diet high in vegetable protein, despite their genetic heterogeneity. However, the prevalence of diabetes in US Pimas was five times higher than the prevalence of diabetes in Mexican Pimas (38% versus 6.9%) in spite of their similar genetic background. Unlike the Mexican Pimas, the US Pimas underwent drastic dietary changes with increasing intake of animal products during the 20th century. This dietary shift is a major contributory factor to the remarkable difference in T2D rate between two genetically homogeneous Pima communities [97].

In 1979, T2D was more common in first generation Japanese migrants on the island of Hawaii (mainly from Hiroshima) than in the Japanese population living in Hiroshima, despite their identical genetic background. A nutritional survey revealed great differences in dietary composition between the Hawaiian Japanese and the Hiroshima Japanese, although total energy consumption was similar. Intake of animal products was elevated among the Hawaiian Japanese while the Hiroshima Japanese consumed the traditional Japanese diet, higher in vegetable protein such soy and lower in animal products [98].

The prevalence of T2D in second-generation Japanese men living in Seattle, Washington (20%) was approximately four times higher than the prevalence of T2D in Japanese men living in Hiroshima (5.3%). A dietary survey conducted in second-generation Japanese American men with T2D showed that their diet was higher in animal products compared to men with normal glucose tolerance. The diet of second-generation Japanese American men with T2D changed from a traditional Japanese diet typically abundant in complex carbohydrates to a Western-type diet with high amount of animal products and refined carbohydrates, suggesting that high levels of animal products in the diet have an etiologic role in the development of diabetes [99]. The prevalence of impaired glucose tolerance in second-generation Japanese Americans living in Seattle, Washington is 36% in men and 40% in women. Among third-generation Japanese American youth, the prevalence of impaired glucose tolerance is 19% in men and 29% in women, suggesting that many second-generation and third-generation Japanese Americans are at risk of future diabetes [100]. The association of meat consumption with diabetes risk in the Japanese American population and other population groups has been confirmed in the Multiethnic Cohort Study, a prospective cohort study of African-American, Native Hawaiian, Japanese-American, and Caucasian, adults [58]. An increase in the rate of T2D during the second half of the 20th century has been also documented in the Japanese youth living in Japan. The prevalence of T2D among high-school children in Japan during the periods 1976 to 1980, 1981–1985 and 1991 to 1995 was 7.3, 12.1 and 13.9 per 100,000 per year, respectively. A traditional Japanese diet consists of rice, fish, soybean products and green vegetables. A rapid shift in dietary habits has been reported from 1950 to 1970. While the daily energy intake has not changed significantly, the consumption of animal products by the Japanese population has increased markedly [101]. A recent prospective study confirms that Westernized dietary habits are a contributing factor to the development of T2D among Japanese Americans. In subjects with normal glucose tolerance at baseline, intake of vegetable protein and complex carbohydrates was inversely associated with development of obesity among lean participants. Animal protein and animal fat intakes were positively associated with development of diabetes in obese subjects [102].

In South Korea marked dietary changes took place during the last decades of the 20th century with a large increase in the consumption of animal products and a fall in the intake of plant-based foods, such as cereals. Simultaneously with this nutritional shift, the rate of diabetes and cardiovascular diseases increased rapidly [89,103,104].

The prevalence of diabetes in China has increased from 2.5% in 1994 to 11.6% in 2010. This rise matches a drastic modification of dietary behavior from a traditional Chinese diet rich in rice and vegetables to a Western-type diet rich in animal products. The intake of cereals and vegetables has decreased markedly in China from 1989 to 1997 while animal food consumption more than tripled. In 2010–2012 the meat consumption of Chinese people was 90 g/day [19,20]. The association of dietary factors with T2D among Chinese subjects aged 30–79 years was examined in a prospective study with a median follow-up of 7.2 years. Multivariable-adjusted analyses showed that a dietary pattern rich in vegetables and fruits and low in red meat and white rice reduced the risk of T2D, among other healthy lifestyle factors such as physical activity [20]. In a large prospective cohort of 74,493 middle-aged Chinese women during an average of 4.6 years of follow-up, processed meat consumption was positively associated with the risk of T2D [105].

Similarly to China, the prevalence of diabetes has increased in other Asian populations, reaching 20% in urban areas of South India, matching a major nutritional change with increased intake of meat. The rate of T2D has mounted in children and adolescents in India reflecting changes in nutrition among the youth. Consistently, the prevalence of T2D is lower in periurban villages in southern India than in urban areas [106].

2. Summary

Numerous investigations since 1935 have provided evidence that consumption of animal products increase the risk of developing T2D, independently of BMI and weight gain. Intake of unprocessed meat and processed meat (bacon, hot dogs, sausages, ham, salami) is strongly and consistently associated with an increased risk of T2D. Lowering animal food consumption is associated with substantially lower T2D incidence. In addition, intake of healthy plant-based foods protects against the risk of developing T2D. High-quality plant foods include nuts, whole grains (rice, wheat, corn), legumes (soy beans, a variety of other beans, peanuts, peas, chickpeas, lentils), fruits, vegetables, vegetable oils, tea, and coffee. Less healthy plant foods are sweetened beverages, fruit juices, refined grains, potatoes, sweets, and desserts. The incidence of diabetes increases progressively among vegans, lacto-ovo-vegetarians, and nonvegetarians. Gradual adherence to a vegan diet offer increasingly greater protection against risk of T2D. Diabetes rate soars in population groups worldwide who shift to dietary habits high in animal products, such as occurred in the Pima Indians of Arizona during the second half of the 20th century and is occurring currently in populations where animal consumption is increasing, such as India and China. T2D is largely preventable via lifestyle changes, including promotion of physical exercise and dietary modifications toward a reduction in the consumption of animal products while incrementing the intake of healthy plant-based food items. High educational level and socio-economic status are associated with this dietary routine. Human observational and interventional studies aimed to define pathogenic mechanisms underlying the protective effect of plant-based food on T2D risk and the most favorable dietary components to prevent T2D are required.

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Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contribution

MAA contributed to the study design, practical performance, analysis of the literature search, preparation and critical review of the manuscript. ERM contributed to the literature search and drafting of the manuscript. MVA contributed to the literature search and data analysis. CFF contributed to the practical performance and preparation of the manuscript. RFC and ECQ contributed to the literature search, preparation and critical review of the manuscript.

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