Plant Protein Consumption and Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Master thesis

Public Health

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Health Sciences

University of Eastern Finland

November 2022

University of Eastern Finland, Faculty of Health Sciences,

School of Medicine

Public Health

Mohan, K: Plant Protein Consumption and Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis

Master's thesis, 61 pages

Supervisors: Professor Tomi-Pekka Tuomainen and MSc Sara Allaouat.

November 2022

Keywords: plant protein, vegetable protein, vegetarian, plant-based, type 2 diabetes mellitus

Abstract

Previous epidemiological research has shown that there is an association between dietary protein – plant and animal - consumption and the risk of type 2 diabetes mellitus. There is however no systematic review that focusses on specifically the association of solely plant protein consumption and the risk of type 2 diabetes mellitus. Thus, in this master thesis, I will conduct a systematic review and meta-analysis to explore the scientific literature on the effect of consumption of plant protein on the risk of type 2 diabetes mellitus.

The electronic scientific databases PubMed and Scopus were systematically searched for original peer-reviewed prospective cohort or case–cohort studies in the English language that assessed consumption of plant protein on the risk of type 2 diabetes mellitus. Twenty studies corresponding to the inclusion criteria were obtained, assessed for quality and analysed. All twenty studies had type 2 diabetes mellitus as the outcome. In addition, one study also had prediabetes as an outcome. All the studies were of good quality.

The results of the systematic review and meta-analysis in this thesis suggest that plant protein consumption lowers the risk of developing type 2 diabetes mellitus. However, studies with better designs and a more comprehensive assessment of plant protein intake and consumption would reinforce the overall body of evidence on the association between plant-based protein and the risk of type 2 diabetes mellitus.

Abbreviations

ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
EPIC	European Prospective Investigation into Cancer and Nutrition
FAO	Food and Agricultural Association
FFQ	Food-frequency questionnaire
FPG	fasting plasma glucose
HbA1c	glycated hemoglobin
HPFS	Health Professionals Follow-Up Study
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses Health Study
NOS	Newcastle-Ottawa Scale
NOS	Newcastle-Ottawa Scale
OGTT	oral glucose tolerance test
PREDIMED	PREvencion con DIeta MEDiterranea
SWHS	Shanghai Women's Health Study
T2DM	Type 2 Diabetes Mellitus
TCHS	Tzu Chi Health Study
WHO	World Health Organisation

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1 Introduction

Globally, there is an increased adherence to fully or partially plant-based diets, and the global supply of proteins is dominated by plant sources. A fully plant-based diet is one that consists of grains, nuts, legumes, fruit, and vegetables and excludes animal products. Other than sustainability issues being the cause for this, recent research has shown that plant-based diets may be one of the key factors in preventing many chronic diseases and conditions (Henchion et al. 2017). Furthermore, diets comprising of plant protein have been associated with increased life span (Levine et al. 2014).

Sufficient protein intake is important to ensure that all the amino acids needed to ensure growth and maintenance of bodily functions is supplied to the body. Contrary to popular opinion, this can be achieved by consuming a fully plant-based diet, even one that does not involve any special food combinations (Melina et al. 2016, Mariotti 2017).

The high content of glutamic acid in plant proteins has been associated with improved blood pressure and may be the reason why plant protein consumption is inversely related with the risk of metabolic syndrome (Shang et al. 2016). Plant proteins, in particular substituting them for animal protein, improves blood lipid profiles, thereby playing a role in preventing cardiovascular disease (Li et al. 2017). The consumption of solely plant protein has been associated with reduced obesity by increasing glucagon activity (McCarthy 1999).

Legumes are part of a dietary pattern recommended for the prevention of cancer (World Cancer Research Fund 2007). A systematic review and meta-analysis by Navhak et al. (2019) showed that soy protein intake significantly lowered breast cancer mortality. The substitution of plant protein for animal protein appears to be protective for the incidence of cancer as shown by a prospective cohort study by Allen et al. (2016). The study showed that a 3% increase in animal protein consumption resulted in a 15% increased risk for developing urothelial cell carcinoma while a 2% increase in plant protein consumption was associated with a 23% lower risk for the cancer.

Another chronic disease that is largely preventable by diet modification is Type 2 diabetes mellitus (T2DM) (Esposito et al. 2015). Diets low in fibre with a high glycaemic index is a risk factor for T2DM

(Liu et al. 2000). Plant proteins, especially legumes are superior to animal protein in the sense that are very low in fat and high in fibre and nutrients. These qualities lack in animal protein. Plant proteins are thereby beneficial in preventing the development of T2DM (Dietary Guidelines for Americans 2015–2020, accessed 2.6.2021). Therefore, it is important to know how the different types of plant proteins are related to the risk of developing T2DM. In this thesis I will examine the strength of evidence supporting the association between dietary plant protein and T2DM in the adult population through a systematic review and meta-analysis.

2 Literature review

2.1 Plant protein

2.1.1 Protein and its importance to the human body

Dietary proteins are proteins from the diet or diet supplementation. They are either plant-based food sources (legumes, grain, beans, nuts) or animal-based food sources (milk, eggs, fish, meat, poultry). Like all proteins, dietary proteins are large molecules consisting of amino acids (FAO, accessed 13.3.2021). By definition, plant protein is simply a meaningful protein food source, which comes from plants. Plant protein comprises of seitan, tofu, seeds, nuts, soya, pulses, tempeh, specific grains, and peas among others. What makes up pulses is a large plant group inclusive of beans (like adzuki, black and kidney beans), chickpeas, split peas, and lentils. Other sources of plant protein comprise of nutritional yeast, almond butter, oatmeal, kale, buckwheat, and spirulina (Ostfeld 2017).

Apart from being the main building blocks of the cells and tissues, hormones, and enzymes of the body, they are essential structural constituents for many physiologic or metabolic responses in humans. Proteins are essential for muscle development and maintenance, tissue repair and turnover, immune function, and defence function. Recent research has shown that proteins play an important role in mental performance and sleep patterns as well as detoxication (FAO, accessed 13.3.2021). It has been shown that proteins also impact satiety and weight management (Veldhors et al. 2008).

2.1.2 Protein demand and consumption

The global population is projected to grow from about 7.8 billion in 2020 to almost 9.5 billion by 2050 causing the demand for animal protein to double by 2050 (Westhoek and Colleagues, accessed 13.3.2021). The world's protein supply is dominated by plant sources at 57% while 18% is made up by meat, 10% by dairy, 6% by fish and shellfish 9% by other animal products. (FAO 2010). In the west, there is an overconsumption of proteins. The adult population consumes an average of 1.3 g/kg of protein per day which is about twice the Estimated Average Requirement of 0.66 g/kg per day (Salter and Lopez 2021). The demand for protein is increasing worldwide as the population grows and positive socio-economic changes are taking place. In addition to the increasing demand of protein-based foods due to population growth and concerns regarding climate change, proteins have been shown to be important in healthy aging (Martone et al. 2017, Delgado 2003). Adequate protein intake has been recognized as one of the main strategies to counteract and prevent muscle atrophy, as well as loss of muscle strength and function in geriatric sarcopenia (Coelho-Junior et al. 2018).

2.1.3 Importance of plant protein

Diets that comprise of mostly legumes, whole grains, nuts, and seeds, with minimal or no animal proteins have been inversely linked to the risk of T2DM, obesity, hypertension, hyperlipidaemia, cardiovascular mortality, and cancer (Dinu et al. 2016). Plant-based proteins are important beyond just the health benefits and their consumption is also linked to improved environmental sustainability. Plant-based foods are generally associated with more effective land use and lower greenhouse gas emissions than animal-based food production, which require vast areas of land (Gonzalez et al. 2011, Tilman et al. 2014). In the European Union, 66% of the agricultural area is used for livestock production while 75% of the animal feed is imported from South America (Westhoek and Colleagues, accessed 2020).

Animal protein consumption is nutritious and healthy; however, its over-consumption poses negative health effects (Klunder et al. 2012). Reducing meat consumption has a greater positive impact on climate change compared to other environmentally friendly actions such as recycling, waste reduction and favouring local organic foods (Pohjolainen et al. 2016, Macdiarmid et al. 2016).

2.1.4 Plant protein and T2DM

In general, dietary protein helps to maintain a lean body mass. In the management of hyperglycaemia dietary protein is considered with regards to glucose amounts derivable from constituent amino acids through gluconeogenesis. Increased dietary protein consumption lowers postprandial blood glucose levels and improves overall blood glucose response in persons with T2DM (Gannon et al. 2003).

Dietary protein triggers the release of both insulin and glucagon. High consumption of branched chain amino acids, especially leucine is associated with increased insulin resistance, and thus with an increased risk of T2DM (Asghari et al. 2018). Conversely, a reduced consumption of branched chain amino acids promote weight loss, reduces adiposity, and improves glycemic control and metabolic health.

A reduced consumption of sulphur containing amino acids. promotes insulin sensitivity by influencing adiposity and metabolic changes in fat and liver tissues. Furthermore, it is associated with a reduction in body weight and enhanced energy expenditure (Dong et al. 2018). Plant protein is both low branched chain amino acid and sulphur content compared to animal protein, thereby playing a preventative role in the development of T2DM (Richter et al. 2015).

The association between dietary protein and T2DM in human studies remains inconsistent. Insulin resistance can be aggravated even if a minimal amount of animal protein is included in an otherwise vegetarian diet. As shown in a cohort study by Chiu et al. (2014) involving Taiwanese Buddhists, vegetarian men who included even a small amount of animal protein in their diets had twice the rate of diabetes compared to fully vegetarian men. Post-menopausal vegetarian women in the same study had one-quarter the rate of diabetes compared to women who included animal protein in their diet. It has been shown in intervention trials, that on the short-term, the consumption of protein instead of carbohydrates increases satiety and supports insulin secretion during a meal. However, while protein increases satiety, which lowers calory intake, a long-term and high consumption of protein has been associated with increased incidence of T2DM (Sluijs et al. 2010, Tinker et al. 2011, Wang et al. 2010). Additionally, it has been demonstrated that a brief rise in plasma amino acid concentrations can directly cause skeletal muscle to become resistant to insulin and boost endogenous glucose synthesis (Rietman et al. 2014).

Dietary protein plays a significant role in regulating glucose. Dietary protein plays a significant role in regulating glucose metabolism. Some longitudinal studies revealed that consuming an excess of dietary protein led to insulin resistance and increased gluconeogenesis, thus worsening glucose homeostasis (Weickert et al. 2011, Linn et al. 2000). In vivo and in vitro studies showed that amino acids contribute to glucose homeostasis by influencing how insulin acts on hepatic synthesis, muscular glucose transport, glucagon and insulin secretion, and expressions of certain genes and proteins (Tremblay et al. 2007, Gulve et al. 1991).

Results vary with regards to specific sources of plant protein. Meta-analyses by Yang et al. (2011) and Liu et al. (2011) showed that the consumption of soy protein had no significant effects on fasting glucose, fasting insulin and HbA1c. The direction of the effect, however, favoured soy consumption.

2.2 Type 2 diabetes mellitus

2.2.1 Epidemiology and prevalence

T2DM is one of the most common metabolic diseases with 415 million cases estimated globally in 2015. This number is expected to increase dramatically in the next decades reaching 642 million by 2040 (Orgutsova et al. 2017).

Once referred to adult-onset diabetes, T2DM is now a disease that affects youth as well. There are ever increasing reports of T2DM in children worldwide, with some children as young as eight years old being affected (Philoker et al. 1998). These children are mostly found in ethnic groups with a high susceptibility to T2DM. Over the past few decades, a child presenting with new onset diabetes in Japan is more likely to have T2DM than T1DM (Kitagawa et al. 1998). There are now also reports of T2DM occurring among Europid (white Caucasoid) teenagers (Drake et al. 2002).

Norhammar et al. (2016) noted that several nationwide European studies on diabetes incidence are based on health service registries, which have reported incidences between three and six cases per 1000 person-years. T2DM is also largely undiagnosed, and this puts people at an increased risk for cardiovascular diseases. On a global perspective, the European subcontinent has one of the lowest proportions of undiagnosed persons with diabetes, even so, this group represents 37.9% of total diabetes prevalence (Cho et al. 2018).

2.2.2 Prediabetes

Reduced insulin sensitivity or increased insulin resistance along with inadequate insulin secretion exist simultaneously even before impaired glucose metabolism is detectable (Faerch et al. 2009). This is commonly termed as the prediabetic or high risk for diabetes state and is of clinical and public health significance because end organ complications have been shown to occur already at this stage (Groop et al. 2000, Praveen et al. 2012).

2.2.3 Diagnosis of T2DM

Most of studies used in this investigation use the American Diabetes Association (ADA) criteria for the diagnosis of T2DM (Diagnosis and classification of diabetes mellitus 2010). According to ADA, a person is diagnosed with T2DM if they meet the following criteria of having: 1) A glycated haemoglobin (HbA1c) level of 6.5% or higher; or 2) a fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher; or 3) a 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or 4) a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher, with classic symptoms of hyperglycaemia (polyuria, polydipsia, polyphagia, weight loss) or hyperglycaemic crisis.

The World Health Organisation diagnostic criteria for T2DM is a fasting plasma glucose 7.0 mmol/L (126mg/dL) or higher or a two-hour plasma glucose of 11.1mmol/L (200mg/dL) or higher (WHO 2006).

2.2.4 Pathophysiology

T2DM occurs when both peripheral insulin resistance and inadequate insulin secretion coexist. Diabetes occurs when insulin secretion is insufficient to compensate for insulin resistance. Several factors including beta-cell dysfunction, insulin resistance, genomic factors and amino acid metabolism play a role in the pathophysiology of T2DM. Reduced glucose transport into muscle cells, increased glucose production in the liver, and accelerated fat breakdown are all caused by insulin resistance which has been linked to raised plasma levels of free fatty acids and proinflammatory cytokines (Medscape 2020). Pancreatic islet alpha cells secrete glucagon by pancreatic islet beta cells secrete insulin. These cells function reciprocally with regards to one another. When a failure of this interplay occurs, there is an excess of glucagon that causes hyperglycaemia (Unger and Orci 2010). The pancreas may atrophy if this hyperglycaemic state is left chronically intreated.

Beta-cell dysfunction, where insulin secretion develops early in the pathologic process (Bacha et al. 2010), is a more severe condition than insulin resistance. Beta-cell dysfunction worsened by insulin resistance causes T2DM. Insulin secretion is disrupted in beta-cell dysfunction. When there is insulin resistance, insulin secretion may still occur, but target tissues show signs of insulin insensitivity. Hyperglycaemia increases when beta-cell failure and insulin resistance worsen, progressing to T2DM (Ashcroft and Rorsman 2012).

Postprandial blood glucose levels rise first in the progression from normal to abnormal glucose tolerance. Fasting blood glucose levels rise as a result if the failure to control hepatic gluconeogenesis.

2.2.5 Risk factors for T2DM

T2DM is a multifactorial disease. Although there is a strong genetic component which is a non-modifiable risk factor, a large proportion of cases are potentially preventable by controlling the modifiable risk factors such as making healthy lifestyle choices.

2.2.5.1 Modifiable risk factors

Obesity

Obesity induces resistance to insulin-mediated peripheral glucose uptake (DeFronzo et al. 1991), thereby increasing the risk of impaired glucose tolerance and T2DM. Reversal of obesity improves glycaemic control. Studies in the NHANES cohorts showed that BMI accounted for about half of the increase in diabetes prevalence in men and 100% in women (Menke et al. 2014).

Physical activity

Low physical activity and sedentary behaviours such as watching television increases the risk of T2DM by encouraging weight gain and reduced energy expenditure (Grontved et al. 2011). In a cohort study of Swedish men, even low physical activity at a young age without weight gain showed an increased risk of diabetes up to 25 years later (Crump et al. 2016).

Diet

Unhealthy dietary choices such as calorie-rich and sugar laden foods and beverages contribute to the risk of T2DM. These include fast foods, animal products and refined grains (Ley et al. 2014). In a large cohort of men, a western diet (characterised by high consumption of red meat, processed meat, high fat dairy products, sweets, and desserts) was associated with and increased risk of T2DM independent of BMI, physical activity, age, or family history. Conversely a prudent diet (characterised by higher consumption of vegetables, fruit, fish, poultry, and whole grains) had a modest reduction in risk for T2DM (van Dam et al. 2002). Lifestyle changes, particularly diet, can be highly effective in preventing and treating T2DM. A Danish study demonstrated that adults aged 60 and over, had a 71% reduction in risk of T2DM from lifestyle interventions (Knowler et al. 2002).

Smoking

Cigarette smoking increases the risk of T2DM possibly by the mechanisms of increasing blood glucose concentration and impairing insulin sensitivity in a glucose challenge intervention (Willi et al. 2007). Smoking also impacts glucose tolerance due to its link to increased abdominal fat distribution (Frati et al. 1996). Smoking cessation is also linked to an increased risk of T2DM; however, the risk was directly proportional to weight gain. The risk of T2DM peaked in five to seven years after cessation and was even associated with an increased risk compared to those who continued to smoke (Hu et al. 2018).

2.2.5.2 Non-modifiable risk factors

Ethnicity

Asians, Hispanics, and African Americans are at an increased risk for developing T2DM compared to white Caucasians (Shai et al. 2006). Modifiable risk factors for diabetes may be related to the ethnic disparity. For example, Bancks et al. (2017) showed that the racial disparity in diabetes risk during young adulthood was associated with biological risk factors as well as with behavioural, psychosocial, socioeconomic and neighbourhood environmental factors.

Age

Age is a major risk factor for T2DM. The ADA recommends the commencement of testing for diabetes at age 45, particularly for the overweight or obese (ADA 2015).

Family history

The risk for T2DM is increased for individuals with a family history of diabetes compared to those without. For example, the risk is up to six-fold for those with both parents with a history of T2DM. Genetic, anthropometric and lifestyle factors are likely mediators for this risk (Scott et al. 2013).

Medical conditions

Cardiovascular disease is associated with an increased risk of diabetes. In a study of non-diabetic patients with coronary artery disease, those with advanced heart failure had nearly double the risk of developing T2DM during a 12-year-follow-up (Tenenbaum et al. 2003). The risk of T2DM is higher in women who have had gestational diabetes. Vounzulaki et al. (2020) showed that women with previous gestational diabetes had a nearly tenfold risk of developing T2DM compared to women without gestational diabetes.

3 Study rationale

There is a continuing and growing trend in consumption of plant-based foods globally. For environmental and health reasons, plant-based dietary protein sources are gaining popularity as alternatives to animal protein. Plant-based diets, especially those consisting of high-quality plant foods are recommended for chronic disease prevention. This study examines how consumption of plant protein, in particular varying levels of long-term high-quality plant protein intake, is associated with T2DM risk.

4 Objectives and methods

4.1 Objectives

The general objective of the study was to conduct a systematic review and meta-analysis of original research articles that examined the association between plant-based dietary protein and the risk of T2DM. The specific aims of this study were:

1. To study the association of plant protein with insulin sensitivity, insulin resistance, and the incidence of T2DM and prediabetes.
2. To examine how variations in types of protein (animal or plant) in the diet are associated with the risk of T2DM.
3. To examine how high long term plant protein intake is associated with the risk of T2DM in men and women.

4.2 Methods

4.2.1 Study design and period

The study design is a systematic literature review and meta-analysis of peer-reviewed research articles. PubMed and Scopus electronic databases were searched through 31.12.2019 for eligible studies.

4.2.2 Search terms

The search terms that were used to find eligible studies were: plant protein, vegan diet, vegetarian diet, vegetable protein, dietary protein, protein intake, legumes, soy, lentils, pulses, cereal, oat, wheat, corn, maize, rice protein flour, teff, seitan, wheat gluten, pea, spelt, hempseed, seed, diabetes, type 2 diabetes, diabetes mellitus, insulin sensitivity, insulin resistance.

4.2.3 Inclusion and exclusion criteria

Studies were included if: i) the study design was a longitudinal prospective cohort or case–cohort; (ii) the exposures were reported as specific plant protein food groups, or plant or vegetable protein (iii) the outcome was the risk of T2DM, i.e. incidence of prediabetes, T2DM, decreased insulin sensitivity, increased insulin resistance; and (iv) human studies. Studies were excluded if they: (i) were review articles, meta-analyses or case reports, and retrospective cohort, cross-sectional or case-control in design; (ii) had inadequate information on the association between the exposure and outcome of interest; or (iii) were not in English.

4.2.4 Search strategy

PubMed Search Strategy (conducted on 2.1.2020).

1. "Plant Proteins, Dietary"[Mesh] OR “plant protein” OR “plant proteins” OR “vegetable protein” OR “vegetable proteins” OR "Diet, Vegetarian"[Mesh] OR “vegetarian diet” OR "Diet, Vegan"[Mesh] OR “vegan diet”.
2. (protein OR proteins) AND (legume* OR soy OR lentil* OR pulses OR cereal* OR oat* OR wheat* OR corn OR maize* OR “rice protein” OR teff OR seitan OR pea OR peas OR spelt OR hempseed* OR seed*).
3. "Diabetes Mellitus, Type 2"[Mesh] OR diabet*
4. "Cohort Studies"[Mesh] OR “cohort study” OR “cohort studies” OR "Prospective Studies"[Mesh] “prospective studies” OR “prospective study” OR "Insulin Resistance"[Mesh] OR "Insulin Resistance" OR “Insulin Sensitivity”.
5. "Humans"[Mesh] OR human OR humans

   (#1 OR #2) AND #3 AND #4 AND 5.

Scopus Search Strategy (conducted on 2.1.2020).

1. “plant protein*” OR “vegetable protein*” OR “vegetarian diet*” OR “vegan diet*”

2. (protein*) AND (legume* OR soy OR lentil* OR pulses OR cereal* OR oat* OR wheat* OR corn OR maize* OR “rice protein*” OR teff OR seitan OR pea* OR spelt OR hempseed* OR seed*.
3. diabet*.
4. "cohort stud* OR "prospective stud*" OR "insulin resistance" OR “insulin sensitivity”
5. human*.

   (#1 OR #2) AND #3 AND #4 AND 5.

3.2.5 Grading of evidence and systematic evaluation of study

The Newcastle-Ottawa scale (NOS) for cohort studies was used as a quality assessment tool in this study. The NOS was jointly developed by the University of Newcastle, Australia, and the University of Ottawa, Canada, to assess the quality of non-randomized studies, including case-control and cohort studies to be included in systematic reviews (Wells et al. 2011). The NOS is available in two versions: one for case-control and the other for cohort studies. The latter was used for the purpose of the current study.

The NOS version for cohort studies consists of eight multiple-choice questions. Up to a maximum of nine points or stars (*) are assigned for the least risk of bias in three domains of the study. The three domains are: 1) subject or study group selection (four questions with a maximum of four stars), 2) group comparability (one question with a maximum of two stars) and 3) assessment of outcome of interest (three questions with a maximum of three stars).

The quality of the studies is rated as good, fair, or poor based on the Agency for Healthcare Research and Quality (AHRQ) standards. Thresholds for converting the NOS to AHRQ standards are as follows:

Good quality (6 to 9 stars): 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.

Fair quality (5 to 7 stars): 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.

Poor quality (0 to 4 stars): 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

5 Results

5.1 Search strategy

The specific search strategy produced 2043 records. After initial exclusion and reviewing the records by abstract, 25 articles were identified. After going through the full text articles, 18 of 25 articles fulfilled the inclusion criteria and were chosen to be included in the systematic review. Another two studies were manually added, bringing the total number of studies included to 20. These comprised of 14 different cohorts. Figure 1 shows the search strategy.

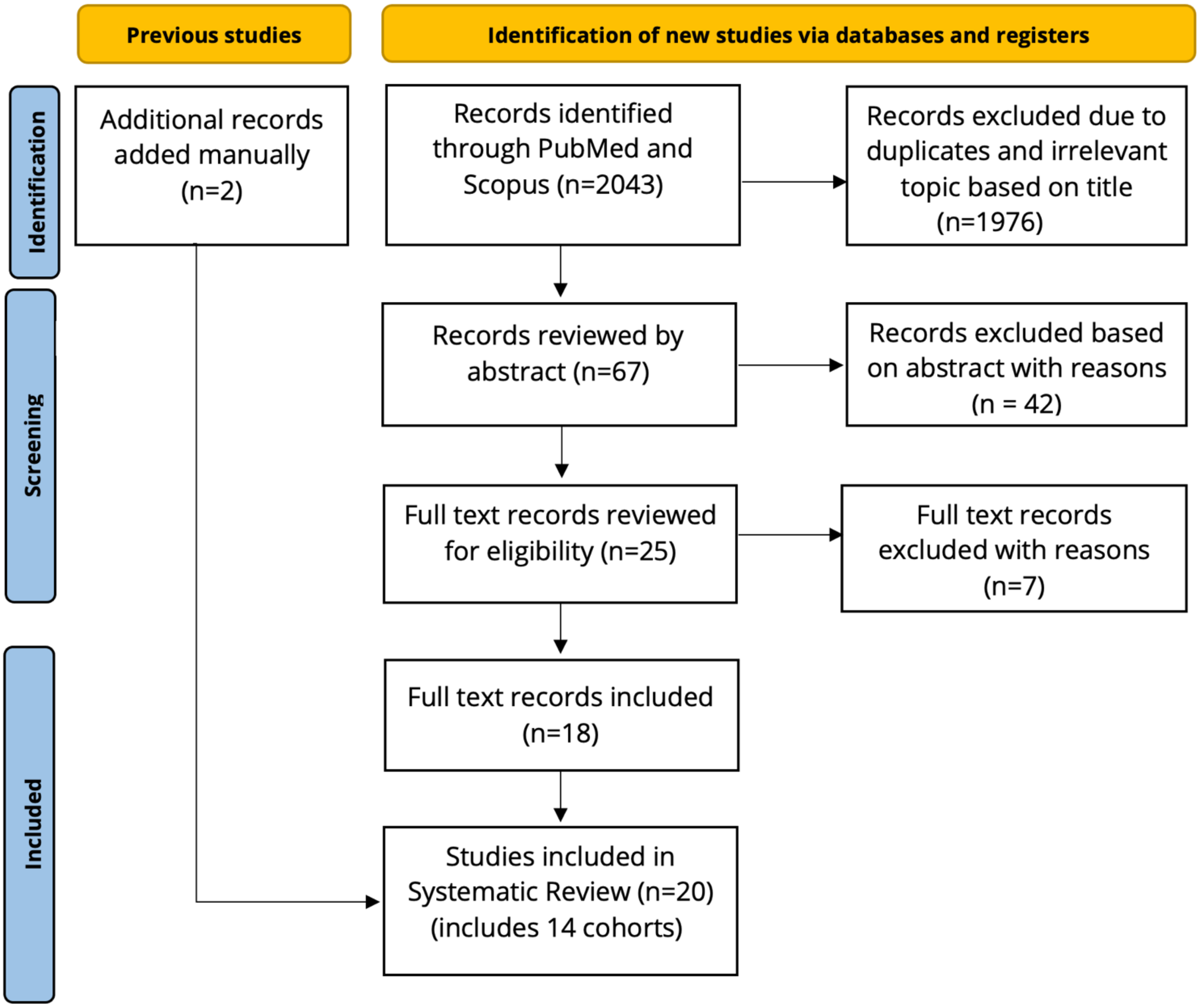

Figure 1. PRISMA flow diagram of search strategy and results.

5.2 Characteristics of the studies

A summary of the characteristics of the studies is shown in Table 1. All twenty studies had T2DM as the outcome. In addition to that the study by Chen et al. (2018) had prediabetes as an outcome.

5.2.1 Design and settings

All the studies were population-based prospective cohorts except one (Van Nielen et al. 2014) which was a population-based case-cohort study. The results showed that five studies were carried out in the USA (De Koning et al. 2011, Halton et al. 2008, Satija et al. 2016, Zong et al. 2018, Malik et al. 2016). One was conducted in the USA and Canada (Tonstad et al. 2013). Seven were conducted in Europe, including Spain (Becerra-Tomas et al. 2018), the Netherlands (Chen et al. 2018, Sluijs et al. 2010), Sweden (Ericson et al. 2013), Greece (Kolouverou et al. 2006), Finland (Virtanen et al. 2017), United Kingdom (Papier et al. 2019). One was a multicentre study consisting of several countries in Europe including France, Italy, Spain, UK, the Netherlands, Germany, Sweden, and Denmark (van Nielen et al. 2014). Five studies from Asia include those from Taiwan (Chiu et al. 2018), Japan (Konishi et al. 2019, Nanri et al. 2015), Singapore (Mueller et al. 2012), China (Villegas et al. 2008). One study was conducted in Australia (Shang et al. 2016).

The study cohorts consisted of the Nurses' Health Study (Halton et al.2008, Zong et al. 2018, Malik et al. 2016, Satija et al. 2016 ,Nurses' Health Study and Nurses' Health Study II (Zong et al. 2018, Malik et al. 2016, Satija et al. 2016), the Health Professionals Follow-Up Study (Zong et al. 2018, Malik et al. 2016, Satija et al. 2016, De Koning et al. 2011), PREvencion con DIeta MEDiterranea (PREDIMED) study (Becerra-Tomas et al. 2018), the Rotterdam Study (Chen et al. 2018), Tzu Chi Health Study (TCHS) (Chiu et al. 2018), Malmo Diet and Cancer cohort (Ericson et al. 2013), ATTICA Cohort study (Kolouverou et al. 2006), Japan Public Health Center-Based Prospective Study (Nanri et al. 2015), the population of Takayama City, Japan (Konishi et al. 2019), Singapore Chinese Health Study (Mueller et al. 2012), European Prospective Investigation into Cancer and Nutrition (EPIC) (Sluijs et al. 2010, Papier et al. 2019), Adventist Health Study-2 (Tonstad et al. 2013), Shanghai Women's Health Study (SWHS)(Villegas et al. 2008), Kuopio Ischaemic Heart Disease Risk Factor Study (Virtanen et al. 2017), and Melbourne Collaborative Cohort Study (Shang et al. 2016).

5.2.2 Study population and duration

The studies were conducted on men and women across a spectrum of age ranges, from 20 to 87 years of age. The shortest study duration was two years (Tonstad et al. 2013) and the longest 28 years (Satija et al. 2016).

5.2.3 Assessment of T2DM

Three studies were self-reported (Konishi et al. 2019, Shang et al. 2016, Tonstad et al. 2013). Six studies were self-reported and validated by medical records or professionals (Chiu et al.2008, de Koning et al. 2011, Halton et al. 2008, Mueller et al. 2012, Nanri et al. 2015, van Nielen et al. 2014). Two were self-reported and validated by supplementary questionnaire (Satija et al. 2016, Malik et al. 2016).

One study was self-reported and detected via a urinary glucose strip test and checked against health register (Sluijs et al. 2010); while one other study was self-reported according to fasting glucose and oral glucose tolerance test results and the use of hypoglycaemic medication (Villegas et al. 2008). One was self-reported and confirmed by physician diagnosis and data from registries (Virtanen et al. 2017). One study used physician diagnosed assessment (Becerra-Tomas et al. 2018, Chen et al. 2018); one used physician diagnosed registry data (Ericson et al. 2013), and one used assessment by clinical examination (Koloverou et al. 2016).

5.2.4 Assessment of vegetable protein intake

One study used the modified diet history method (Ericson et al. 2013), two studies used the semi-quantitative food-frequency questionnaire (FFQ) (Halton et al. 2008, Koloverou et al. 2016). One study used mainly the FFQ which was developed and validated in each country of study (van Nielen et al. 2014). The rest of the studies used the FFQ.

5.2.5 Types of plant protein

Plant proteins that were included in most of the studies were in the form of legumes, lentils, chickpeas, dry beans and fresh peas, whole grains, nuts, legumes, vegetable oils, wholegrain cereals, cereal products, refined grains, and soy.

Several studies included only a certain or more specific type of protein. For example, soy foods including fried soy foods, nonfried soy foods, soy protein, and soy isoflavone (Konishi et al. 2019). Mueller et al. (2012) studied individual non-fermented soy items, unsweetened and sweetened soy products, and soy components. One study classified the exposure only as vegetable protein (Sluijs et al. 2010). Tonstad et al. (2013) did not have the individual types of protein available, but instead classified the diets into vegan, lacto-ovo vegetarian, pesco-vegetarian, semi-vegetarian, and non-vegetarian.

Zong et al. (2018) studied gluten-containing ingredients which included wheat, wheat flour, wheat bran, wheat germ, wheat berries, wheat cream, wheat gluten, rye and rye flour, barley and barley malt flour, cooked cereal, bulgur, couscous, farina, beer, and pasta.

5.2.6 Association of plant protein intake and T2DM

A summary of study exposures and outcomes is shown is Table 2. The results of the studies are inconsistent for the association of type of vegetable protein intake and risk of T2DM. Overall vegetable protein consumption is inversely associated with the risk of T2DM.

Type of plant protein

High legume, lentil, and chickpea consumption was inversely related to T2DM (Becerra-Tomas et al. 2018). Intake of fibre-rich bread and cereals was inversely associated with T2DM. No significant associations were seen between intakes of refined cereals or legumes and T2DM (Ericson et al. 2013).

Quintiles of total legume consumption and three legume groups (peanuts, soybeans, and other legumes) that are mutually exclusive were inversely associated with incidence of T2DM incidence. For total legumes the multivariate-adjusted relative risk of T2DM for the upper quintile compared with the lower quintile was 0.62 (95% CI: 0.51, 0.74) and for soybeans 0.53 (95% CI: 0.45, 0.62). The consumption of soy protein (protein derived from soybeans and their products), soy products (other than soy milk) and T2DM were not significantly correlated (Villegas et al. 2008).

The dose–response analysis in the Zong et al. (2018) investigation revealed a mainly linear inverse relationship between gluten consumption up to 12 g/day and T2DM. Following multivariate adjustment, the highest gluten quintile had a pooled HRs and 95% CI of 0.89 (0.85, 0.93) and the lowest 0.80 (0.76, 0.84) for T2DM. Further adjusting for cereal fibre resulted in a marginal weakening of the link. When added bran intake was higher, the correlation between gluten intake and T2DM strengthened.

Unsweetened soy intake was associated with a reduced risk of T2DM across all consumption frequency categories as was isoflavone; a compound found in soy (Mueller et al. 2012).

Type of diet

A consistent vegetarian diet as well as converting from a non-vegetarian to a vegetarian pattern was inversely associated with risk of T2DM compared to a non-vegetarian diet (Chiu et al. 2018).

In the Chen et al. (2018) study, a higher score on the plant-based dietary index was linked to lower insulin resistance, lower prediabetes risk, and lower T2DM risk after controlling for sociodemographic and lifestyle factors. After further BMI adjustment, correlations for the risk of T2DM and longitudinal insulin resistance reduced and remained statistically significant, but not for the risk of prediabetes.

When compared to low adherence, medium and high adherence to the Mediterranean diet (characterised by diets rich in vegetables, fruit, nuts, whole grain, olive oil) was found to decrease diabetes risk by 49% (95% CI: 0.30, 0.88) and 62% (95% CI: 0.16, 0.88) respectively. The highest predictive ability was seen in wholegrain cereals, fruits, and legumes (Koloverou et al. 2016). Vegetarian including vegan diets were protective for the risk of T2DM (Papier et al. 2019).

Vegans (OR 0.381; 95% CI 0.236-0.617), lacto-ovo vegetarians (OR 0.618; 95% CI 0.503-0.760) and semi-vegetarians (OR 0.486, 95% CI 0.312-0.755) had a lower risk of diabetes than non-vegetarians (Tonstad et al. 2013). A plant diet index (PDI) and high plant diet index (hPDI) were inversely associated with T2DM. The association of T2DM with PDI was considerably attenuated when additionally adjusted for body mass index (BMI), while that with hPDI remained largely unchanged.

The unhealthy plant diet index (uPDI) was positively associated with T2DM even after BMI adjustment (Satija et al. 2016).

Sex

A high score for vegetable protein and fat was not significantly associated with the risk of T2DM overall but was inversely associated with T2DM in men younger than 65 years of age (De Koning et al. 2011). Konishi et. al (2019) found that the risk for developing T2DM was reduced for total soy food intake. However, in men, there were no significant associations between soy intake and the risk of diabetes.

Regarding the score for high plant protein and fat, although the OR of T2DM tended to decrease with increasing score in both men and women, the association was not statistically significant (Nanri et al. 2015). Plant protein intake was inversely associated with incident T2DM in women only. Comparing by quintiles overall, plant protein intake was not associated with the incidence of T2DM (Shang et al. 2016).

Energy percentage

Halton et al. (2008), found no association between total protein, animal protein, or vegetable protein and risk of T2DM. A low carbohydrate-diet score was developed by combining the percentage of energy as carbohydrate, percentage of energy as vegetable protein, and percentage of energy as vegetable fat. In a comparison of the 10th and 1st deciles for this score, the multivariate RR of T2DM was 0.82 (95% CI: 0.71, 0.94). Similarly, vegetable and plant protein intake were not associated with T2DM in the studies by Sluijs et al. (2010) and Van Nielen et al. (2014).

In age-adjusted models, percentage of energy from vegetable protein was associated with a lower risk of T2DM, but associations were attenuated after further adjustment for lifestyle and dietary factors. The association remained in the pooled analyses (comparing extreme quintiles from the fully adjusted model including BMI). Substitution of vegetable protein for animal protein, substitution for carbohydrate from refined grains, potatoes, and added sugar with vegetable protein and substitution for total carbohydrate with vegetable protein were all protective for the risk of T2DM (Malik et al. 2017). Plant protein was inversely associated with T2DM. Replacing 1%

of animal protein energy with plant protein energy was associated with 18% (95% CI 0, 32) decreased risk of T2DM. After adjusting for BMI, this association remained (Virtanen et al. 2017).

5.3 Quality assessment of studies

A quality assessment summary of twenty studies is shown in Table 3. All studies were, based on the Agency for Healthcare Research and Quality (AHRQ) standards, considered to be of good quality, i.e. an overall score of 6 to 9 stars and satisfying the criteria of 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain. Out of the twenty studies, four studies had 6 stars (Malik et al. 2016, Satija et al. 2016, Nanri et al. 2015, Mueller et al. 2012), three studies had 7 stars (Becerra-Tomas et al. 2018, Chiu et al. 2018, Halton et al. 2008), nine studies had 8 stars (Chen et al. 2018, De Koning et al. 2011, Koloverou et al. 2016, Konishi et al. 2019, Papier et al. 2019, Shang et al. 2016, Tonstad et al. 2013, van Nielen et al. 2014, Zong et al. 2018) and four studies had 9 stars (Ericson et al. 2013, Sluijs et al. 2010, Villegas et al. 2008, Virtanen et al. 2017).

5.4 Results of the meta-analyses

Meta-analyses were performed by calculating pooled risk-ratios (RR) using an inverse-variance random-effects model, to show the association of plant protein intake with T2DM.

The forest plot in Figure 2 shows that animal protein intake is associated with higher risk of T2DM, with a pooled RR of 1.34 (95% CI, 1.14, 1.57) compared to plant protein intake. The forest plot in Figure 3 shows that long-term plant protein intake is associated with a lower risk of T2DM, with a pooled RR of 0.79 (95% CI, 0.72, 0.86). There is a high heterogeneity among the studies with an I^2 of 96% ($p < 0.001$) and I^2 of 91% ($p < 0.001$) was observed for each of the analyses respectively. As shown in Figures 4 and 5 respectively, a higher long-term plant protein intake is protective for T2DM in both men, pooled RR of 0.73 (95% CI, 0.59, 0.86) as well as for women, pooled RR of 0.77 (95% CI, 0.66, 0.90). Heterogeneity among the studies is high with an I^2 of 94% ($p < 0.001$) and 96% ($p < 0.001$) respectively.

Table 1. Study characteristics.

Study	Study cohort	Study Design and Setting	Sample size	Study population	Follow-up period(years)
Becerra-Tomas et al. 2018	PREvencion con DIeta MEDiterranea (PREDIMED)	Population-based prospective cohort, Spain	7447	5365 men (55-80 years), 2082 women (60–80 years)	4.3
Chen et al. 2018	Rotterdam Study I, II, III	Population-based prospective cohort, The Netherlands	6770	2796 men and 3974 women (mean 62.0 ± 7.8 years)	7.3
Chiu et al. 2018	Tzu Chi Health Study (TCHS)	Population-based prospective cohort, Taiwan	2918	men and women (18–87 years)	5
De Koning et al. 2011	Health Professionals Follow-Up Study	Population-based prospective cohort, USA	40,475	men (40–75 years)	20
Ericson et al. 2013	Malmo Diet and Cancer cohort	Population-based prospective cohort, Sweden	27140	Men and women (45–74 years)	12
Halton et al. 2008	Nurses' Health Study	Population-based prospective cohort, USA	85 059	Women (30–55 years)	20

Koloverou et al. 2016	ATTICA Cohort study	Population-based prospective cohort, Greece	3042	1514 men (18–87 years), and 1528 women (18–89 years).	10
Konishi et al. 2019	Japanese population	Population-based prospective cohort, Japan	13,521	5883 men and 7638 women (35–69 years)	10
Mueller et al. 2012	Singapore Chinese Health Study	Population-based prospective cohort, Singapore	43176	men and women (45–74 years)	5.7
Nanri et al. 2015	Japan Public Health Center-Based Prospective Study	Population-based prospective cohort, Japan	64,674	27,799 men and 36,875 women (40–59 years)	5
Papier et al. 2019	European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study	Population-based prospective cohort, UK	45314	men and women aged (35–69 years)	17.6
Satija et al. 2016	Nurses' Health Study	Population-based prospective cohort, USA	69949	Women (30–55 years)	28
Satija et al. 2016	Nurses’ Health Study 2	Population-based prospective cohort, USA	90239	women (25–42 years)	20
Satija et al. 2016	Health Professionals Follow-Up Study	Population-based prospective cohort, USA	40539	men (40–75 years)	24

Shang et al. 2016	Melbourne Collaborative Cohort Study	Population-based prospective cohort, Australia	21523	61.7% women (31–76 years)	11.7
Sluijs et al. 2010	European Prospective Investigation into Cancer and Nutrition (EPIC)-NL	Population-based prospective cohort, The Netherlands	38094	Women (49–70 years)	10
Tonstad et al. 2013	Adventist Health Study-2.	Population-based prospective cohort, USA, Canada	41387	15,200 men and 26,187 women (30 years and older)	2
van Nielen et al. 2014	European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct	population based case-cohort, France, Italy, Spain, UK, The Netherlands, Germany, Sweden, and Denmark	28,557	men and women (20–78 years)	12
Villegas et al. 2008	Shanghai Women's Health Study (SWHS)	Population-based prospective cohort, China	64,227	women (40–70 years)	4.6
Zong et al. 2018	Nurses' Health Study	Population-based prospective cohort, USA	69,276	women (30–55 years)	4.24
Zong et al. 2018	NHS 2	Population-based prospective cohort, USA	88,604	women (24–42 years)	4.24
Zong et al. 2018	Health Professionals Follow-Up Study	Population-based prospective cohort, USA	41,908	men (40–75 years)	4.24

Malik et al. 2016	Nurses Health Study	Population-based prospective cohort, USA	72992	women (30–55 years)	24
Malik et al. 2016	Nurses Health Study 2	Population-based prospective cohort, USA	92088	women (24–42 years)	18
Malik et al. 2016	Health Professionals Follow-up Study	Population-based prospective cohort, USA	40722	men (40–75 years)	22
Virtanen et al. 2017	Kuopio Ischaemic Heart Disease Risk Factor Study	Population-based prospective cohort, Finland	2332	men (42–60 years)	19.3

Table 2. Study exposure and outcomes.

Study	Type of plant protein/exposure	Measurement of Exposure	Assessment of diet	Outcome	Outcome diagnosis and criteria	Results
Becerra-Tomas et al. 2018	Legumes, lentils, chickpeas, dry beans, and fresh peas	Food consumption tables comparing quartiles	FFQ	266 DM cases	Physician diagnosed, American Diabetes Association criteria	Highest legume quartile to lowest (HR: 0.65; 95% CI: 0.43, 0.96; P-trend = 0.04; and HR: 0.67; 95% CI: 0.46-0.98; P-trend = 0.05, respectively). Highest chickpeas consumption quartile to lowest (HR 0.68; 95% CI: 0.46, 1.00; P-trend = 0.06. Total legumes consumption. (HR: 0.55, 95% CI: 0.32, 0.93, p 0.03), lentil consumption (HR 0.18, 95% CI 0.05, 0.65, p = 0.01). Consumption of chickpeas, dry beans, and fresh peas unrelated.
Chen et al. 2018	Whole grains, nuts, legumes, vegetable oils, refined grains (among others)	PDI comparing extreme quintiles	FFQ	642 DM cases, 928 prediabetes cases	DM and prediabetes physician diagnosed, WHO.	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: beta = -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 (0.73; 0.92)]. After additional adjustment for BMI, associations attenuated and remained statistically significant for longitudinal insulin resistance [beta = -0.05 (- 0.06; - 0.04)] and T2D risk [HR = 0.87 (0.79; 0.99)], but no longer for prediabetes risk [HR = 0.93 (0.85; 1.03)].
Chiu et al. 2018	Whole grain, soy	Vegetarian diet vs reverted vegetarian vs converted vegetarian vs non-vegetarian	FFQ	183 DM cases	Self-reported on questionnaire or HbA1c>6.5% (in uncertain cases, medical records reviewed)	Consistent vegetarian diet (HR: 0.65, 95% CI: 0.46, 0.92), converting from a nonvegetarian to a vegetarian pattern (HR: 0.47, 95% CI: 0.30, 0.71) compared to non-vegetarian.
De Koning et al. 2011	Whole grains, nuts, legumes	Dietary scores	FFQ	2689 DM cases	Self-reported on questionnaire, validated by medical records	A high score for vegetable protein and fat not significantly associated with the risk of T2D overall. Baseline scores were used in a comparison of the top with the bottom quintile vegetable protein and fat score (HR: 0.95; 95% CI: 0.84, 1.07; P for trend = 0.49); but was inversely associated with T2D

						in men aged <65 y (HR: 0.78; 95% CI: 0.66, 0.92; P for trend = 0.01, P for interaction = 0.01).
Ericson et al. 2013	Legumes, cereal products	Modified dietary history	Modified diet history method,	1709 DM cases	Physician diagnosed diabetes registry data	Intake of fibre-rich bread and cereals was inversely associated with T2DM (HR 0.84; 95 % CI 0.73, 0.98; P for trend = 0.004). No significant associations were seen between intakes of refined cereals or legumes and T2DM.
Halton et al. 2008	Whole grain, vegetable protein	Dietary scores comparing deciles	Semiquantitativ e FFQ	4670 DM cases	Self -reported on questionnaire based on National Diabetes Data Group criteria and confirmed by records by blinded endocrinologist.	No association between total protein, animal protein, or vegetable protein and risk of T2DM. Low carbohydrate-diet score using percentage of energy as carbohydrate, percentage of energy as vegetable protein, and percentage of energy as vegetable fat. The multivariate RR of T2DM was 0.82 (95% CI: 0.71, 0.94) in a comparison of the 10th with the 1st decile for this score (P for trend = 0.001).
Kolovero et al. 2016	Wholegrain cereals and legumes	MedDietScore, vegetarian like dietary pattern characterised by fruit, vegetables,	Semiquantitativ e FFQ	191 DM cases	Clinical examination based on ADA criteria.	Medium and high adherence to the Mediterranean diet was found to decrease diabetes risk by 49% (95% CI: 0.30, 0.88) and 62% (95% CI: 0.16, 0.88), respectively,

	legumes, bread, Greek rusk, pasta					compared with low adherence. Wholegrain cereals, fruits and legumes had the greatest predictive ability.
Konishi et al. 2019	Total soy foods, fried soy foods, nonfried soy foods, soy protein, and soy isoflavone	Dietary history	FFQ	438 DM cases	Self-reported	HRs were 0.45 (95% CI: 0.30, 0.68; P-trend = 0.001) for total soy food intake. In men, there were no significant associations between soy intake and the risk of diabetes.
Mueller et al. 2012	Individual non-fermented soy items, unsweetened and sweetened soy products, and soy components	Dietary categories and comparing quintiles	FFQ	2252 DM cases	Self-reported by telephone interview, validated by hospital database and supplementary questionnaire	Hazard ratios (HRs) and 95% CI for diabetes across unsweetened soy intake categories (none, 1–4/month, 1–2/week, 3–4/week, ≥ 5/week) were: 1 (referent), 0.81 (0.67–0.97), 0.76 (0.63–0.91), 0.76 (0.63–0.92), and 0.72 (0.59–0.89), respectively (p0.015), isoflavone (HR for the fifth compared to the first quintile. 0.76; 95% CI: 0.58–1.00; P for trend = 0.08).
Nanri et al. 2015	Cereal, legume, nut, vegetable protein (unspecified)	Dietary scores	FFQ	1191 DM cases	Self-reported on questionnaire and medical records	Regarding the score for high plant protein and fat, although the OR of T2DM tended to decrease with increasing this score in both men and women, the association was not statistically significant (P for

						trend = 0.07 in men and 0.09 in women).
Papier et al. 2019	Beans, pulses, soy products (excluding soy milk), nut	Dietary history	FFQ	1224 DM cases	Health record linkage through National Health Service (NHS) Central Registers based on WHO ICD 9/10 criteria.	Vegetarian diet (including vegan) HR = 0.63, 95% CI 0.54–0.74, adjusted for BMI (HR = 0.89, 95% CI 0.76–1.05).
Satija et al. 2016	Whole grains, nuts, legumes, vegetable oils	PDI, hPDI, uPDI comparing extreme deciles. PDI=plant dietary index, hPDI=healthy PDI, uPDI=unhealthy PDI	FFQ	7711 DM cases (NHS) 5200 DM cases (NHS 2) 3251 DM cases (HPFS)	Self-reported, validated by supplementary questionnaire, diagnosis criteria based on National Diabetes Data Group	PDI and hPDI were inversely associated with T2D (PDI: hazard ratio [HR] for extreme deciles 0.51, 95% CI 0.47–0.55, p trend < 0.001; hPDI: HR for extreme deciles 0.55, 95% CI 0.51-0.59, p for trend < 0.001). The association of T2D with PDI was considerably attenuated when we additionally adjusted for body mass index (BMI) categories (HR 0.80, 95% CI 0.74-0.87, p for trend < 0.001), while that with hPDI remained largely unchanged (HR 0.66, 95% CI 0.61-0.72, p for trend < 0.001). uPDI was positively associated with T2D even after BMI adjustment (HR for extreme deciles 1.16, 95% CI 1.08-1.25, p for trend < 0.001).

Shang et al. 2016	Grains, legumes, nuts	Total protein energy intake compared by quintiles	FFQ	929 DM cases	Self-reported by face to face or telephone interview	Plant protein intake was inversely associated with incidence T2D in women only (OR; 0.60; 95% CI: 0.37, 0.99, p =0.001). Comparing by quintiles overall, plant protein intake was not associated with the incidence of T2D (OR 1.02 (0.73 1.42) 0.94)
Sluijs et al. 2010	Vegetable protein bread (43%), fruit and vegetables (14%), and potatoes (9%)	Total protein intake, total animal protein intake and total vegetable protein intake compared by quintiles	FFQ	918 DM cases	Self-reported and detected via a urinary glucose strip test, Dutch Centre for Health Care Information electronic register	After adjusted for age and sex, for total protein HR in highest vs lowest quartile for risk of T2DM was 1.85 (CI 1.53–1.25) p <0.001. Animal protein 1.73 (1.43–2.10) p <0.001 Vegetable protein intake was not related to risk of T2DM 1.02 (0.85–1.23) 0.64.
Tonstad et al. 2013	NA	Vegan, lacto ovo vegetarian, pesco vegetarian, semi-vegetarian vs non-vegetarian	FFQ	616 DM cases	Self-reported, validated with questionnaire	Vegans (OR 0.381; 95% CI 0.236-0.617), lacto ovo vegetarians (OR 0.618; 95% CI 0.503-0.760) and semi-vegetarians (OR 0.486, 95% CI 0.312-0.755) had a lower risk of diabetes than non-vegetarians.
van Nielen et al. 2014	Rice, legumes, bread	Total protein intake in quintiles	Mainly FFQ developed and validated in each country	12403 DM cases	Self-report, linkage to primary care registers and secondary care registers,	Plant protein intake was not associated with T2DM (per 10 g: 1.04 [0.93-1.16], P for trend = 0.098).

					medication use (drug registers), hospital admissions, and mortality data.	
Villegas et al. 2008	Beans, lentils, peanuts, peas, and soybeans	The average daily intake of individual food items (g/d) was combined to compute the following food groups: total legumes and 3 mutually exclusive groups soybeans (dried and fresh), peanuts, and other legumes	FFQ	412 DM cases	Self-reported according to criteria 1) fasting glucose concentration ≥7 mmol/L on 2 separate occasions, 2) an oral-glucose-tolerance test with a value ≥11.1 mmol/L, and 3) use of hypoglycemic medication (i.e., insulin or oral hypoglycemic drugs).	Inverse association between quintiles of total legume intake and 3 mutually exclusive legume groups (peanuts, soybeans, and other legumes) and T2DM incidence. The multivariate-adjusted relative risk of T2DM for the upper quintile compared with the lower quintile was 0.62 (95% CI: 0.51, 0.74) for total legumes and 0.53 (95% CI: 0.45, 0.62) for soybeans. The association between soy products (other than soy milk) and soy protein consumption (protein derived from soy beans and their products) with T2DM was not significant.
Zong et al. 2018	Gluten-containing ingredients included wheat, wheat flour, wheat bran, wheat germ, wheat berries,	7-day dietary record	FFQ	7088 DM cases (NHS) 5460	Self-reported on questionnaire based on National Diabetes Data Group and American Diabetes	After multivariate adjustment, pooled HRs and 95% CIs for T2DM, from low to high gluten quintiles, were (p trend < 0.001): 1 (reference); 0.89 (0.85, 0.93); 0.84 (0.80, 0.88); 0.78 (0.74, 0.82) and

	wheat cream, wheat gluten, rye and rye flour, barley and barley malt flour, cooked cereal, bulgur, couscous, farina, beer, and pasta.			DM cases (NHS2) 3399 DM cases (HPFS)	Association criteria and confirmed by records by blinded endocrinologist.	0.80 (0.76, 0.84). The association was slightly weakened after further adjusting for cereal fibre, with pooled HRs (95% CIs) of (p for trend < 0.001): 1 (reference); 0.91 (0.87, 0.96); 0.88 (0.83, 0.93); 0.83 (0.78, 0.88) and 0.87 (0.81, 0.93). Dose–response analysis supported a largely linear inverse relationship between gluten intake up to 12 g/day and T2DM. The association between gluten intake and T2DM was stronger when intake of added bran was also higher (p interaction = 0.02).
Malik et al. 2016	Whole grains, nuts, peanuts, peanut butter, legumes	Total protein energy intake compared by quintiles	FFQ	7214 DM cases (NHS) 5032 DM cases (NHS 2) 3334 DM cases (HPFS)	Self-reported based on ADA criteria and Supplementary questionnaires	In the pooled analysis of the 3 cohorts, highest vs lowest quintile of plant protein intake showed a decreased risk of T2DM, HR 0.91 (CI 0.84, 0.98, p = 0.01). Substitution of vegetable protein for animal protein HR 0.77 (CI 0.70, 0.84, p<0.001). Substitution for total carbohydrate with vegetable protein HR 0.78 (CI 0.71, 0.86, p<0.001).

Virtanen et al. 2017	Grain products, legumes, nuts, and seeds	Energy adjusted protein intakes comparing quartiles	FFQ	432 DM cases	Self-reported physician diagnosis and data from national hospital discharge registry and the Social Insurance Institution of Finland register for reimbursement of medicine expenses used for T2D	Plant protein (multivariable-adjusted extreme quartile HR 0.65; (95%, CI 0.42, 1.00; p= 0·04). Replacing 1% of energy from animal protein with energy from plant protein was associated with 18% (95% CI 0,32) decreased risk of T2D. This association remained after adjusting for BMI.

Table 3. Grading of study quality according to the Newcastle-Ottawa Scale (NOS).

Study	**Selection**				**Comparability**	**Outcome**			**Total**
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at start of study		Assessment of Outcome	Follow-up long enough for outcome to occur	Adequacy of follow up	
Becerra-Tomas et al. 2018		*	*	*	**	*		*	7
Chen et al. 2018	*	*	*	*	**	*		*	8

Chiu et al. 2018	*	*	*		**	*		*	7
De Koning et al. 2011	*	*	*	*	**	*	*	*	8
Ericson et al. 2013	*	*	*	*	**	*	*	*	9
Halton et al. 2008	*	*	*	*	*	*	*		7
Koloverou et al. 2016	*	*	*	*	**	*	*		8
Konishi et al. 2019	*	*	*	*	**		*	*	8
Mueller et al. 2012	*	*	*	*	**		*		6
Nanri et al. 2015	*	*	*	*	**		*		6
Papier et al. 2019	*	*	*	*	**	*	*		8
Satija et al. 2016	*	*	*	*	**		*		6
Shang et al. 2016	*	*	*	*	**	*	*		8

Sluijs et al. 2010	*	*	*	*	**	*	*	*	9
Tonstad et al. 2013	*	*	*	*	**		*	*	8
van Nielen et al. 2014	*	*	*	*	**	*	*		8
Villegas et al. 2008	*	*	*	*	**	*	*	*	9
Zong et al. 2018	*	*	*	*	**	*	*		8
Malik et al. 2016	*	*	*	*	**		*		6
Virtanen et al. 2017	*	*	*	*	**	*	*	*	9

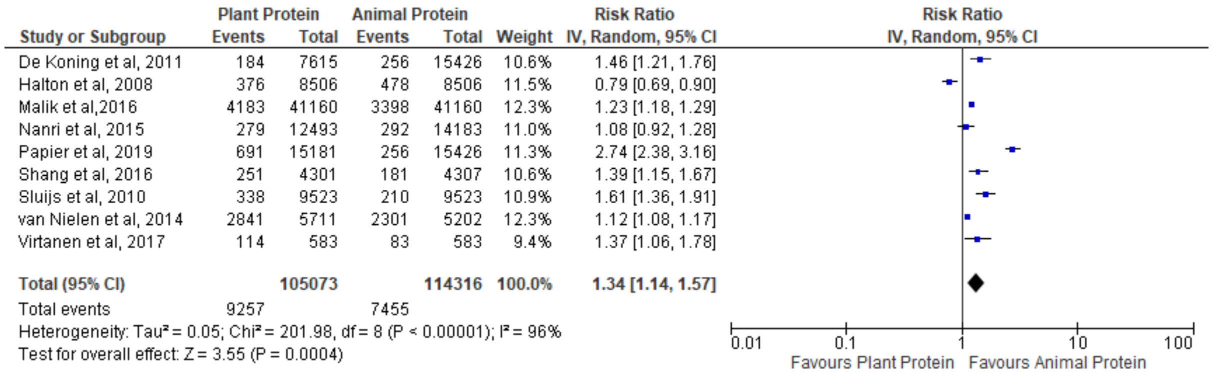

Figure 2. Results of meta-analyses. Long-term protein intake and risk of T2DM: Risk ratios for plant protein versus animal protein.

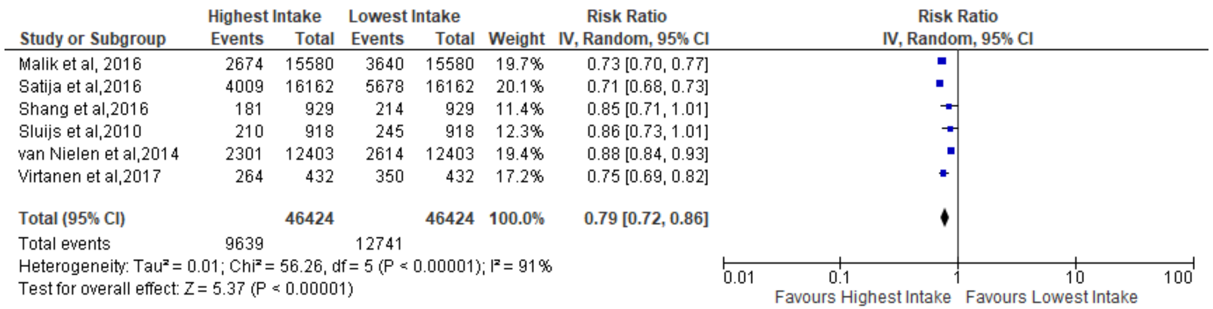

Figure 3. Results of meta-analyses. Long-term plant protein intake and risk of T2DM: Risk ratios for highest versus lowest intake

Study or Subgroup	Highest Intake Events	Highest Intake Total	Lowest Intake Events	Lowest Intake Total	Weight	Risk Ratio IV, Random, 95% CI
De Koning et al, 2011	593	8095	539	8095	17.5%	1.10 [0.98, 1.23]
Malik et al,2016	510	8144	833	8144	17.6%	0.61 [0.55, 0.68]
Nanri et al, 2015	133	6142	173	6279	15.2%	0.79 [0.63, 0.98]
Satija et al, 2016	780	12161	1131	12161	17.8%	0.69 [0.63, 0.75]
Virtanen et al, 2017	83	583	119	583	14.4%	0.70 [0.54, 0.90]
Zong et al, 2018	522	8381	904	8381	17.6%	0.58 [0.52, 0.64]
Total (95% CI)		**43506**		**43643**	**100.0%**	**0.73 [0.59, 0.89]**
Total events	2621		3699			

Heterogeneity: Tau² = 0.06; Chi² = 82.33, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 3.04 (P = 0.002)

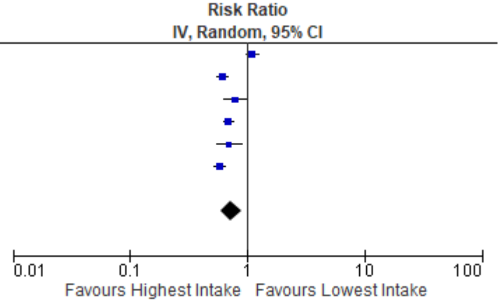

Figure 4. Results of meta-analyses. Long-term plant protein intake and risk of T2DM in men: Risk ratios for highest versus lowest intake

Study or Subgroup	Highest Intake Events	Highest Intake Total	Lowest Intake Events	Lowest Intake Total	Weight	Risk Ratio IV, Random, 95% CI
Halton et al, 2008	1000	25517	920	25517	17.5%	1.09 [1.00, 1.19]
Malik et al,2016	2164	91409	2807	91409	18.2%	0.77 [0.73, 0.81]
Nanri et al, 2015	97	8140	119	7904	11.8%	0.79 [0.61, 1.03]
Satija et al, 2016	3203	48056	4516	48056	18.3%	0.71 [0.68, 0.74]
Villegas et al, 2008	313	12845	412	12845	15.9%	0.76 [0.66, 0.88]
Zong et al, 2018	2001	31576	3298	31576	18.2%	0.61 [0.58, 0.64]
Total (95% CI)		**217543**		**217307**	**100.0%**	**0.77 [0.66, 0.90]**
Total events	8778		12072			

Heterogeneity: Tau² = 0.03; Chi² = 131.05, df = 5 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.33 (P = 0.0009)

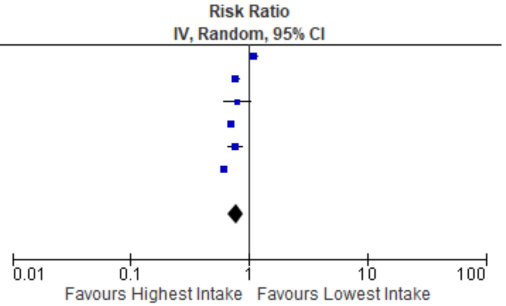

Figure 5. Results of meta-analyses. Long-term plant protein intake and risk of T2DM in women: Risk ratios for highest versus lowest intake

6 Discussion

Despite inconsistent results, in general, consumption of plant protein appears to be inversely associated with the risk of developing T2DM in prospective cohort and case-cohort studies. Several factors appear to affect the association between the consumption of plant protein and T2DM. These factors include the amount of plant protein consumed, the quality and type of plant protein, sex of the study participants, conversion to a plant-based diet from a non-plant-based one, and replacement of energy in the diet with plant protein. The results of the meta-analysis show that a higher adherence to a plant protein diet lowers the risk for T2DM. The study findings show that adhering to a plant-based diet over a period of at least four years is associated with lower T2DM risk.

In the meta-analysis, both men and women appear to have a lower risk of T2DM by adhering more to a plant protein-based diet. In the individual studies, as shown by Shang et al. (2016) and Konishi et al. (2019), the negative association between plant protein or soy and T2DM was observed in women only. While the exact mechanism is unclear, the negative association could be due to other protective lifestyle factors, such as, for example, lower alcohol consumption. However, this needs to be researched further.

The risk of T2DM appears to be reduced when a small percentage of animal protein in the diet is replaced by plant protein (Malik et al. 2016, Virtanen et al. 2017). Chiu et al. (2018) showed that converting from a non-vegetarian to a vegetarian pattern reduced the risk of T2DM (HR: 0.47, 95% CI: 0.30).

Replacing a small portion of carbohydrates with plant protein is negatively associated with the risk of T2DM. One explanation for this negative association might be that a lesser amount of carbohydrate intake under isoenergy conditions leads to a lesser amount of glucose absorbed, causing a reduced storage of glycogen and finally a decrease in glycogenolysis rate. Another possible explanation is that there is an increased insulin secretion from increased gluconeogenesis, as amino acids serve as substrates for gluconeogenesis. Hyperglemia is then prevented from this change in glucose metabolism (Gannon et al. 2004, Nuttal et al. 2004, Tremblay et al. 2007).

High versus low adherence to a Mediterranean-type diet was associated with a lower risk for T2DM (Koloverou et al. 2016, Malik et al. 2016, Satija et al. 2016, Nanri et al. 2015).

6.1 Strengths and limitations of study

The present study has several strengths. The systematic review includes results from all available prospective population-based cohort and case-cohort studies with large number of study participants and outcome of interest. The studies included are representative for different subgroups in different countries.

This study also has some limitations. Due to the prospective-cohort design of the included studies, the true effect size might be underestimated and the true associations between the effect of the exposure to plant protein consumption and the outcome of T2DM cases may be biased towards the null. In observational studies such as those used here, the residual or unmeasured confounding factors cannot be eliminated.

The dietary intake in included studies is self-reported through food frequency questionnaires. This could have resulted in, for example, a misclassification of the protein consumed by the participants, which could have biased the results in this study.

Plant-based diets are difficult to classify as they may include vegan diets, vegetarian diets, lacto-ovo vegetarian diets and semi-vegetarian diets. This leads to differences in the manner in which plant proteins are defined in in the studies.

There are also differences in the sources of plant protein in different regions of the world. For example, in the case of grains, they were usually in the form of bread in Scandinavia, bread and cereals in the USA and rice in Asia (Johnsen et al. 2015, Jacobs et al. 1999, Zhang et al. 2011). Foods such as soy products are consumed more commonly in Asian populations compared to non-Asian populations (Zamora-Ros et al. 2012).

There are differences in the sociocultural characteristics of the study populations in this review. The findings might therefore not be generalizable. Furthermore, these studies were conducted in relatively high-income countries whereby the general food quality might be better and more highly regulated compared to the food quality in lower income countries (Pawlak 2017, Dehghan et al. 2017).

6.2 Mechanisms explaining observed associations

Plant protein such as nuts, legumes and wholegrains are rich in unsaturated fatty acids, phenolic compounds, and fibre. These substances improve blood pressure and insulin sensitivity as well as have antioxidant properties which are all beneficial in preventing T2DM (Kahleova et al. 2018, Yokoyama et al. 2014). There are less oxidative stress markers in a plant-based diet, reducing systemic inflammation, which is involved in the pathway that causes T2DM (Kahleova et al. 2011).

Soy protein may inhibit insulin secretion from pancreatic β cells or inhibit lipogenesis and enhance lipolysis in the adipose and liver to reduce adiposity (Bathena et al. 2002). This protective effect may also be associated with biologically active ingredients such as phytoestrogen in soybeans (Jayagopal et al. 2002).

Adherence to a plant-based diet has also been shown to prevent excess weight gain, even in the long-term (Barnad et al. 2014, Huang et al. 2016) and individuals following a plant diet tend to have lower body mass indices (Tonstad et al. 2009), as well as lower visceral fat (Kahleova et al. 2011). Furthermore, the consumption of plant-based protein means there is decreased consumption of meat, particularly red meat. Red meat is high in saturated fat; advanced glycation end products; nitrosamines; and haem-iron dietary elements, which have been linked to insulin resistance (Ley et al. 2014, Aune et al. 2009, Shulman 2014). Plant protein is associated with less weight gain because it has less branched chain amino acids leucine, isoleucine, and valine methionine when compared to animal protein (Richter et al. 2015). Higher dietary intake of the sulphur containing methionine, as well as glycine, which is found abundantly in animal protein, is positively associated with insulin resistance and T2DM (Wittenbecher et al. 2015).

Oro-sensory stimulation and satiation that comes from chewing plant protein such as wholegrain and cereals (Wanders et al. 2011) lead to eating less amounts of food. Dietary patterns such as the traditional Mediterranean diet, which consists of mostly plants and moderate animal product consumption, has been shown to reduce the incidence of T2DM by as much as 30% even without change in BMI (Salas-Salvado et al. 2014).

Several of the studies in this systematic review showed that the quality of the plant protein appeared to affect the risk of developing T2DM. A randomized controlled trial by Lee et al. (2016) showed that a brown-rice-based vegan diet with low-glycaemic index foods, such as legumes and avoidance of processed rice or wheat, lowered haemoglobin A1c levels by 0.3 units more than compared with a conventional diabetic diet.

7 Conclusion and recommendations for future research

Glucose regulation and control is affected by the quantity and quality of dietary protein. Many factors, such as an individual's nutrigenetic and nutrigenomic profile, affect the association between dietary intake and the development of disease. Different individuals have different responses to different nutritive factors and dietary manipulations. The relationship between plant protein intake and its glucoregulatory effects over time, and in certain types of populations, could be better studied by conducting randomised controlled trials.

Current studies on vegetable and plant protein have focused on the more conventional or traditional sources of protein associated with the risk of T2DM. These proteins were foods such as soy, grain, and cereal.

Innovative plant protein sources such as texturized vegetable proteins are increasingly used as alternatives to meat and dairy products. Future studies could undertake research on how these 'new' types of protein are related to the risk of diabetes. The glucoregulatory properties in plant protein foods are also affected by their compositions of their nutrient content. Plant proteins formed into meat substitutes often contain other non-protein components such as fat, carbohydrates, vitamins, and minerals that affect their glucoregulatory properties. Other factors that affect the glucoregulatory properties are added substances and preservatives. Methods of processing, such as fermentation, which are common in plant protein-based foods to improve taste and mimic real meat, also affect the glucoregulatory properties. Fermented soy, for example, contains different probiotic strains from raw soy. Future studies could investigate whether these plant protein foods have the same protective properties against T2DM as the raw or unprocessed forms of protein.

In conclusion, the results of this systematic review and meta-analysis suggest that an improved long-term intake of plant-based diet lowers the risk of developing T2DM. Decreased adherence to plant-based diets was associated with a higher risk of T2DM.

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