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Is type 2 diabetes reversible with diet? A meta-analysis of randomized controlled trials

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Preface

This meta-analysis is a master thesis part of the Public Health Nutrition master study. The idea of writing about type 2 diabetes and diet is mainly due to the recurring problem of metabolic abnormalities, locally and globally. As with many other non-communicable diseases, the proposed treatment and maintenance of metabolic problems is found in pharmaceuticals. Western medicine and the drugs they provide is excellent at treating acute problems such as fractures or pain, but has failed at finding a solution to the non-communicable disease problem which is the primary cause of morbidity and mortality globally [123; 205]. This thesis therefore looks at the possibility of treating non-communicable lifestyle conditions, such as type 2 diabetes, through lifestyle. An idea that seems very logical, at least at the surface.

I would like to give a huge thank you and a wave of appreciation to Asgeir Brevik, my supervisor and living encyclopedia for this master thesis. Developing and writing a meta-analysis of this scale alone is a big task in itself, but it would have been very difficult if he hadn't answered every question I had.

Oslo, May 2022 Kristian Watvedt

Summary

Introduction: Type 2 diabetes mellitus (T2DM), defined by HbA1c values above 6.5% (48 mmol/mol), and it's precursor prediabetes, defined by HbA1c values above 5.7% (39 mmol/mol), is a major health challenge worldwide. The prevalence of both T2DM, and prediabetes which is one of the main criterias for metabolic syndrome (MetS), has risen dramatically since the 1960's with the introduction of industrialized food processing. Much like obesity, which it has a high correlation with, T2DM is fundamentally due to excessive intake of poor-quality food eventually overloading the cells with energy. The aim of this meta-analysis is therefore to examine the possibility and efficacy of treating T2DM and its precursor through diet, evident by remission or large reductions in HbA1c, by including Randomized Controlled Trials (RCT's) of patients with T2DM or MetS.

Methodology: A systematic search was performed on PubMed of RCT's including (1) patients with T2DM/MetS or relevant conditions, (2) HbA1c measured and above 6.5% (T2DM) or 5.7% (MetS/prediabetes), (3) any type of dietary intervention, including fasting, (4) and primary studies only. The efficacy of dietary interventions on glycemic control (HbA1c) were assessed by pooling data from each included RCT. Studies focusing on exercise, drugs, or surgery that affects the metabolism (e.g., bariatric surgery) were excluded. Risk of bias was assessed based on the Cochrane Handbook.

Results: Of a total 652 studies screened, 51 studies were included in the analysis (a total of 3281 patients). The intervention diets varied greatly in design and appeared more effective at lowering HbA1c than the comparator diets (SMD, -0.61; 95% CI, -0.76 to -0.47; $p < 0.00001$) (Figure 4). Analysis of studies with better adherence (total of 1509 patients) showed a significantly greater reduction in HbA1c compared to the main analysis (SMD, -0.80; 95% CI, -1.00 to -0.59; $p < 0.00001$) (Figure 5). Remission occurred in 17 out of the 51 studies. Limitations of the evidence was minimal as the Risk of Bias assessment was acceptable.

Conclusion: An intervention diet (typically low-carb, high-fiber, low-GI/GL, keto) was more efficacious at improving glycemic control in patients with T2DM or MetS than comparator diets (typically low-fat or hypocaloric diets). A recurring factor in the diets producing good results seems to be the elimination of processed food, especially processed carbohydrates. Based on observations made in this meta-analysis, reversing T2DM and prediabetes with diet is both possible and practicable even with high HbA1c values.

Keywords: Type 2 diabetes, Diet, Dietary interventions, Glycemic control, Meta-analysis, Randomized controlled trials, Hba1c, Remission, Quantitative, Ultra-processed food.

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List of abbreviations

ADA: American Diabetes Association

BMI: Body Mass Index

BMR: Basal Metabolic Rate

C: Control group

CI: Confidence Interval

CRP: C-reactive Protein

E%: Percentage of daily energy intake

FPG: Fasting Plasma Glucose

GI: Glycemic Index

GL: Glycemic Load

HbA1c: Hemoglobin A1c

HDL: High-density Lipoprotein

I: Intervention group

IDF: International Diabetes Federation

IF: Intermittent Fasting

IHD: Ischemic Heart Disease

ITT: Intention-to-treat

Kcal: Kilocalories

KDA: Korean Diabetes Association

MetS: Metabolic Syndrome

NAFLD: Non-alcoholic Fatty Liver Disease

NS: Non-significant

OHA: Oral Hypoglycemic Agent

RCT: Randomized Controlled Trial

SD: Standard Deviation

SMD: Standardized Mean Difference

T2DM: Type 2 Diabetes Mellitus

UPF: Ultra-processed Food

1. Introduction

In the 50s and 60s, seemingly healthy Americans began developing heart attacks with growing regularity. With little information available, dietary fat was unjustifiably made into a villain and blamed for the increased prevalence of heart disease and stroke. Unfortunately not realized at the time, cutting out dietary fat meant replacing it with carbohydrates (especially when designing processed food products), which in the developed world was often highly refined and processed. A report released in 1977, Dietary Goals for the United States, led to the development of the dietary guidelines, where recommended intake of carbohydrates were set to 55-60% of daily energy intake on the basis that dietary fat was vile and unhealthy – a claim that apparently was a work of fiction as it was not shown in clinical trials at the time [66]. From this point forward, both obesity and type 2 diabetes mellitus (T2DM) rates began rising [50, p. 27-37]. In 1980, an estimated 108 million people worldwide suffered from diabetes. In 2014, this number had increased dramatically to 422 million (a 290% increase!). China went from a 1% diabetes prevalence in 1980, to a staggering 11.6% in 2013. The International Diabetes Federation (IDF) estimates that 1 in 10 adults worldwide will have diabetes by the year 2040. In 2001, less than 3% of newly diagnosed diabetes cases in adolescents was type 2. 10 years later, in 2011, it had increased to 45%. It has gotten to the point where T2DM could be considered a plague [50, p. 27-37].

T2DM was the ninth leading cause of death in 2019 with an estimated 1.5 million deaths directly caused by diabetes [215]. According to a recent report, T2DM caused over 100,000 deaths in 2021 in the US [197]. To make matters worse, these numbers are greatly underreported. For example, a study of colon cancer patients found that diabetic patients had a 42% increased risk of all-cause mortality relative to non-diabetics [133]. For many cases in which cancer is the primary cause of death, the true cause is the combined effect of diabetes and cancer. Only the latter is reported. The adverse impact of T2DM and prediabetes is certainly greater than the numbers can tell us.

Besides lifestyle interventions, the treatment of T2DM and prediabetes mainly consists of maintenance work, using insulin therapy or other blood sugar lowering medications to keep the disease in check so that the people afflicted can retain their eating habits [177]. There are some medical/general practices that treat the disease with diet and exercise, knowledge that has become more common the past years [127; 203; 204]. Preventing T2DM in those at high risk with diet and exercise is also well documented [93; 113; 153; 165]. However, many still

see T2DM as a chronic disease that they have to live with. Knowledge about treating the disease with diet and exercise are not consistently talked about by doctors and medical personnel or even mainstream media, and people that are diagnosed with the disease often have to examine the possibilities themselves by researching the internet [177]. Organizations such as IDF has a lot of useful information for newly diagnosed diabetics, recommending a healthy diet and exercise as a cornerstone in managing the disease, but not necessarily treating it [74]. This meta-analysis is a master thesis about examining the effects of diet and nutrition on T2DM, and what the clinical evidence says about treating the disease with diet (characterized by reductions of glycemic markers down to normal levels) and the possibility of achieving remission.

The objective of this analysis is therefore:

- To examine the possibility of achieving remission of T2DM and prediabetes with diet by synthesizing evidence from Randomized Clinical Trials (RCT's) recruiting patients with T2DM or Metabolic Syndrome (MetS).

1.1. Type 2 Diabetes Mellitus, Hyperglycemia and Insulin Resistance

Diabetes Mellitus is a group of metabolic disorders characterized by hyperglycemia, elevated levels of glucose in the bloodstream. Type 2 is by far the most common, accounting for approximately 90% of cases, and is the topic of this study as it is driven by lifestyle and diet [50, p. 32; 94]. T2DM typically develops gradually over many years from normal to pre-diabetes to full-blown T2DM [50, p. 37]. The risk increases with age, and more importantly, obesity – which is why bariatric surgery and hypocaloric (low energy intake) feeding has shown success in establishing a reverse route from cure to cause [195]. Obesity and T2DM is so strongly correlated with one another that the term "diabesity" has been proposed [87; 146]. The development of metabolic diseases such as T2DM is fundamentally due to excessive intake of poor quality food (same as obesity), evident by the restoration of normal blood glucose days after bariatric surgery or a very low hypocaloric diet [195; 196; 219]. However, it is important to note that around 30% of obese adults are metabolically healthy, and around 36% of newly diagnosed diabetics have a body mass index (BMI) of less than 25 kg/m^2, which is considered normal [50, p. 56]. The underlying issue seems to be fat deposition. Visceral fat, accumulation of fat around and inside the intra-abdominal organs such as the liver (also referred to as ectopic fat), is strongly correlated with T2DM. Subcutaneous fat,

deposited underneath the skin, has in contrast a weak correlation with T2DM. This explains why some people can be obese and at the same time metabolically healthy (as the extra fat they carry is mostly subcutaneous), and skinny people with a normal BMI can be metabolically unhealthy due to fat being deposited in the abdominal/visceral area, giving rise to the term "skinny fat" [50, p. 56]. The reason for this can be that adipose tissue cannot keep pace with the energy storage needs associated with chronic energy excess [156]. How this happens is explained in the next paragraphs.

Even though hyperglycemia is the biggest identifying factor and characterization of T2DM, it is only a symptom. Hyperglycemia occurs due to insulin resistance, which is the failure of insulin to effectively lower blood glucose levels [50, p. 37]. Insulin is an anabolic hormone produced by the pancreas to signal the uptake of substrates (substances acted upon by enzymes, such as glucose) from broken-down macronutrients (carbohydrates, protein, fat) out of the blood stream and into cells [50, p. 37]. Carbohydrates (glucose/sugar) stimulate the biggest secretion of insulin, protein (amino acids) stimulate insulin secretion moderately, while fat (fatty acids) stimulate insulin secretion to a very small degree [50, p. 64-66]. Carbohydrates and protein have to travel via the liver for processing after it gets absorbed in the small intestines; fat does not. Since liver processing is not required, neither is insulin signaling, and dietary fats therefore leave insulin levels relatively unchanged. Once our immediate energy needs have been met, the liver processes the remaining substrates and stores it for later use as either fat (triglycerides) in adipose tissue or glycogen (storage form of glucose) in liver and muscle tissue. The fundamental role of insulin is therefore to move substrates/nutrients out of the bloodstream and into cells, and to store energy for later use. Eat food → increase insulin → store excess energy as fat or glycogen. The opposite happens when we go without food for several hours, such as between meals or overnight (typically referred to as fasting): insulin goes down and another hormone, glucagon, rises and signals to the body that blood sugar is getting low. This stimulates another cascade of hormones and enzymes to burn stored energy (glycogen and fat) for fuel, turning it into glucose in the liver to keep blood glucose levels stable so every glucose-dependent cell in the body can thrive [50, p. 64-66]. An important function of insulin is therefore to inhibit lipolysis (breakdown of stored fat for energy) and reduce plasma levels of fatty acids, switching the main fuel source away from fats and towards carbohydrates/sugars [26].

Insulin resistance and its origin is explained by the overflow phenomenon [50, p. 75-83]. The body normally secretes insulin in bursts, as with all hormones. This allows insulin levels to go

up and down in response to food or even the circadian rhythm. In healthy people, substrate molecules such as glucose enter and leave the cells in equal amounts. Balanced episodes of feeding (high insulin) and fasting (low insulin) allows the body to produce hormonal bursts to decide how substrates are handled. Glucose is stored as glycogen in the liver and muscle tissue, or converted into fat and exported to adipose tissue for storage. However, with consistent hypersecretion of insulin from e.g. refined carbohydrate consumption and no fasting period to balance it out, more glucose enters than the cells can manage. An increasing amount of glucose has to be processed in the liver cells. Over time (remember that T2DM risk increases with age as well) the cells overflow with glucose as they reach their capacity and eventually stop responding to insulin. The cell is now insulin resistant to indicate that its limit has been reached [50, p. 75-83]. Insulin resistance in other words represents a feedback regulation of energy oversupply in cells to control mitochondrial overloading by substrates. Insulin resistance cuts down the substrate uptake of cells to attenuate the load of the mitochondria, the part of the cell which produces energy from glucose [217]. It represents a biological adaptation to an ever-increasing stimulus, much like how too much alcohol creates an alcohol resistance/tolerance. Removing the stimulus removes the resistance [50, p. 75-83; 219].

To compensate the insulin resistance, the body produces more insulin to force more glucose into the cell, but this only works for so long [50, p. 75-83; 219]. With the cells overflowing with glucose, it eventually spills out into the bloodstream and raises blood glucose levels which again tells the pancreas to produce more insulin. This consistent secretion of insulin to keep the highly variable and peaking blood glucose levels relatively stable is hyperinsulinemia – high insulin levels in the blood. Fasting insulin levels increases from healthy to nondiabetic obese to prediabetic obese to diabetic obese. A metabolically sick person with hyperglycemia can therefore have relatively stable blood glucose levels, although with greater variability and peaks than a healthy person, since it’s kept in check by high insulin levels. In addition, since the liver is full of glucose, it desperately tries to get rid of it by converting it to fat (triglycerides) and exporting it to adipose tissue for storage. If more fat is created than can be exported (either because liver cells are full of glucose and/or adipose tissue has reached maximum capacity), fat backs up in the liver, an organ not designed for fat storage, and fatty liver is the result. Eventually this fat also spills over into the other intra-abdominal organs. This is why abdominal obesity, or visceral fat, is strongly correlated with T2DM. Insulin resistance causes a compensatory hyperinsulinemia, which in turn promotes

more storage. Insulin, originally secreted in bursts, is now consistently secreted more and more to move excess energy into storage, but there seems to be nowhere to put it. Eventually, the body must make room for storage in the organs. This cycle continues until you address the underlying issue, insulin resistance, by emptying the cells of glucose [50, p. 75-83; 219].

A simplified analogy for this is to picture a subway train (a cell) full of people (glucose) arriving at your stop. The train conductor (insulin) signals the doors to open so that you (a glucose molecule) can get on, but the train is so full that the doors just partly open to reveal a train packed with people. The train has insulin resistance. A group of subway pushers comes along and pushes you into the already cramped train. Hyperinsulinemia is the subway pushers [50, p. 80-81].

The different cutoff values defining pre-diabetes (also referred to as impaired glucose tolerance) and full-fledged T2DM is based on blood glucose levels, as hyperglycemia is an identifying factor. Prediabetes, or impaired glucose tolerance, is one of five criteria for MetS, and is therefore included in this study. MetS diagnosis requires **three** out of the **five** following components: **central/visceral obesity**, BMI > 30 kg/m^2 or preferably waist circumference > 102 and 88 cm for men and women respectively; **raised blood pressure**, systolic/diastolic >= 130/85 mm Hg; **raised triglycerides**, >= 150 mg/dl; **low HDL-cholesterol**, < 40 or 50 mg/dl for men and women respectively; **fasting hyperglycemia**, fasting plasma glucose (FPG) >= 100 mg/dl [4; 60]. The different tests and their respective cutoff values are shown below (Table 1).

Table 1: Cutoff values for clinical diagnosis of prediabetes and T2DM [6]

	Normal	**Prediabetes**	**T2DM**
HbA1c (%)	< 5.7	5.7 – 6.5	>= 6.5
FPG (mg/dl)	< 100	100 - 126	>= 126
OGTT (mg/dl)	< 140	140 - 200	>= 200

HbA1c (hemoglobin A1c) is the measurement used in this analysis. Hemoglobin is a protein found in red blood cells carrying oxygen around the body. The lifespan of these blood cells is effectively a little over 3 months. During this period, glucose molecules attach themselves to the hemoglobin in proportion to the body's blood glucose levels. The A1C test therefore

reflects your body's glucose levels the past three months. This can easily be tested with a hemoglobin A1C test as it does not require a fasting state. [50, p. 34].

1.2. Risk Factors Associated with Hyperglycemia and Hyperinsulinemia

HbA1c values above as low as 5% shows a continuous increase in the associated risk for cardiovascular disease, cardiovascular death, and death from all causes [91; 162; 176]. Elevated HbA1c values also continuously increases the risk for frailty [208], cognitive decline and dementia [36], COVID-19 hospitalization and death [28], and cancer mortality [16], suggesting that lowering your glucose values even if they are below traditional cutoff points for T2DM and MetS can make a difference.

In addition, your blood glucose and insulin levels can have abnormally large spikes even though your HbA1c values are relatively stable – HbA1c reflects your average glycemia the past months after all. High blood glucose variability, or high blood glucose and insulin levels, is associated with endothelial dysfunction [89; 124; 192; 210; 213], an increased risk of Alzheimer's Disease [117], cardiovascular disease and all-cause mortality [223], cardiovascular death [106], cancer and cancer death [67; 193; 201], mortality [132], and an accelerated development of atherosclerosis [65]. Hyperinsulinemia, unrelated to change in plasma glucose concentration, also results in increased hunger, greater food intake, and heightened palatability of sweet food [169].

MetS and insulin resistance is associated with an increased risk of frailty [19; 161; 220], increased risk of periodontitis [21], increased systemic inflammation and reduced lung function [105], increased risk of cognitive dysfunction and dementia [144], increased risk of cardiovascular events – even independent from T2DM [175], and an increased risk of a range of cancers including endometrial cancer [172], pancreatic cancer [79; 174], colorectal cancer [79; 174] and breast cancer [79].

1.3. Food Processing and its Importance for Treating Metabolic Diseases

Considering that the rate of obesity and T2DM began rising drastically at the same time the new dietary guidelines advocated replacing dietary fat with carbohydrates, one might draw the conclusion that carbohydrates are the new enemy and attribute the rise in metabolic diseases to this specific macronutrient. Indeed, many attribute the rise in metabolic diseases to

increased consumption of carbohydrates [102], reflected by the fact that low-carbohydrate diets are among the most studied eating patterns for dealing with T2DM and excess weight [46]. However, dietary fat was replaced with mostly refined carbohydrates, which is very different from carbohydrates occurring in its natural form (whole foods). Refined, processed carbohydrates have a higher carbohydrate density and more rapid absorption than their unprocessed counterparts due to a higher nutrient concentration being available as soon as the food reaches the small intestines, leading to higher blood glucose and insulin spikes and even adverse bacterial growth in the small intestines [190; 225]. Processed carbohydrates cause more insulin secretion, calorie for calorie, than any other food, and are consistently associated with the most weight gain in cohort studies [142]. It is indeed important to consider the amount of processing involved when looking for a "dietary root cause" to the epidemic of metabolic diseases we have today. The next paragraphs will therefore try to explain the link between food processing, intact cell structures with whole foods and proxy measurements for this such as carbohydrate density and GI/GL, and its importance in designing a dietary intervention for treating metabolic diseases such as T2DM and MetS.

Carbohydrate density is a term describing the amount of carbohydrates that are available in food [190]. It is similar to glycemic index (GI) - how high your blood sugar rises after consumption, and glycemic load (GL) – multiplying the GI of a food by the grams of carbohydrates in that food [119], but they do not necessarily correlate with one another. The main difference is that carbohydrate density makes the distinction between cellular and acellular carbohydrates, terms coined by Ian Spreadbury [190]. Cellular carbohydrates have most of their cell walls intact when the food reaches the small intestines, slowing the digestion and keeping the nutrients unavailable from the bacteria that resides there [58]. The nutrients remain "locked in" until most of the cell walls are breached by digestive processes, while some cells pass through to be digested by bacteria in our large intestines [190]. Acellular carbohydrates are similar to refined or processed carbohydrates. These do not have their cell walls intact (e.g. flour, sugar) and will influence human absorption kinetics due to a higher nutrient concentration [8; 59; 147], leading to increased insulin and glucose spikes while also adversely feeding bacterial growth in the small intestines [58; 159; 190; 194]. Crucially, cell walls are thought to remain mostly intact when cooking [145]. A master thesis examining the effects of processing on structural and cellular damage shows this directly; unprocessed and boiled food had approximately 100% intact cellular structure (reduced by around 20% through chewing), and a relationship between an increased processing degree and

decreased percentage of intact cells were identified [185]. Intensely processed foods like flours had such an extensive structural damage that no intact cell structures were found in the samples [185] – and would by definition be classified as an acellular, high-GI/GL, high carbohydrate density food.

For context: cellular carbohydrates, like root tubers, fruits, leaves and stems, can have a carbohydrate density of up to 23 percent. Acellular, processed carbohydrates like flour, sugar, and even whole grains, have a carbohydrate density as high as 75 percent [190]. Foods with a low carbohydrate density also has a relatively low/medium GI and GL, on average. There are some exceptions to this; a potato has a high GI and GL, similar to white bread in fact [119]. Low GI < 55, medium GI = 56-69, high GI > 70, commonly reported in percent, where white bread is 100 for reference. Low GL < 10, medium GL = 11-19, high GL > 20, commonly reported in grams per food [119]. Carbohydrate density, GI and GL tells us something about the degree of processing in the diet. One measurement might be better than the other, and each of them has their flaws, but a low to medium GI/GL diet will look similar to a whole foods/minimally processed diet with mostly intact cell walls when they enter the upper gastrointestinal tract. Whole grains might be an exception to this [225]. Even though they are generally medium GI/GL, whole grains have seen mixed results from studies, and nutrition experts often disagree on their health benefits. This might be due to the extrusion process that most cereal grains undergo, where high heat and pressure leads to several chemical and physical changes to the grain, including inactivation of endogenous enzymes and mechanical damage to the cell walls. Whole, untreated grains and whole grains treated with the extrusion process might act very differently on our gastrointestinal tract even though the fiber content is the same and both are regarded as whole foods [225]. For example, pigs that were fed extruded grains had a less diverse and beneficial microbiota composition than pigs fed untreated grains [136].

Studies on GI/GL report that a high-GI/GL meal would limit the availability of metabolic fuels in the late postprandial period (3-5 hours after eating) which promotes excessive food intake, decreased fat oxidation, lower energy expenditure, and stimulate stress hormone secretion [119; 120; 189; 207]. Low-GI diets leads to increased satiety and decreased hunger [118], reflected in two major trials that used special measures to improve compliance which found greater weight loss on a low-GL vs. high-GL diet [97; 182]. Reducing GL appears to attenuate the biological adaptations antagonizing weight loss, such as decreased energy

expenditure [44; 160], and produces increased weight loss in individuals with high insulin secretion [43].

The proposed mechanisms behind these findings are that within the first 2 hours, a high-GI/GL produces incremental blood glucose concentrations that can be at least twice that of a low-GI/GL meal containing identical nutrients and energy [119]. This stimulates a high insulin-to-glucagon response, promoting uptake of circulating fuels from the blood by insulin-responsive tissues, stimulation of glycogenesis (glycogen production) and lipogenesis (fatty acids production), and suppression of gluconeogenesis (glucose production) and lipolysis. Between 2 to 4 hours after eating a high-GI/GL meal, nutrient absorption from the gastrointestinal tract declines, but the biological effects of the high insulin-to-glucagon ratio persists. Blood glucose levels proceeds to fall rapidly, often into the hypoglycemic range. 4 to 6 hours after eating (late postprandial period), the low circulating concentration of metabolic fuels trigger a counterregulatory hormone response that restores normal blood sugar by stimulating glycogenolytic and gluconeogenic pathways, elevating free fatty acid concentrations – resembling a fasted state only reached after many hours without food. By contrast, a low-GI/GL meal would not produce these cascades in the late postprandial period owing to continued nutrient absorption from the gastrointestinal tract and hepatic glucose output [119]. From this perspective, resisting hunger and adhering to a diet to attenuate metabolic abnormalities isn't just a matter of discipline, but rather a biological problem involving how our bodies distribute the calories we consume. The carbohydrate-insulin model referenced below also tries to explain this perspective.

Ultra-processed foods (UPF's), or processed food which are less severe in terms of processing but often used interchangeably, are industrial formulations made entirely or mostly from substances extracted from foods (oils, fats, sugar, starch, and proteins), derived from food constituents (hydrogenated fats and modified starch), or synthesized in laboratories from food substrates or other organic sources [129]. Products include burgers, frozen pasta, pizza and pasta dishes, nuggets and sticks, crisps, biscuits, confectionery, cereal bars, carbonated and other sugared drinks, and various snack products [138]. UPF and processed food, introduced with the industrialized food system, is one of the hallmarks of a Western diet and is linked to a wide variety of non-communicable diseases [13; 14; 34; 130; 131; 138]. The risk of developing T2DM increases gradually with the consumption of UPF's such that each 10% increase in UPF consumption increases the risk significantly, which is especially alarming considering several high-income countries get over 50% of their daily energy intake from

UPF's [103]. European and Latin American countries reportedly get 25-60% of their daily energy intake from UPF's according to nationwide food surveys [191]. UPF also predicts dietary quality in populations [116; 125; 141], meaning dietary patterns based on UPF constitutes a low quality diet and is associated with one or more negative health outcomes [77].

Flour, for instance, is a processed carbohydrate source available through the milling of grains and has a very high GI/GL due to the cell wall rupturing, leaving the small intestines exposed to an unusually high concentration of energy [190]. Even though milling was used by pre-agriculture humans, the level of consumption of this acellular food source during the last century is unprecedented in a historical context [225]. In addition, flour is often used together with other acellular macronutrients such as extracted oils and starches to make UPF products, which has become a staple of the Western diet [225]. Food made this way is also hyper-palatable (stimulating the brain's reward system), and is in that regard very difficult to shy away from when it's a staple of nearly every grocery store [137]. Grains, originally a whole food, has now been broken down and turned into shelf-life durable, palatable, ready-to-consume products that are energy dense, has a high GL, and are low in fiber, micronutrients and phytochemicals [138]. These are also aggressively advertised by the same transnational companies that make them, with reduced prices, making low consumption of UPF's unlikely and displacement of minimally processed whole foods likely [138].

Another less severe example of a processed carbohydrate source is white rice, another grain. This food has not had any cell wall rupturing, but the protective bran around the grain consisting of fiber and other nutrients has been removed. The only thing left of the grain is the starch, without any fiber to accompany it, and the GI/GL/carbohydrate density is therefore higher. Hu et al. (2012)[70] showed a linear dose-relationship between white rice consumption and risk of T2DM in a study involving more than 350 000 subjects [204].

Tribes who live mostly free from the industrialized food system boast fasting insulin and blood glucose levels below what would be considered healthy in the western population [108; 112]. They also have lower leptin levels (a hormone produced by fat cells that regulates hunger; high concentrations are prevalent in most people that consume a Western diet due to leptin resistance) and are basically free from diabetes, atherosclerosis, and excess weight [107; 110; 111]. These people eat a 60-70E% (percentage of daily energy intake) carbohydrate diet consisting of medium GI and GL foods like tubers and fruit [49]. The food however is not processed and have mostly intact cell walls upon consumption, and as such

have a low carbohydrate density (whole foods). This explains why they can eat a carbohydrate-rich diet and still be relatively free from metabolic abnormalities. This "ancestral diet" that these tribes are eating is often referred to as a Paleolithic diet (reflecting what our ancestors ate in the paleolithic era) and has been used in nutritional interventions to great effect [83; 84; 109], likely due to stimulation of whole foods consumption since processed food was not part of our ancestors diet. In addition, transitioning to a Western diet quickly made the people originally living in one of these tribes overweight, suggesting that this is not due to genetics, but rather diet quality [112]. As UPF identified by acellular nutrients is an important predictor of diet quality, it is not far-fetched to hypothesize the following: that the industrialized processing of food that entered our food system when obesity and diabetes prevalence began rising during the low-fat era (1960s) is somehow responsible for the non-communicable disease epidemic we have today, including but not limited to MetS and T2DM.

A model that tries to explain this is the carbohydrate-insulin model. It proposes that highly refined and processed carbohydrates, such as flour and sugar, eventually causes hyperinsulinemia due to constantly stimulating high insulin secretion. This causes too much of what we eat to get stored for later use. When our storage is full, it spills over into the intra-abdominal organs and progressively shuts them down. The model forms the basis of many popular low-carbohydrate diets such as the Atkins diet, which was used to treat obesity to great effect for most of the 20th century before dietary fat was vilified. The model remains incomplete, however it is still one of the best answers for treating metabolic abnormalities such as diabetes and obesity because it eliminates processed and refined carbohydrates from the diet [50, p. 68].

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was used as a methodology and flow-chart guide for this article [152; 164]. A completed PRISMA checklist, the search string and relevant filters, and the GRADE-approach assessment can be found under Appendixes.

2.1. Data Sources

A systematic literature search of PubMed was performed to identify randomized controlled trials (RCTs) studying the effects of any kind of dietary intervention on patients with T2DM or MetS. Non-alcoholic fatty liver disease (NAFLD) was included in the search due to its involvement in T2DM. The search was completed in august 2021 (approximately) with no year restriction and consisted of the following: a combination of keywords (MetS, T2DM, "impaired glucose tolerance", etc.) in title and/or abstract AND different dietary keywords (including "diet*", ketogenic, fasting, whole foods etc.) in title and/or abstract; search filters "randomized controlled trial" and "humans". The completed search string can be found under Appendixes.

2.2. Study Selection and Data Collection

RCTs identified through the search on PubMed were screened for eligibility using the following inclusion criteria: (1) study participants (patients) must have T2DM or a relevant condition including MetS, impaired glucose tolerance or NAFLD, (2) HbA1c or FPG must be measured at baseline and end of trial, and be above 6.5% or 100 mg/dl respectively, (3) intervention must be any form of dietary intervention or fasting (e.g. time-restricted feeding, intermittent fasting), (4) primary studies only. The following exclusion criteria were also applied: (1) no surgery that affects the metabolism in a significant way (e.g. bariatric surgery), and (2) studies primarily focusing on the effect of exercise or a diabetic drug were excluded. Studies only measuring FPG and not HbA1c were later excluded after the screening process (n = 12) due to the large number of studies that had to be reviewed in full-text, since this meta-analysis only had one reviewer (author). In addition, having only one glycemic measurement in the analysis makes it more manageable.

Study attributes and information about the diet interventions were collected after several full-text reviews (Table 2) by one reviewer (author) and included the following: first author, year of publication and country; trial design; intervention duration; diet information and daily intake of relevant nutrients for the comparator diets; number of patients (N); patient age; patient sex; HbA1c measured at baseline; the baseline condition of the patients; and relevant inclusion criteria as reported by the respective studies. The studies had randomized patients to an intervention diet of any kind and a control diet of any kind and reported metabolic parameters both pre- and post-intervention.

Since the lifespan of red blood cells and the hemoglobin protein is a little over 3 months on average [50, p. 34], crossover trials not utilizing a washout period had only their first period used in the analysis to avoid the carry-over effect. An exception to this was crossover trials combining both study periods, and crossover trials where the authors reported no carry-over effects. Data from per-protocol analysis was always used when available instead of intention-to-treat analysis (ITT), although authors of the included studies often reported no differences between the two methods. This paper focuses on the efficacy of diets to treat metabolic abnormalities such as T2DM and MetS, and not the effect of being assigned to a dietary intervention. ITT estimates the effect of assignment, whereas per-protocol estimates the efficacy of the treatment itself (e.g. a diet) but are prone to bias [12]. In addition, outcome data reported at earlier time periods (e.g. 3 months instead of 12 months) was used in the analysis instead of the full study duration when available. Adherence to the diet is one of the biggest limitations of testing the efficacy of a dietary intervention since people generally have a hard time following a strict diet for an extended period of time, especially if the diet differs a lot from their previous eating patterns [41; 69; 72; 93; 101; 202; 221]. This is observable by the rebound effect that most long-term studies report, generally occurring after a couple of months. Guldbrand et al. (2012)[61], one of the included studies lasting for 24 months, report this effect occurring after approximately 6 months. A lack of compliance to the diet is also a major threat to the viability of a study, and a serious challenge in long-term dietary intervention studies [37]. Considering that the HbA1c test reflects your body's glucose levels over the past three months, the study outcomes reported at 3 months or longer were used in the analysis instead. In practice, this meant turning one study from a duration of 8 months down to 4 months, four studies from 12 months to 6 months, two studies from 12 months to 3 months, and one study from 24 months to 6 months. This is reported under "intervention duration" in Table 2.

2.3. Risk of Bias and Quality Assessment

A Risk of Bias-table was filled out based on the Cochrane Handbook for each included study to assess its quality. Selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases were explored for its potential impact on each study through the following domains: sequence generation and allocation concealment; blinding of participants and personnel, and other potential threats to validity; blinding of outcome assessment and other potential threats to validity; incomplete outcome data; and selective outcome reporting.

Studies were scored as unclear, low, or high risk of bias on each domain based on available information in each study. If reported information regarding a certain bias was inadequate, unclear risk of bias was used. In addition, the quality of each diet was assessed in terms of processing degree – less processing means higher quality. The rationale for this is discussed in the introduction. The degree of follow-up and support was also assessed because it can indicate how well patients adhere to their respective diets. Studies with a high-quality diet and adherence-improving measures such as strict follow-up or behavioural classes therefore differentiate themselves from other studies.

The GRADE-approach [31; 64; 184] was used as a quality assessment of the overall outcome (HbA1c reduction) in addition to personally assessing the quality of the intervention and control diets.

2.4. Data Analysis and Statistical Methods

The efficacy of dietary interventions on glycemic control (HbA1c) were assessed by pooling data from each included RCT. The effect size of the continuous variable, HbA1c, were presented as the weighted standardized mean difference (SMD) with 95% confidence intervals (CIs). Serum HbA1c values of post-treatment intervention diets were compared against the respective comparator diets, although the nature of this analysis is not a competition – any improvement is good improvement, regardless of which diet it is. A random-effects model was used when high heterogeneity was observed ($I^2 > 50\%$), which was the case in this analysis. In addition, a random-effects model distributes the weight of each study more evenly than a fixed-effects model since it gives more weight to studies with a small sample size [23]. Studies with smaller sample sizes are generally better at measuring the efficacy of a diet since it allows the investigators to implement stricter follow-up and individual adjustments, including but not limited to weight stabilization or an individual washout-period, for instance. This can help improve the patients' adherence and the validity of the results (e.g. glycemic control was improved because of the diets metabolic effect and not necessarily because of weight loss). Because this analysis includes a moderate-to-large number of studies, the sample sizes and patient characteristics in each study will vary to a large degree. A random-effects model is more appropriate in such cases [23].

Mean values, standard deviations (SD), and total number of patients who completed the study were entered into RevMan 5.4.1 (Cochrane Collaboration) for statistical analysis by one

author. When important information such as mean and SD was unavailable, the procedures of the Cochrane Handbook was used [198; 199]. In the case where mean change SD was not reported, it was calculated by following the Cochrane Handbook with an imputed correlation coefficient of 0.80. P-values of 0.05 or less were considered statistically significant. A sensitivity analysis was performed for studies where a special attention to adherence was implemented, including but not limited to strict and frequent follow-up (defined by having a follow-up or unannounced telephone call every week or biweekly for the study duration), behaviour classes, different forms of support, and/or full food provision provided by the authors – based on the observation that food provision and increased motivation leads to better adherence [139]. Frequent follow-up sessions can help keep patients motivated. Logically, these studies often had a smaller sample size since implementing measures to improve adherence is expensive and time-consuming. A sensitivity analysis was also performed where included studies had discontinued insulin therapy, or excluded patients requiring insulin therapy, to explore the possibility that insulin therapy might affect the diet intervention. Funnel plots for main analysis and subsequent sensitivity analyses were used to detect the existence of publication bias, where a symmetrical funnel plot suggests a low risk of publication bias. Forest Plots were used to display the results of the included studies which are sorted alphabetically.

For clarification, a successful remission of T2DM is defined as HbA1c < 6.5% (48 mmol/mol) [167]. For prediabetes, its HbA1c < 5.7% (39 mmol/mol). See table 1 for an overview.

3. Results

3.1. Selection of Studies

The process of searching and screening relevant studies for inclusion is displayed as a flow-chart in Figure 1. After developing a search string, a total of 652 citations were identified from PubMed. These studies were then subsequently taken through a screening of titles and abstracts. A total of 524 studies were excluded based on titles and abstracts alone. The remaining 128 studies were further screened in full-text for eligibility. After full-text screening, 77 studies were excluded due to the following reasons: HbA1c not measured, secondary study, baseline values below respective T2DM/MetS threshold, resistance exercise or diabetic drug being the primary intervention focus. 51 studies met the inclusion criteria and were included in the analysis.

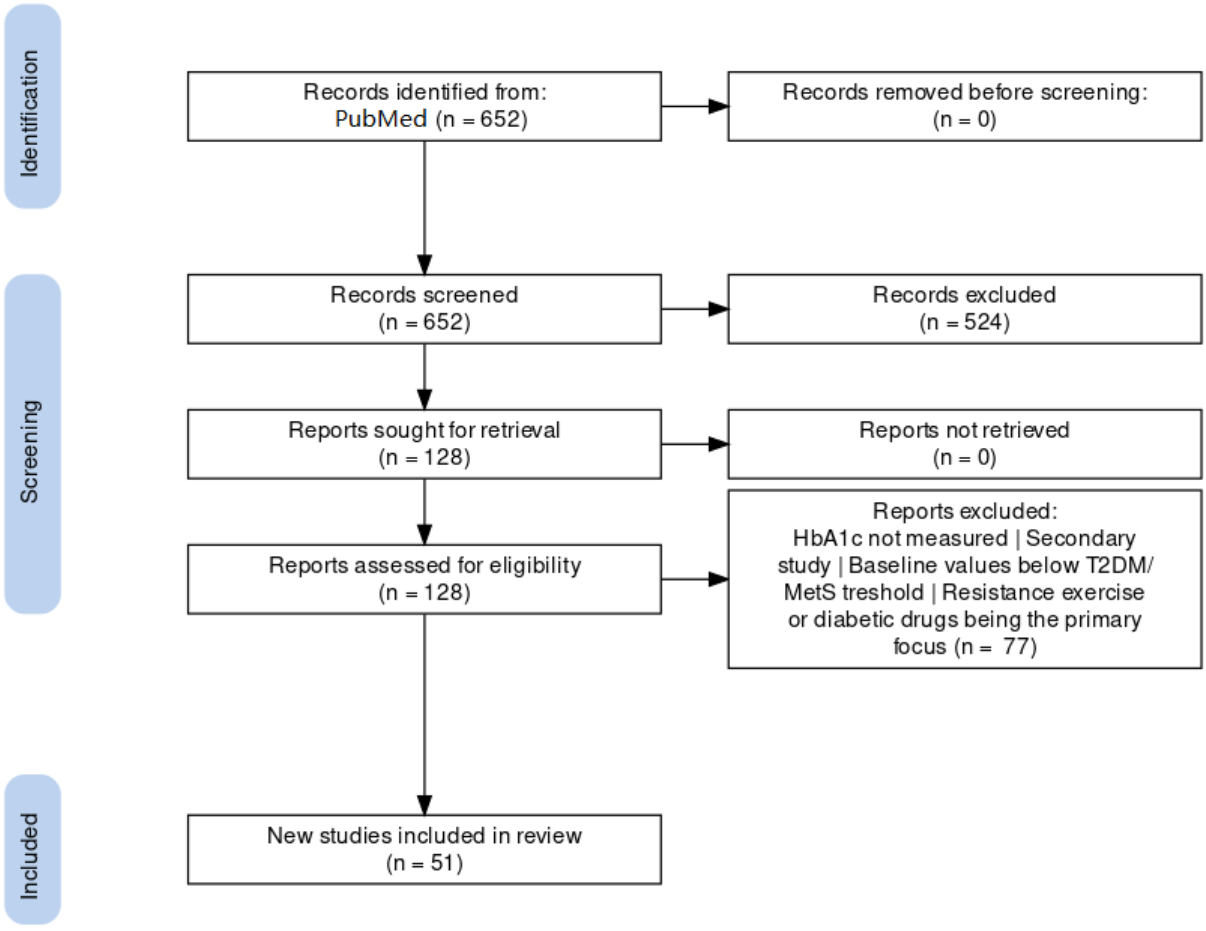

Figure 1: Study selection flow-chart. Abbreviations: T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome.

3.2. Study Characteristics

Characteristics of included studies are displayed in Table 2. In total, 46 studies included only patients with T2DM, 4 studies included only patients with MetS (exception: Bekkouche et al. (2014)[20] included patients with MetS, but with HbA1c levels of 10.3% at baseline, and should thus have been categorized as T2DM patients), and 1 study included patients with both T2DM and MetS. Most patients had a baseline comorbidity of T2DM/MetS and overweight/obesity, as the diabetic condition correlates with overweight and obesity. Study duration ranged from 3 weeks to 2 years. Intervention group patients were assigned to a variety of diets, the most frequent being various forms of low-carbohydrate and low-GI/GL diets, high-fiber diets, very-low carbohydrate ketogenic diets, and low-fat diets. The control group patients typically received some form of low-fat diet, and/or a diet based on the diabetes guidelines of the respective country where the study was conducted (e.g. American Diabetes Association[ADA]). These regular, guidelines-inspired diets are often low-fat diets. Almost every control diet was hypocaloric since organizations such as the ADA and IDF recommends it.

Table 2: Characteristics of included studies.

Study (country)	Trial Design	Intervention Duration	Diet (relevant daily intake/information)	N	Age, Mean ± SD (years)	Male, N (%)	HbA1c, Mean ± SD (%)	Baseline Condition	Inclusion Criteria
Alfawaz 2018 (Saudi-Arabia) [5]	2-centre, randomized controlled trial	12 months (month 6 used in analysis)	I: intensive lifestyle management (fat < 30E%, fiber 15g/1000kcal, less processed carbs)	73	43.4 ± 7.8	22 (16.1)	5.8 ± 0.4	MetS	FPG: 5.6-6.9 mmol/L
			C: general diabetic advice	85	42.3 ± 11.2	21 (17.9)	5.6 ± 0.5		
Andrews 2011 (England) [9]	Multicentre, parallel-group randomized controlled trial	12 months (month 6 used in analysis)	I: intensive diet (UK dietary guidelines inspired, low fat, 5-10% weight loss)	246	60.1 ± 10.2	158 (64.3)	6.64 ± 0.93	T2DM	Diagnosed with T2DM within the previous 5-8 months; Age > 30 years
			C: standard diet	93	59.5 ± 11.1	62 (66.7)	6.72 ± 1.02		
Barbosa-Yañez 2018 (Germany) [17]	Parallel group randomized controlled trial	3 weeks	I: very low-carbohydrate diet (<40g carbs, 1200-1500 kcal)	16	63 ± 8	5 (31.3)	6.7 ± 1	T2DM	Age: 18-79 years; T2DM
			C: low-fat diet (<30E% fat, 1200 kcal)	20		9 (45)	6.2 ± 0.6		
Barnard 2006 (US) [18]	Randomized controlled trial	22 weeks	I: low-fat vegan diet (10E% fat, high fiber, whole foods, ad libitum)	49	56.7 ± 11.8	22 (45)	8.0 ± 1.1	T2DM	FPG > 6.9 mmol/L OR Prior diagnosis of T2DM with hypoglycemic meds >= 6 months
			C: regular diet (ADA, 500-1000 kcal deficit)	50	54.6 ± 13.3	17 (34)	7.9 ± 1.0		
Bekkouche 2014 (Algeria) [20]	Randomized controlled trial	12 weeks	I: mediterranean diet (300 caloric deficit, 43g fiber, 41E% carbs)	36	56 ± 8 (pre-dropout)	3 (8.3)	10.3 ± 3.8	MetS	3 or more MetS criteria (FPG > 110mg/dl)
			C: healthy controls	18	48 ± 6	5 (27.8)	6.0 ± 3.1		

Brown 2020 (England) [24]	Prospective, parallel-group, non-blinded randomized clinical trial	12 months	I: total dietary replacement (600 kcal the first 12 weeks, thereafter 1000-1200 kcal)	45	58.5 ± 10.4	20 (44.4)	8.7 ± 1.7	T2DM	T2DM and obesity treated with insulin
			C: caloric restriction (600 kcal deficit)	45	56.1 ± 10	19 (42.2)	9.3 ± 1.7		
Carter 2018 (Australia) [29]	Parallel-group, randomized clinical trial	12 months	I: intermittent energy restriction 5:2 (500 kcal, 2 days/week)	46	62 ± 8.8	49 (50.5)	7.2 ± 1.2	T2DM	Age >= 18 years; BMI >= 27; T2DM
			C: continuous energy restriction (1200-1500 kcal/day)	51			7.5 ± 1.4		
Corley 2018 (New Zealand) [33]	Non-blinded, parallel-group, randomized controlled trial	12 weeks	I: Non-consecutive fasting 5:2 (ad libitum:800 kcal)	19	58 ± 8	11 (57.9)	8.2 ± 1.3	T2DM	Age > 18 years; HbA1c: 6.7-10%; BMI: 30-45
			C: Consecutive fasting 5:2 (ad libitum:800 kcal)	18	62 ± 8.3	11 (61.1)	8.4 ± 1.8		
Daly 2005 (England) [39]	Multicentre, randomized controlled trial	12 weeks	I: hypocaloric low-carbohydrate diet (33.5E% carbs, 1300 kcal/day)	51	58.2 ± 11.1	25 (49)	9 ± 1.4	T2DM	BMI >= 30 kg/m^2; HbA1c: 8-12%; Serum creatinine < 150 µmol/l
			C: hypocaloric low-fat diet (32.9E% fat, 1400 kcal)	51	59.1 ± 10.6	24 (47)	9.1 ± 1.2		
Davis 2009 (US) [40]	Non-blinded, two-arm, randomized clinical trial	12 months (month 3 used in the analysis)	I: hypocaloric low to moderate-carbohydrate diet (from 25g to 24E% carbs, 1600-1800 kcal)	55	54 ± 6	10 (18.2)	7.5 ± 1.5	T2DM	Age > 18 years; BMI >= 25 kg/m^2; HbA1c: 6-11%; T2DM for at least 6 months
			C: hypocaloric low-fat diet (25E% fat, 1600-1800 kcal)	50	53 ± 7	13 (26)	7.4 ± 1.4		

Elhayany 2010 (Israel) [45]	Prospective randomized clinical trial	12 months	I: low-carbohydrate mediterranean diet (35E% carbs, 30g fiber, low-GI)	61	55.5 ± 6.5	31 (50.8)	8.3 ± 1	T2DM	Age: 30-65 years; BMI: 27-34 kg/m^2; HbA1c: 7-10%; TG: 1.8-4.5 mmol/l; Creatinine < 123.2 µmol/l; No change in diabetic medication for 3 months
			C: regular diet (ADA, 50-55E% carbs, 15g fiber)	55	56 ± 6.1	27 (49.1)	8.3 ± 0.8		
Fabricatore 2011 (US) [47]	Single-site, parallel-group, randomized clinical trial	10 months	I: hypocaloric low-glycemic load diet (1200-1800 kcal)	40	52.8 ± 1.4	8 (20)	6.6 ± 0.2	T2DM	Age: 18-65 years; BMI: 27-45 kg/m^2
			C: hypocaloric low-fat diet (<=30E% fat, 1200-1800 kcal)	39	52.5 ± 1.3	8 (20.5)	7 ± 0.2		
Gannon 2004 (US) [51]	Randomized clinical crossover trial (5 week washout)	5x5 weeks	I: high-protein low-biologically-available-glucose diet (20E% carbs, 36g/day fiber, weight stabilized)	8	63.3 ± 7.8	8 (100)	9.6 ± 0.7	T2DM	T2DM criteria of FPG > 105 mg/dl (NDDG)
			C: regular diet (50E% carbs, 24g/day fiber, starchy foods, weight stabilized)	8					
Gannon 2011 (US) [52]	Randomized clinical crossover trial (5-12 week washout)	5x5 weeks	I: high-protein low-biologically-available-glucose diet (30E% carbs, weight-stable caloric intake)	8	61 ± 5.9	8 (100)	8.8 ± 5.7	T2DM	T2DM criteria of FPG > 105 mg/dl (NDDG)
			C: regular diet (AHA, 50E% carbs, weight-stable caloric intake)	8					

Gerhard 2004 (US) [56]	Randomized clinical crossover trial (6-12 week washout)	6x6 weeks	I: ad libitum low-fat high-fiber diet (60E% carbs, 36g fiber)	11	50.4 ± 4.8	3 (27.3)	6.8 ± 1	T2DM	T2DM treated with OHA's and/or diet
			C: ad libitum high-monounsaturated fat diet (45E% carbs, 25g fiber, more processed carbs)	11					
Goday 2016 (Spain) [57]	Prospective, open-label, multi-centric, parallel-group randomized clinical trial	16 weeks	I: very low calorie ketogenic diet (until achieved weight loss target, thereafter 1500-2200 kcal)	45	54.89 ± 8.81	15 (33.3)	6.89 ± 1.06	T2DM	Age: 30-65 years; BMI: 30-35 kg/m^2
			C: caloric restriction (45-60E% carbs, 500-1000 kcal deficit)	44	54.17 ± 7.97	16 (36.4)	6.88 ± 1.03		
Guldbrand 2012 (Sweden) [61]	Prospective, parallel-group, randomized clinical trial	24 months (month 6 used in analysis)	I: low-carbohydrate diet (20E% carbs, 1600-1800 kcal)	30	61.2 ± 9.5	14 (46.7)	7.5 ± 3.1	T2DM	T2DM diagnosis treated with diet and/or medication
			C: low-fat diet (55-60E% carbs, 1600-1800 kcal)	31	62.7 ± 11	13 (41.9)	7.2 ± 2.9		
Itsiopoulos 2010 (Australia) **[76]**	Randomized clinical crossover trial (no washout, periods merged)	12x12 weeks	I: ad libitum mediterranean diet (44E% carbs, 36g fiber, 2200 kcal)	27	59 ± 7.5	16 (59.3)	7.1 ± 6.3	T2DM	Well-controlled T2DM
			C: regular diet (21g fiber, 1800 kcal)						
Jalilvand 2020 (Iran) **[78]**	Single-blind, parallel-group, randomized clinical trial	8 weeks	I: low-fructose diet (8g fructose, 2000 kcal)	20	53 ± 7.96	8 (40)	7.33 ± 1.23	T2DM	Age: 40-70 years; BMI: 18.5-30 kg/m^2
			C: regular diet (25g fructose, 2000 kcal)	20	53.03 ± 7.38	8 (40)	7.72 ± 1.25		

Jenkins 2012 (Canada) **[80]**	Parallel-group, randomized clinical trial	12 weeks	I: low-glycemic load legume diet (25g/1000kcal fiber)	60	58 ± 9.9	32 (53)	7.4 ± 0.8	T2DM	HbA1c: 6.5-8.5%; T2DM for 6 months; Stable OHA dose for 2 months.
			C: wheat fiber diet (18g/1000kcal fiber, acellular fiber source)	61	61 ± 7.8	29 (48)	7.2 ± 0.8		
Jimenez-Cruz 2003 (Mexico) **[82]**	Randomized clinical crossover trial (6 week washout)	6x6 weeks	I: hypocaloric low-glycemic index diet (34g fiber, 86 GL, 1500 kcal)	14	59 ± 9	6 (42.9)	8.5 ± 1.05	T2DM	BMI > 25 kg/m^2; T2DM (HbA1c > 6.5%)
			C: hypocaloric high-glycemic index diet (25g fiber, 139 GL, 1600 kcal)				8.6 ± 1.12		
Jönsson 2009 (Sweden) **[83]**	Randomized clinical crossover trial (first period only due to carry-over effect)	12x12 weeks	I: paleolithic diet (1550 kcal)	13	64 ± 6	10 (76.9)	6.6 ± 0.6	T2DM	C-peptide > 0; HbA1c > 5.5%; Creatinine < 130 µmol/L; Stable weight and medication use for 3 months
			C: regular diet (ADA, 1900 kcal)						
Kahleova 2010 (Czech Republic) **[86]**	Open-label, parallel-group, randomized controlled trial	24 weeks	I: hypocaloric vegan diet (60E% carbs, 500 kcal deficit)	37	54.6 ± 7.8	17 (46)	7.6 ± 1.4	T2DM	Age: 30-70 years; HbA1c: 6-11%; BMI: 25-53 kg/m^2
			C: hypocaloric regular diet (50E% carbs, 500 kcal deficit)	37	57.7 ± 4.9	18 (49)	7.7 ± 1.2		
Kunduraci 2020 (Turkey) **[95]**	Randomized controlled trial	12 weeks	I: intermittent energy restriction (25% energy restriction, 16:8 IF)	32	47.44 ± 12.28	16 (50)	6.56 ± 1.75	MetS	Age: 18-65 years; BMI > 27 kg/m^2; MetS
			C: continuous energy restriction (25% energy restriction)	33	48.76 ± 12.24	15 (45.5)	6.41 ± 1.44		

Larsen 2011 (Australia) [96]	Single-centre, parallel-group, randomized controlled trial	12 months (month 3 used in analysis)	I: hypocaloric high-protein diet (40E% carbs, 30E% protein, 30% energy reduction)	53	59.6 ± 7.6	30 (57)	7.89 ± 0.9	T2DM	Age: 30-75 years; BMI: 27-40 kg/m^2; HbA1c: 6.5-10%
			C: hypocaloric high-carbohydrate diet (55E% carbs, 30% energy reduction)	46	58.8 ± 9.7	18 (39)	7.78 ± 0.9		
Lee 2016 (Korea) [99]	Open-label randomized clinical trial	12 weeks	I: ad libitum vegan diet (1500 kcal, 34g fiber, unprocessed food)	46	57.5 ± 7.7	6 (13)	7.7 ± 1.3	T2DM	Age: 30-70 years; HbA1c: 6-11%; use of OHA >= 6 months
			C: ad libitum regular diet (KDA, 1560 kcal, 25g fiber)	47	58.3 ± 7	12 (25.5)	7.4 ± 1		
Li 2017 (Germany) [104]	Randomized controlled pilot trial	16 weeks	I: 7-day fast → mediterranean diet (300 kcal fasting days)	23	64.7 ± 7	NA	7.6 ± 0.7	T2DM	Age: 25-75 years; abdominal obesity; BMI > 25 kg/m^2; at least 1 of either: low HDL-C, elevated BP, hypertriglyceridemia
			C: mediterranean diet	23	65.4 ± 5.7	NA	7.8 ± 0.8		
Liu 2018 (China) [114]	Double-blind, parallel-group, randomized controlled trial	12 weeks	I: low-carbohydrate high-protein omega-3 diet (42E% carbs, weight-stable caloric intake, mostly whole foods)	31	51.9 ± 4.8	16 (51.6)	7.16 ± 0.26	T2DM	HbA1c: 6.5-7.5%; Age: 40-60 years; BMI: 18.5-23.9 kg/m^2; SPB: 90-120 mmHg; DBP: 60-90 mmHg
			C: high-carbohydrate low-protein diet (54E% carbs, weight-stable caloric intake, less whole foods)	30	49.7 ± 5.4	15 (50)	7.10 ± 0.25		

Luger 2013 (Austria) [121]	Randomized controlled trial	12 weeks	I: high-protein caloric restriction (40E% carbs, 30E% protein, 1300 kcal, very similar to C)	22	61 ± 5.7	14 (63.6)	7.8 ± 1.4	T2DM	T2DM patients on insulin therapy
			C: standard-protein caloric restriction (55E% carbs, 15E% protein, 1300 kcal, very similar to I)	22	63.7 ± 5.2	6 (27.3)	7.6 ± 0.9		
Ma 2008 (US) [122]	Randomized controlled trial	12 months (month 6 used in analysis)	I: low-glycemic index diet (78 GI, 97 GL, 35E% carbs, 1370 kcal)	19	53.5 ± 8.4	8 (42.1)	8.1 ± 1.2	T2DM	HbA1c >= 7%; Age >= 21 years; T2DM diagnosis
			C: regular diet (80 GI, 140 GL, 38E% carbs, 1700 kcal, ADA)	21		11 (52.4)	8.7 ± 1.3		
Masharani 2015 (US) [126]	Randomized controlled outpatient trial	3 weeks	I: paleolithic diet (3000 kcal, weight-stable)	14	58 ± 8	NA	7.3 ± 2.1	T2DM	Age: 50-69 years; T2DM diagnosis
			C: regular diet (ADA, 3000 kcal, weight-stable)	10	56 ± 13	NA	7 ± 1.5		
Medina-Vera 2019 (Mexico) [128]	Placebo-controlled, single-centre, double-blind, randomized clinical trial	12 weeks	I: hypocaloric high-fiber diet (500 kcal deficit, 30g fiber, 50E% carbs, fiber and protein supplement)	28	50.4 ± 8.7	8 (32)	7.5 ± 1.3	T2DM	Age: 30-60 years; BMI: 25-39.9 kg/m^2; T2DM for 1-7 years
			C: placebo diet (same as I-diet, except the supplement which was a placebo)	25	49.8 ± 10.6	11 (45.8)	6.9 ± 1		

Michalczyk 2020 (Poland) [134]	Randomized clinical trial	12 weeks	I: low-calorie ketogenic diet (20% caloric deficit, 8E% carbs)	50	42 ± 7	0 (0)	5.87 ± 0.94	MetS	BMI > 25 kg/m^2; Age: 30-60 years; glucose > 5.5 mmol/L; insulin > 10 uU/mL
			C: regular western diet (50E% carbs, processed energy-dense food)	50	41 ± 6	0 (0)	5.86 ± 0.60		
Miller 2011 (US) [135]	Parallel-group, randomized clinical trial	5 weeks	I: six-serving low-glycemic index diet	15	49.6 ± 6.7	6 (40)	8.84 ± 1.8	T2DM	Age: 40-65 years; HbA1c >= 7%; T2DM >= 1 year
			C: eight-serving low-glycemic index diet	20	52.6 ± 5.9	6 (30)	8.86 ± 1.8		
Morris 2020 (UK) [140]	Randomized controlled feasibility trial	12 weeks	I: low-carbohydrate diet (26E% carbs, 800-1000 kcal)	21	69 ± 10	12 (57)	7.9 ± 3.5	T2DM	BMI > 30 kg/m^2; T2DM
			C: regular diet (UK diabetes diet)	12	64 ± 13	3 (25)	7.4 ± 2.9		
Nowotny 2015 (Germany) [148]	Parallel-group, randomized controlled feasibility trial	8 weeks	I: L-Risk high-fiber diet (300 kcal deficit, 30g fiber – mostly acellular)	17	55 ± 7	8 (47)	6.5 ± 0.4	T2DM	Age: 18-69 years; BMI >= 30 kg/m^2; T2DM for <= 5 years
			C: H-Risk low-fiber diet (300 kcal deficit, < 10g fiber)	20	53 ± 10	9 (45)	6.3 ± 0.7		
Otten 2017 (Sweden) [150]	Single-blind, randomized controlled trial	12 weeks	I: paleolithic diet (ad libitum, 1700 kcal, 23g fiber, 1700 REE)	15	60 ± 8.1	10 (66.6)	7.1 ± 0.6	T2DM	BMI: 25-40 kg/m^2; Age: 30-70 years; weight stable for 6 months
			C: paleolithic diet with resistance training (ad libitum, 1000 kcal, 14g fiber, 1700 REE)	14	61 ± 5.9	9 (64.3)	7.3 ± 0.6		

Pavithran 2020 (India) [157]	Prospective randomized controlled trial	24 weeks	I: low-glycemic index diet (calorie-matched with C, whole-grain cereals)	18	52 ± 7.7	9 (50)	8.28 ± 0.91	T2DM	Age: 35-65 years; HbA1c: 7-10%; unchanged medication for 3 months
			C: regular diet (calorie-matched with I, more processed food)	18		12 (67)	8.18 ± 0.98		
Pearce 2011 (Australia) [158]	Randomized controlled trial	12 weeks	I: high-protein high-cholesterol diet (30% energy restriction, 2 eggs)	31	59.8 ± 8.4	13 (41.9)	7 ± 1	T2DM	Age: 20-75 years; BMI: 25-40 kg/m^2; HbA1c < 9%
			C: high-protein low-cholesterol diet (30% energy restriction, lean protein)	34	59.1 ± 8	16 (47)	7 ± 1		
Ramal 2018 (US) [166]	Mixed-method, experimental, randomized controlled pilot trial	6 months	I: high-fiber diet with support courses (13g fiber)	17	53.35 ± 6.74	4 (23.5)	8.53 ± 1.7	T2DM	HbA1c > 6.5%
			C: low-fat diet with no support courses (11g fiber)	15	52.93 ± 13.11	3 (20)	9.57 ± 1.7		
Rock 2014 (US) [168]	Two-centre, parallel-group, randomized controlled trial	12 months (month 6 used in analysis)	I: hypocaloric low-carbohydrate diet (1200-2000 kcal, 45E% carbs)	77	57.3 ± 8.6	40 (52)	7.3 ± 1.4	T2DM	Age >= 18 years; BMI: 25-45 kg/m^2; T2DM
			C: universal care (500-1000 kcal deficit, 55E% carbs)	76	56.8 ± 9.3	32 (42.1)	7.4 ± 1.1		

Saslow 2014 (US) [178]	Single-site, parallel-group, randomized clinical pilot trial	12 weeks	I: low-carbohydrate ketogenic diet (ad libitum, 20-50g carbs excluding fiber)	16	64.8 ± 7.7	7 (43.8)	6.6 ± 0.3	T2DM / MetS	Age > 18 years; HbA1c > 6%; BMI > 25 kg/m^2
			C: hypocaloric moderate-carbohydrate diet (ADA, 500 kcal deficit, 45E% carbs)	18	55.1 ± 13.5	2 (11.1)	6.9 ± 0.7		
Saslow 2017 (US) [179]	Parallel-group, online randomized clinical trial	32 weeks (week 16 used in analysis)	I: low-carbohydrate ketogenic diet (ad libitum, 20-50g carbs excluding fiber)	12	53 ± 10.2	6 (50)	7.1 ± 0.4	T2DM	Age > 18 years; HbA1c: 6.5-9%; BMI > 25 kg/m^2; Access to internet
			C: low-fat create your plate diet (ADA, 1500 kcal, 130g carbs)	13	58.2 ± 6.7	4 (31)	7.2 ± 0.3		
Sato 2017 (Japan) [181]	Prospective, open-label, parallel-group, randomized clinical trial	6 months	I: low-carbohydrate diet (130g carbs, 1400 kcal)	30	60.5 ± 10.5	23 (76.6)	8 ± 1	T2DM	Age: 20-75 years; HbA1c > 7.5%; BMI > 23 kg/m^2
			C: caloric restriction (50-60E% carbs, 1600 kcal)	32	58.4 ± 10	24 (75)	8.3 ± 1		
Skytte 2019 (Denmark) [186]	Open-label, randomized clinical crossover trial (no washout, periods combined)	6x6 weeks	I: carbohydrate-reduced high-protein diet (30E% carbs, 2400 kcal, 32g fiber)	28	64 ± 7.7	20 (71.4)	7.6 ± 0.8	T2DM	HbA1c: 6.5-11%; Age > 18 years;
			C: conventional diabetes diet (50E% carbs, 2400 kcal, 41g fiber)						
Wang 2018 (China) [209]	Prospective, single-blind, randomized controlled trial	12 weeks	I: low-carbohydrate diet (39E% carbs, 1800 kcal)	24	66.79 ± 9.12	13 (54.2)	7.43 ± 1.39	T2DM	Age > 18 years; T2DM; No change in OHA/insulin for 2 weeks
			C: low-fat diet (56E% carbs, 1750 kcal)	25	61.20 ± 11.71	13 (52)	7.79 ± 1.20		

Watson 2016 (Australia) [211]	Two-arm, parallel-group, randomized clinical trial	6 months	I: high-protein diet (33E% carbs, 30% energy reduction first 3 months)	32	54 ± 8	17 (53)	8 ± 1.3	T2DM	BMI >= 25 kg/m^2; HbA1c: 6.5-10%; Age: 18-70 years
			C: high-carbohydrate diet (51E% carbs, 30% energy reduction first 3 months)	29	55 ± 8	16 (55)	8.1 ± 1.5		
Wolever 2008 (Canada) [214]	Randomized controlled trial	12 months	I: low-carbohydrate diet (2000 kcal, 39E% carbs, 110 GL, 59 GI)	54	58.6 ± 8.8	25 (47)	6.1 ± 0.9	T2DM	FPG >= 7 mmol/L; Age: 35-75 years; BMI: 24-40 kg/m^2; HbA1c <= 130% of the upper limit of normal
			C: low-glycemic index diet (1800 kcal, 52E% carbs, 133 GL, 55 GI)	56	60.6 ± 7.6	43 (66)	6.2 ± 0.8		
Yamada 2014 (Japan) [216]	Single-centre, comparative, two-arm, open-label, randomized clinical trial	6 months	I: low-carbohydrate diet (70-150g carbs, ad libitum, 1600 kcal reported at study end)	12	63.3 ± 13.5	7 (58.3)	7.6 ± 0.4	T2DM	HbA1c: 6.9-8.4%; Had received caloric restriction guidance at least once
			C: caloric restriction (50-60E% carbs, 1600 kcal at study end)	12	63.2 ± 10.2	5 (41.6)	7.7 ± 0.6		
Yusof 2009 (Malaysia) [218]	Randomized controlled trial	12 weeks	I: low-glycemic index diet (1500 kcal, 50-60E% carbs, 26g fiber, 53 GI)	51	NA	NA	7.68 ± 1.13	T2DM	HbA1c < 12%; FPG < 15 mmol/L; T2DM for at least 3 months
			C: conventional carbohydrate exchange (1550 kcal, 50-60E% carbs, 11g fiber, 64 GI)	49	NA	NA	7.51 ± 1.24		

Zhao 2018 (China) **[224]**	Open-label, parallel-group, randomized clinical trial	12 weeks	I: high-fiber diet (1800-2000 kcal, 55E% carbs, 37g fiber)	27	58.4 ± 32.2	11 (40.7)	8.27 ± 1.40	T2DM	Clinically diagnosed T2DM (HbA1c > 6.5%)
			C: usual care (1800-2000 kcal, 55E% carbs, 16g fiber)	16	59.7 ± 24	7 (43.8)	8.31 ± 1.52		

Abbreviations: SD, standard deviation; I, intervention; C, control; E%, percentage of energy intake; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; BMI, body mass index; GI, glycemic index (%); GL, glycemic load (g/day); ADA, american diabetes association; KDA, korean diabetes association; NDDG, national diabetes data group; OHA, oral hypoglycemic agents; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; NA, not available.

3.3. Risk of Bias and Funnel Plot

Appraisal of the individual studies' risk of bias is reported in Figure 2. Two studies had a high risk of attrition bias due to a large amount of dropouts [20], and the attrition rate and number of patients who completed the study didn't match [179]. One study had a potentially high risk of selection bias because of inadequate random sequence generation and between-group difference in baseline values [20], however the study used healthy participants as controls. Two studies had a potentially high risk of selection bias because of inadequate allocation concealment, however both studies reported similar baseline values by the authors [128; 216]. Nine studies had a potentially high risk of other biases: crossover design with no washout period [76; 186], crossover design with reported carry-over effects [83], crossover design with a 5-week washout period only and no information about potential carry-over effects reported by the authors [51], between-group difference in HbA1c at baseline [78; 122], between-group differences in parameters such as weight, BMI and fat mass at baseline [95], between-group differences in C-reactive protein (CRP) and fasting glucose at baseline [214], between-group difference in insulin resistance at baseline [224].

The differences in baseline parameters between groups were notable (e.g. HbA1c 0.5-0.6% between-group difference), but modest, and was most likely a result of small sample sizes and not because of any selection bias. The studies not utilizing a washout period, or a washout period with an inappropriate length, did not report any information about potential carry-over effects. The exception to this was Itsiopoulos et al. (2011)[76] reporting that the diet sequence did not influence the outcome and as such pooled the data into one period. Jönsson et al. (2009)[83] did report a carry-over effect due to no washout period being utilized, and because of this only the first period of that study was used in this analysis – essentially turning the crossover study into a parallel-group study with potential weaknesses (low sample size and a significant between-group difference in HbA1c at baseline – 6.2% vs 6.9% in intervention and control group respectively).

The risk of bias assessment of the included studies was generally acceptable. The funnel plot did show some asymmetry, and could therefore indicate a risk of publication bias. Most of the included studies fall in along the dotted line, however, and the deviating circles are studies who enrolled very sick diabetic patients which can explain the large reductions in HbA1c presented in the results [51; 166; 224]. The funnel plot is shown in Figure 3.

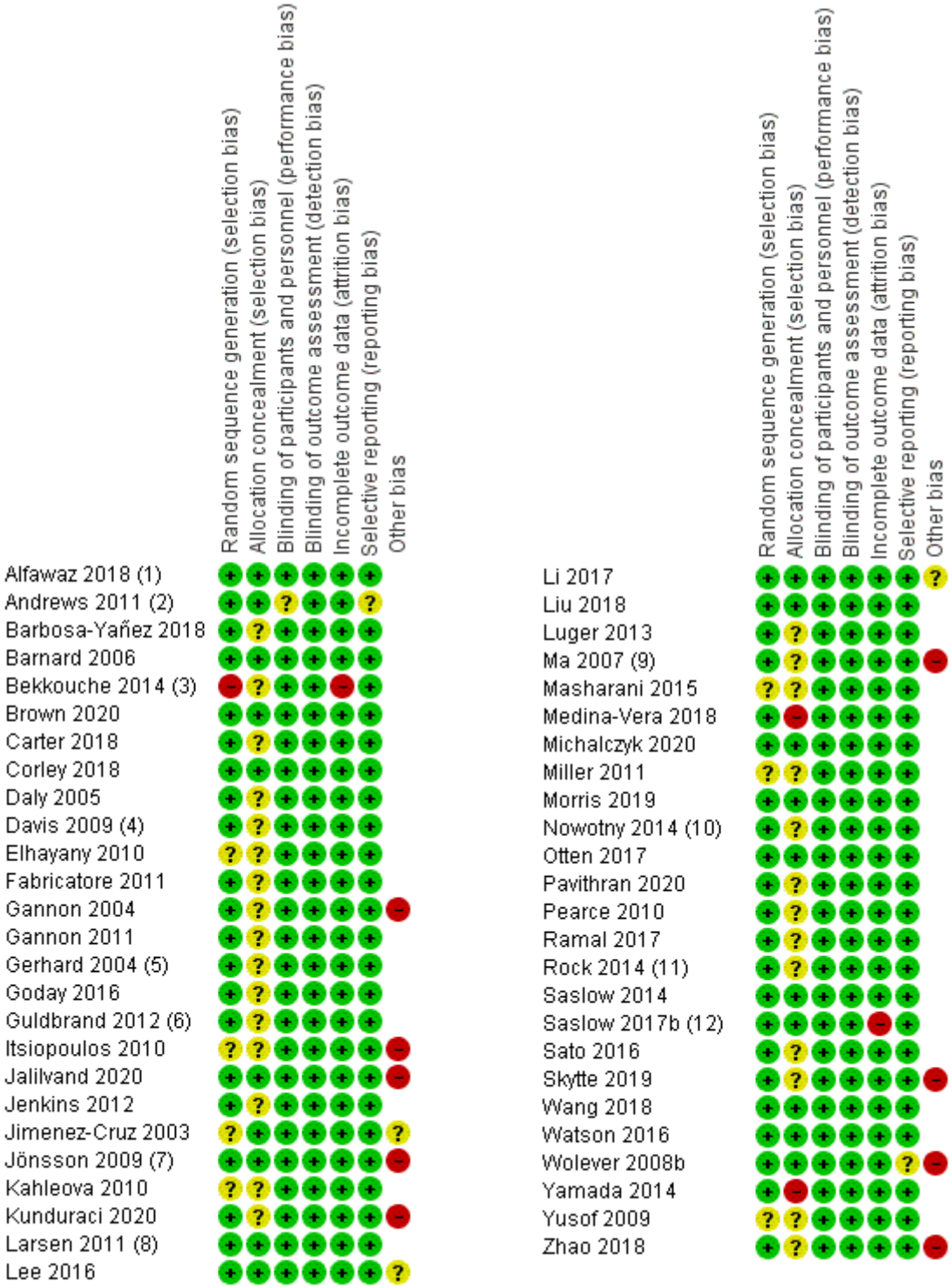

Figure 2: Risk of Bias summary.

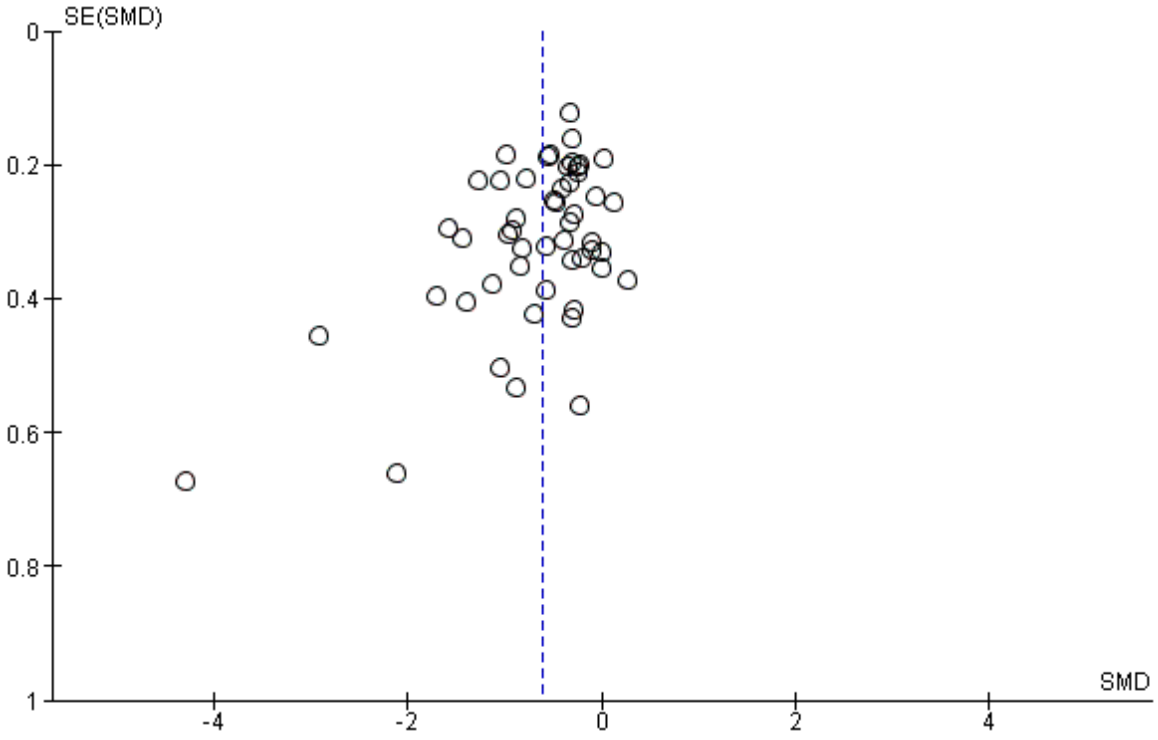

Figure 3: Funnel Plot of included studies.

3.4. The Effect of Diet on Glycemic Control

Studies of patients with T2DM and MetS were included in the same analysis as differentiating between them in a subgroup analysis did not produce significantly different results. Overall, in the main analysis (total of 3281 patients), the intervention diets appeared more effective at lowering HbA1c than the comparator diets (SMD, -0.61; 95% CI, -0.76 to -0.47; I^2 = 73%; p < 0.00001; high quality evidence) (Figure 4). However, several included studies showed significant reductions in the control group as well [18; 33; 45; 52; 57; 83; 96; 122; 150; 158; 179; 211; 224]. Sensitivity analysis of studies excluding insulin therapy, and studies who put extra emphasis on adherence (see page 15), were performed. Analysis of studies excluding insulin therapy showed no significant differences in HbA1c reduction compared to the main analysis (Appendix 5). Analysis of studies implementing extra measures to improve adherence (total of 1509 patients) showed a significantly greater reduction in HbA1c compared to the main analysis (SMD, -0.80; 95% CI, -1.00 to -0.59; I^2 = 70%; p < 0.00001; high quality evidence) (Figure 5). Six studies in the sensitivity analysis had a high risk of bias in one domain each [51; 76; 78; 128; 179; 186], reported under 3.3. Risk of Bias and Funnel Plot.

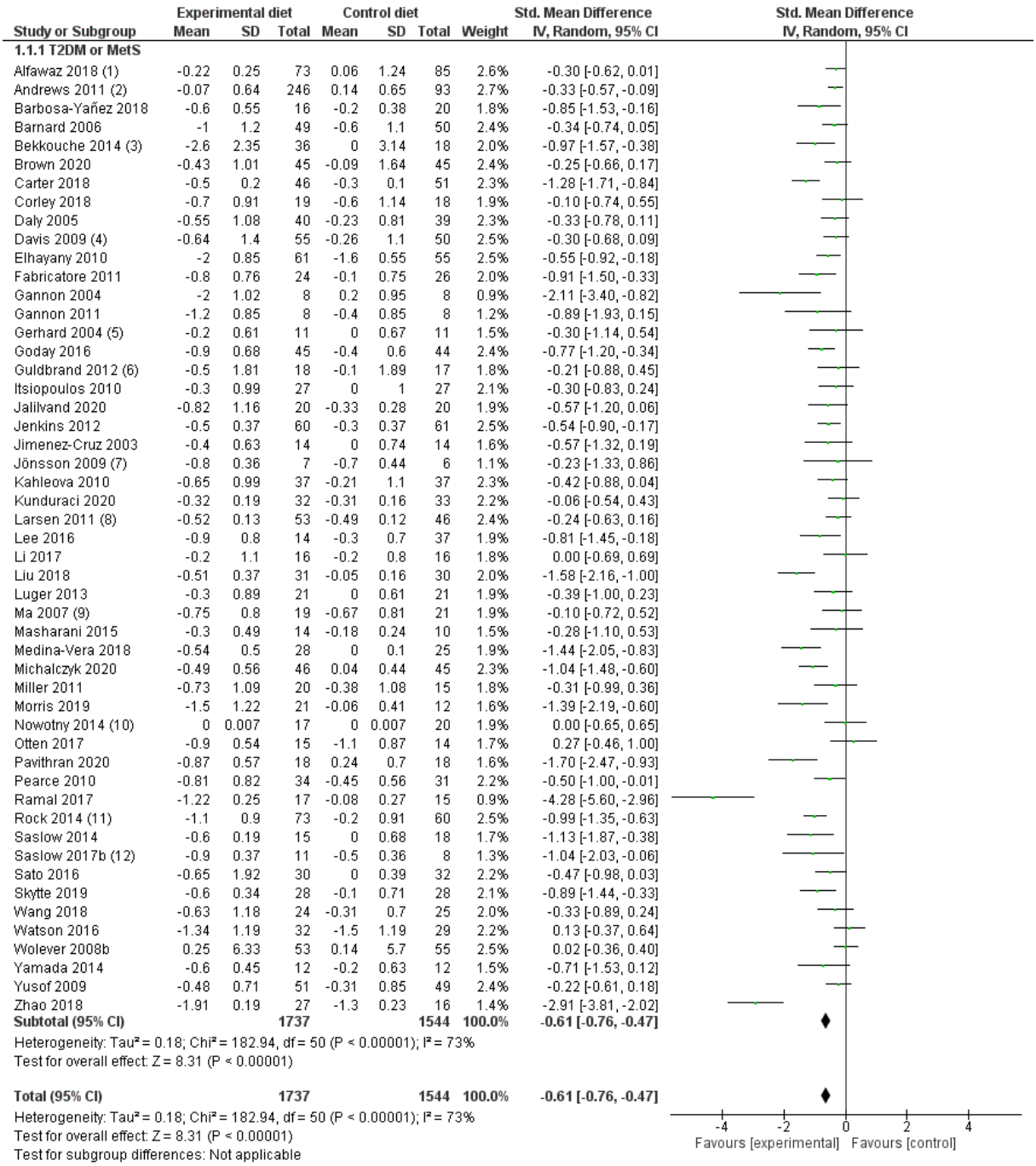

Figure 4: Forest Plot for association between glycemic control and diet in patients with T2DM and MetS. Abbreviations: T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; SD, standard deviation; CI, confidence interval; NS, non-significant.

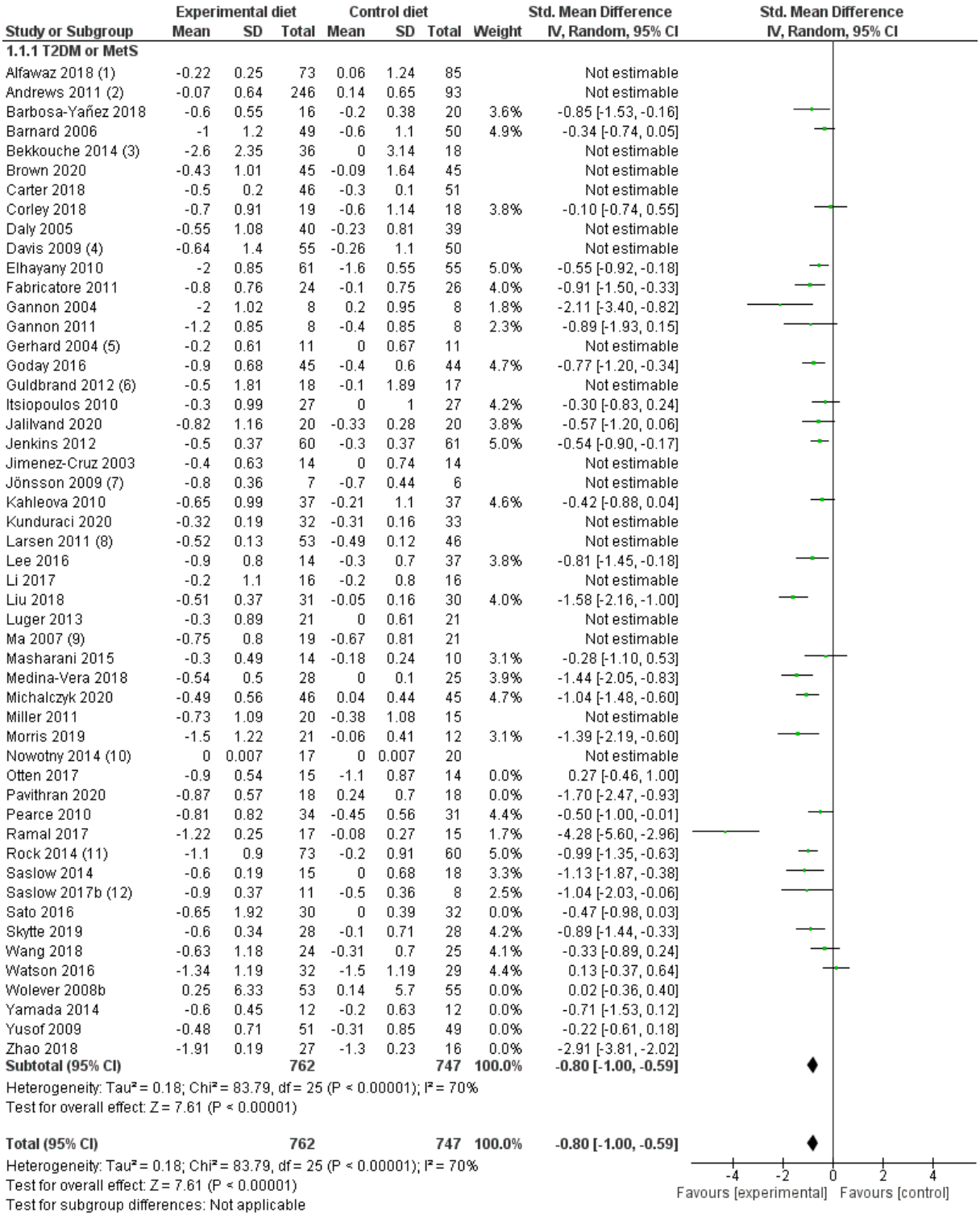

Figure 5: Forest Plot for association between glycemic control and diet in patients with T2DM and MetS in studies with improved adherence. Eligible studies indicated by the visible horizontal lines on the right side. Abbreviations: T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; SD, standard deviation; CI, confidence interval.

3.5. Remission of Type 2 Diabetes Mellitus and Prediabetes

Remission of either T2DM or MetS occurred in a number of patients in 17 out of 51 studies. Most of the respective studies achieved remission of T2DM down to HbA1c values below 6.5%, which means a regression from T2DM to prediabetes (for HbA1c diagnostic threshold values of T2DM and MetS – prediabetes, see Table 1). Hence, patients achieved remission of T2DM down to prediabetic HbA1c values in 13 out of the 17 studies [17; 45; 57; 78; 99; 140; 150; 158; 168; 178; 179; 211; 224]. The majority of these patients belonged to the intervention group, but some patients achieved remission in the control group as well [57; 150; 211]. 2 other studies out of the 17 total included patients who achieved remission of T2DM down to prediabetic and even normal HbA1c values in the intervention group [47], and in both intervention and control group [83]. These patients did not have very high baseline HbA1c values however, with a mean ± SD value of 6.6 ± 0.2 and 6.6 ± 0.6 respectively. The last 2 out of the 17 studies included patients who achieved a remission of MetS (prediabetes) down to normal HbA1c values [5; 134], however the baseline HbA1c values in these studies were just above the prediabetic threshold with a mean ± SD of 5.8 ± 0.4 and 5.87 ± 0.94 respectively.

4. Discussion

In this meta-analysis of 51 RCT's, I examined the efficacy of various diets compared to comparator diets (primarily low-fat or regular diabetic guidelines-inspired diets) on glycemic control in patients with T2DM or MetS. The diets varied considerably in design, but were primarily low-carbohydrate diets, low-GI/GL diets, and diets with a high fiber content and a small degree of processing (e.g., paleolithic diet). Four main findings were observed (1, 2, 3, 4).

These findings appear to be largely in line with other systematic reviews and meta-analysis on the subject. A systematic review and meta-analysis of different dietary approaches to the management of T2DM included 20 RCT's and reported improved glycemic control and cardiovascular markers with low-carbohydrate, low-GI, Mediterranean, and high-protein diets compared to the respective control diets [3]. Mediterranean diets achieved the largest HbA1c reduction of a mean -0.47%. Another systematic review and meta-analysis on the effect of diet and resistance exercise on T2DM prevention included 23 articles, and reported modest

glycemic improvement and weight loss in at risk and prediabetic adults [2]. This is in line with the study by Otten et al. (2017)[150], where the group that included resistance training in addition to the paleolithic diet saw greater improvement in glycemic control than the group that was limited to just the paleolithic diet. Another meta-analysis of educational and behavioural interventions for T2DM included 18 RCT's, and reported modest glycemic control improvement with a mean HbA1c reduction of -0.43% [53]. A systematic review and meta-analysis of carbohydrate restriction for T2DM [188] and a meta-analysis of dietary fiber interventions for T2DM [163] got similar results.

4.1. Main Findings

Main finding number (1): an intervention diet from 5 weeks and up to 6 months were more effective than the conventional diabetic guidelines-inspired, low-fat diets for glycemic control in patients with T2DM and MetS. Any type of intervention diet (low-carbohydrate, ketogenic, low-fat, low-GI/GL, high-fiber etc.) were able to produce desirable results as long as the diet design was good, meaning the food was mostly whole foods with a minimal degree of processing, and the patients had a good adherence to the prescribed diet. Some comparator diets also achieved significant results, atleast for a short time. The comparator diets were often hypocaloric, meaning they have the potential to induce desirable results for a limited amount of time until the body's basal metabolic rate (BMR) adjusts, and/or had a higher fiber content which can be an indicator of minimal processing degree. If the patients managed to adhere to such a diet, significant results were observed.

The ADA has begun offering guidance on low-carbohydrate and very low-carbohydrate diets instead of their typical low-fat hypocaloric strategy [46; 68]. This can be a sign that a paradigm shift has happened in the conventional diabetic guidelines treatment of T2DM and prediabetes. However, the IDF still only recommends hypocaloric diets in their report about managing the disease in primary care [73]. Still the hypocaloric low-fat comparator diets, which struggle to achieve significant results in this study, might not be an up-to-date representation of the support/treatment offered by the different diabetes organizations. The diabetic guidelines-inspired comparator diets in this analysis might have achieved significantly better results if the diets were low- or very low-carbohydrate instead of caloric restriction and/or low-fat.

Main finding number (2): the optimal study duration seemed to be around 3 months, up to a maximum of 6 months. Two major factors are potentially responsible for this. One is that the HbA1c test reflects your body's average blood glucose levels for the past 3 months, hence the minimal study duration to observe the most optimal results is around that time frame. The second factor is that people generally have a hard time adhering to a regimen that they did not choose themselves, as explained in *2.2. Study Selection and Data Collection*.

Based on the included studies in this analysis, most patients managed to adhere to the prescribed diet to a certain degree for approximately 3-4 months on average. After around 3 months, the efficacy of the prescribed diet began to fall off. Blood glucose levels began rising towards baseline values after approximately 3 months on average, referred to as a rebound effect, reflecting the possibility that the patients of the study reverted back to their normal eating habits. This is the main reason why this analysis used numbers from month 3 or 6 when available instead of the full study duration, which was 12 or 24 months typically. Every study with a duration of 12 or 24 months observed the same thing: significant improvement in glycemic control for the first 3 or 4 months, followed by a rebound effect that would, in most cases, nullify the improvements or even make it worse by the time the study was completed. The few exceptions to this were Elhayany et al. (2010)[45] and Fabricatore et al. (2011)[47] which lasted 12 months and 10 months, respectively, likely due to increased adherence through frequent follow-up.

Main finding number (3): the most effective intervention diets seemed to be low-carbohydrate diets, high-fiber (approx. 30g/day) diets such as the paleolithic diet, ketogenic diets (sometimes called a very-low carbohydrate diet) and low-GI/GL diets as they produced the largest effect sizes. Restriction of carbohydrates, which are often processed, and/or a high fiber intake mainly through vegetables and other cellular foods seems to be a design that worked consistently in this analysis. Both a higher fiber intake, the limitation of carbohydrates, and a low GI and GL can be an indicator of a minimally processed diet with mostly cellular foods. High fiber intake and low-GI/GL can also indicate foods with low energy density. Foods that are high in energy density increase energy intake while foods that are low in energy density decrease energy intake, generally [170; 171]. The intake of dietary fat and protein is also increased on most of the successful diets in this analysis. Both fiber, protein and fat intake has well-known effects on satiety, which can be essential in adhering to a diet long-term [143].

Some of the studies also had the patients eat enough calories to maintain their current weight (weight-stable). This means that the reduction in HbA1c is due to diet, and that the diet is easier to follow since the patients doesn't go hungry like on a hypocaloric diet. The same thing is true for ad libitum diets, which was used frequently, and ketogenic diets since the main ketone body produced endogenously on such a diet suppresses appetite [151; 154; 155]. Patients can eat until they feel full, like they normally do, and still improve their glycemic control. This is important because even though restricting caloric intake can improve both weight and glycemic control short-term, it reaches a plateau when the body's BMR adjusts to the new caloric intake (see next paragraph). In addition, following a hypocaloric diet is difficult as the patients feel hungry most of the time, resulting in a rebound more often than not. According to Fildes et al. (2015)[48], the failure rate of the "eat less" hypocaloric strategy for weight loss to attain or maintain normal weight is 99.4% for overweight individuals (30-35 BMI). For morbidly obese people, the failure rate is 99.9% (40-45 BMI). The best interventions are the ones that you can consistently maintain, and feeling satiated and satisfied with your diet will help immensely long-term.

Contrary to popular belief, eating less and moving more is for the most part not a consistent strategy for weight loss and metabolic health improvement. The calories in, calories out advice have been told for several decades now, and obesity and metabolic diseases are still rising. So, is the advice incorrect or is it a worldwide lack of willpower? The former seems to be the most logical choice, as people are generally strong-willed when their health is at risk due to intrinsic motivation. The body can adjust its BMR (the energy that keeps every organ and unconscious system in your body functioning) by approximately 40% [50, p. 59]. When you go on a hypocaloric diet your body senses the reduced energy intake and resultantly slows down its BMR to compensate, meaning reduced weight loss and increased hunger [92]. The body's multiple overlapping hormonal systems that signal hunger and satiety cannot be ignored by raw willpower for an extended period of time for most people, and so a hypocaloric dietary strategy is doomed to fail most of the time [50, p. 59-60].

Seen through an evolutionary lens, your body never wants to lose weight as that stored energy is vital for survival [173]. This is true even today, though our food environment is vastly different. Reducing your energy intake may lead to some brief weight loss, but it also results in a compensatory increase in hunger (e.g., through the hormone leptin), and that feeling continues until the patient gives up or the BMR adjusts to the hypocaloric energy intake after an extended period of time [15; 173]. Getting to the latter point is indeed an insurmountable

task for many people. According to Leibel, Rosenbaum, and Hirsch (1995)[100], reducing weight results in compensatory changes in energy expenditure, which oppose the maintenance of a body weight that is different from the initial weight. This, combined with the theory that the body has a "set point" of body fat that it desperately tries to defend should it change in any way, may in part explain the poor long-term efficacy of caloric restriction treatments [90].

Main finding number (4): studies with increased focus on improving adherence showed a significantly greater reduction in HbA1c compared to the main analysis (Figure 5). More frequent follow-up sessions, either in-person or by telephone, behaviour lessons, and support classes are known to increase adherence [183]. This reflects how important adherence to the prescribed diet is in dietary intervention studies. Indeed, a lack of focus on adherence by the study authors in nutritional interventions can mask the potential true effect of dietary factors on improving a variety of lifestyle diseases.

An important side-note is that measuring adherence with questionnaires that the participants fill out themselves is misleading, as people are very inaccurate when it comes to self-reporting of any kind of nutrition-related information [10; 115]. This is a frequent problem in nutritional epidemiology, and potentially one of the reasons why studies often find conflicting results on the same topic [55; 180]. Nutritional epidemiology is apparently intrinsically unreliable, which aggravates the problem [75]. On the other hand, not focusing on improving adherence could reflect a real-world scenario more accurately since dropouts are a part of a real-life intervention. Although one could argue that in the real world most people going on a diet to reverse a lifestyle disease is going to be doing so out of inner motivation and a drive to succeed because their health is at risk. Hence, not taking measures to improve adherence in dietary interventions to reflect a real-world scenario more accurately could be pointless. Either way, it's a matter of efficacy of the diet vs. the effect of being assigned to a diet intervention. The former is examined with trials employing good adherence strategies (e.g., feeding trials or high-quality RCT's with full food provision), while the latter is commonly examined with trials employing relatively few follow-up sessions with several weeks or months in between and adherence measured through patient self-reporting. Per-protocol and ITT analysis is also done, respectively. Though both types of studies have their perceived ideal scenarios, only the studies with good adherence are going to accurately show if a diet works or not.

4.2. Miscellaneous Findings

A majority of the successful remissions in this analysis were possible because of relatively low baseline values (17 out of 51 studies). Indeed, other studies that achieved large significant reductions in HbA1c in this analysis did not report any successful remission because of the recruitment of very sick patients with high HbA1c values. Studies that stand out are the ones with very sick patients who still achieved a decent remission rate given the circumstances. Elhayany et al. (2010)[45], Lee et al. (2016)[99], Morris et al. (2020)[140], Watson et al. (2016)[211] and Zhao et al. (2018)[224] recruited patients with a mean HbA1c of 7.7% or greater at baseline, and still saw a significant remission rate down to prediabetic values in the intervention groups. Watson et al. (2016)[211] achieved this in the control group as well.

Bekkouche et al. (2014)[20] observed the biggest reduction in HbA1c in this analysis within the intervention group, with a mean ± SD of -2.6 ± 2.35. These patients had a mean ± SD baseline HbA1c of 10.3 ± 3.8, however, and the participants included in the control group were healthy. Elhayany et al. (2010)[45] also stands out as one of the few studies that managed to achieve significant improvements in glycemic control despite the long study duration (12 months), with a mean ± SD HbA1c reduction of -2.0 ± 0.85 and -1.6 ± 0.55 in the intervention and control group, respectively. Both Bekkouche et al. (2014) and Elhayany et al. (2010) used the mediterranean diet, which is popular in dietary intervention studies as it contains a lot of fiber, whole foods, and is generally low-GI/GL. This hits the same notes as described in main finding (3), allowing patients to feel satiated and improving their metabolic health simultaneously. Satiated patients also typically report higher adherence to the diet [11]. Elhayany et al. (2010), along with Fabricatore et al. (2011)[47], are the only studies with a long duration (almost a year or more) that managed to avoid the rebound effect and thus achieve beneficial results. These two studies had better adherence compared to similar studies of equal length or longer. This suggests that the differentiating factor is perhaps ameliorating the weakness of poor adherence as much as possible in nutritional clinical trials.

Masharani et al. (2015)[126] reported a mean ± SD reduction of -0.3 ± 0.49 HbA1c in just 3 weeks in the intervention group, utilizing a paleolithic diet design consisting of a weight-stabilized energy intake of around 3000 kcal/day. Improvements in glycemic control in such a short time while being weight-stabilized is impressive. The improvements are therefore specifically due to the diet design. A paleolithic diet consists of almost no processed food and a lot of fiber, partly consistent with the tribes' diet, reflecting how important the diet quality is

for improving glycemic control. It would be interesting to see how the results change if the study had lasted longer.

Gerhard et al. (2004)[56] and Nowotny et al. (2015)[148] got non-significant results in their studies. The reason for this is unclear in both studies, however one potential reason might be the acellular focus of the diet design. Both studies had diets containing a high fiber intake (25g/day and above), but it is unclear how much this benefits glycemic control when most of this comes from acellular sources such as flour and whole grains (read: paragraphs about acellular food and whole grains**)**. Contrastingly, several studies with acellular or processed diet design have seen significant results. The problem is therefore not only unclear, but also multifactorial.

The comparator diet used in the study by Otten et al. (2017)[150] included resistance training of about three hours a week. Both intervention and control group were prescribed a paleolithic diet, but it mainly differed in the amount of exercise. That being said, both groups achieved good results, but the large HbA1c reduction in the control group is misleading because of the resistance training and lower energy intake. Resistance training is very impactful in improving glycemic control and insulin sensitivity for a number of reasons, including but not limited to mitochondrial efficiency and increased daily energy demands [25; 30; 32; 35; 42; 187]. Hence, studies with a focus on resistance training was excluded in the screening process as it can make diets seem more efficacious than they really are. Otten had resistance training only in the control group in his study, and as such was included in this analysis since the intervention group is still relevant.

A sensitivity analysis restricted to studies with minimally processed/cellular diets should have been done in this meta-analysis to further investigate the diet-glycemic control relationship. However, most studies that fit the inclusion criteria in this analysis does not report food items or related information about what the patients actually ate. Information regarding the diets is reported to a certain degree in Table 2, but limited transparency by the study authors makes it hard to establish if the diets are based on whole foods, processed food, or something in between. The few studies that actually included a list of foods eaten by the patients were limited to a sample menu of a day or two, and the dietary information reported in Table 2 is as such often based on these lists. Generally, only macronutrient composition (e.g., protein, fat, carbohydrates) and relevant information such as fiber content of the diets were reported by the

study authors. Things like fiber content and the total GI/GL of the diets were used as proxy measurements in an attempt to evaluate the diet quality as accurately as possible.

The sensitivity analysis excluding studies with patients on insulin therapy was performed based on the hypothesis that insulin therapy can attenuate the dietary effects on glycemic control. This hypothesis is based on insulins anabolic and anti-catabolic effects, and studies that consistently report increased weight and fat mass gain on insulin therapy [27; 206]. Even though the sensitivity analysis yielded no significant differences in HbA1c reductions compared to the main analysis, the studies that excluded insulin therapy were few. In addition, most of these studies had other weaknesses such as adherence issues or bad diet design which could contribute to the lack of results. More research on this association is therefore required.

While many of the included studies reported the intervention diet as “low-carbohydrate”, there is no clear consensus of how low the carbohydrate intake has to be for a diet to be labeled as such. Oh, Gilani, and Uppaluri (2021)[149] reports that low-carbohydrate diets restrict carbohydrate intake to below 26E%, based on the proposition by the institute of medicine that Americans obtain 45-60E% from carbohydrates. Last and Wilson (2006)[98] proposes that the carbohydrate intake should be under 60g/day, or atleast under 20E%. This is based on the Atkins diet, which is the prototypical low-carbohydrate diet. However, 60g/day of carbohydrates is typically in the ketogenic diet range. The ADA has defined the low-carbohydrate diet to be < 130g of carbohydrates per day which seems to be an accurate definition, although they continue to downplay it’s benefits [1; 7]. Some studies labeling the diet as low-carbohydrate in this analysis have the carbohydrate intake set to anything between 26-45E%. These diets would more accurately classify as moderate-carbohydrate diets if the <20E% limit or <130g/day limit is to be used. Lowering the carbohydrate intake in these studies down to the low-carbohydrate range might have resulted in larger reductions because of how common it is for consumed carbohydrates to be processed, adversely affecting blood glucose levels. Eliminating or reducing the carbohydrate intake is by no means a necessity for improving health through nutrition however, if it comes from quality sources. For instance, Elhayany et al. (2010)[45] classified the intervention diet as “low-carbohydrate” while reporting the carbohydrate intake to be 35E%. Importantly, the diet also contained a lot of fiber and an overall low-GI, which can be an indicator of whole foods with intact cellular structures and therefore of high quality. This might explain the results.

A general practice in England offered a low-carbohydrate diet (<130g carbs/day) to patients from 2013 to 2019. By 2019, 128 patients with T2DM and 71 patients with prediabetes opted to follow the low-carbohydrate diet for a mean duration of 23 months. A secondary analysis report of their data showed that drug-free T2DM remission was achieved in 46% of the diabetic patients, and 93% of patients with prediabetes achieved normal HbA1c values [203]. The practice uses a low-carbohydrate diet with additional advice on lowering GI and GL through elimination of sweets, white rice, potatoes etc. This reflects main finding (3) with the success of high-glycemic carbohydrate elimination, also seen in the included study by Elhayany et al. (2010)[45]. Additionally, a mean duration of 23 months means that it is very likely that the diet was easy to follow and provided a satiating effect. On the other hand, it could also mean that the patients were unusually motivated to ameliorate their metabolic disease.

The use of medications to treat T2DM, specifically oral hypoglycemic agents (OHA) such as Metformin and Glibenclamide, significantly modified the gut microbiota of T2DM patients compared to healthy subjects in the study by Medina-Vera et al. (2019)[128]. Although fitting the inclusion criteria for this analysis, the study by Medina-Vera is originally a study on the microbiota of T2DM patients. They found that Metformin alone or in combination with Glibenclamide reduced F. prausnitzii, a Gram-positive species associated with anti-inflammatory properties and thought to be a sensor of intestinal health. OHA's such as Metformin were used in almost every study included in this analysis. If such commonly used diabetic medications can alter the gut microbiota in metabolically sick patients, it may adversely affect the beneficial impact of diet on metabolic health. In addition, studies report reduced testosterone levels [71] and offspring birth defects [212] in men with T2DM using metformin. These are not enough to establish a causal relationship, however, and should be viewed skeptically as it requires further study.

While outside the scope of this analysis, the vast majority of included studies reported a remarkable improvement in cardiovascular and lipid parameters from the intervention diet. A significant improvement in triglyceride/HDL-ratio were observed in every study with the exception of those that didn't report it [29; 52; 135; 209], one study that had non-significant results [56], one study that reported an increase instead of a reduction likely due to severe adherence problems evident by the observed rebound effect [214], and one study where the parameters did not change [33]. Elevated triglycerides, or a high triglyceride to HDL-cholesterol ratio, is a strong predictor of coronary disease and heart attacks [38; 54]. Men with

conventional risk factors for Ischemic Heart Disease (IHD) also have a low risk for IHD if they have a low ratio of triglycerides to HDL-cholesterol [81]. Also, the few studies that reported CRP and fibrinogen saw a reduction in those parameters as well. CRP is a commonly used indicator for systemic inflammation. Associations between even minor CRP elevation and future major cardiovascular events has been made, perhaps reflecting the importance of lowering CRP levels especially if you are at risk [22]. Fibrinogen is a protein in the blood which plays a major role in inflammation and atherogenesis (plaque formation in the arteries) since it forms a fibrous mass during coagulation. Elevated levels of plasma fibrinogen is association with an increased risk of cardiovascular disorders such as stroke and IHD [88].

Judging from the included studies in this analysis, diets efficacious at improving glycemic control also improves a range of other metabolic and lipid parameters important for cardiovascular health. This might not come as a surprise since UPF and processed food is associated with increased risk of cardiovascular disease incidence and mortality, and the limitation of ultra-processed/processed food is a common factor in the diets efficacious at improving glycemic control in this analysis [85].

4.3. Limitations, Weaknesses and Strengths

A limitation of the evidence presented in this analysis could be the risk of bias assessment, which were present in 13 out of 51 studies (read: 3.3. Risk of Bias and Funnel Plot). However, most of the high risk of bias entries have arguably minimal impact on the results. The small differences in baseline values felt insignificant in terms of impacting the results, but had to be reported for transparency. In reality, these differences were most likely caused by a small sample size rather than selection bias [78; 95; 122; 214; 224]. Bekkouche et al. (2014)[20] had a high risk of attrition and selection bias, however the large amount of dropouts was as reported by the authors due to the study being conducted in a very poor community, and the risk of selection bias was due to healthy controls being used. A high attrition rate in the intervention group when the control group consists of healthy people presents little risk for bias to occur in dietary interventions, because the relationship between the intervention and control group doesn't change [63]. Arguably, the only studies that had a potentially impactful high risk of bias were the following: Saslow et al. (2017)[179] where the attrition rate and number of patients who completed the study didn't match; and the cross-over studies at high risk of other bias related to carry-over effects from not utilizing a

sufficient washout period: Gannon & Nuttall (2004)[51] reported no carry-over effects which might indicate that the 5-week washout period was sufficient. Skytte et al. (2019)[186] did not report carry-over effects either, but used no washout period which is suspicious. Itsiopoulos et al. (2011)[76] pooled the data from each period into one, reporting that the diet sequence did not have an effect. Jönsson et al. (2009)[83] reported carry-over effects which is why the first period only was used in this analysis, resulting in potential weaknesses and risks as the study was essentially turned into a parallel-group study with baseline differences in HbA1c and other parameters.

This study has several weaknesses. One of them is the use of only one database for the study selection and data collection (PubMed). Even though PubMed contains citations from MEDLINE, science journals and books, restricting the search to only one database will most likely result in several studies going unnoticed. However, this analysis was conducted by one person as part of a master thesis. Time and workload are therefore important limiting factors, and restricting the screening process to one database helps a lot in that regard. The search string developed for this analysis is also a weakness. I had to restrict the number of citations visible to be able to go through everything in a reasonable timeframe, and the method used to accomplish this was to exclude certain keywords. This resulted in a very long search string which could have led to some studies being excluded without a screening process. However, these excluded studies are most likely few in number since the excluded keywords were carefully chosen and typically related to experimental drugs etc.

Another weakness is the use of only HbA1c as a marker for glycemic control. Combining HbA1c with FPG, or using FPG instead of HbA1c, would better reflect the dietary effects on glycemic control. While HbA1c is easier to test since it does not require participants being in a fasted state, a relatively long time is needed before potential reductions can be observed. FPG on the other hand is more time sensitive and can provide valuable insight into how much glycemic control improves in a short amount of time. FPG was originally meant to be included in this analysis, but was excluded in fear of workload and complication issues.

Restricting the data collection from long-duration studies (often a year or more) down to 6 months or less could be a weakness as it can make the analysis biased towards short-term results. Most diets, even poorly designed, can have a short-term improvement in glycemic control – hypocaloric diets are a prime example of this since they might induce favorable changes through weight loss until the body adapts to the new energy level intake. If you

combine this with very sick patients (e.g., HbA1c > 7-8%), then drastic short-term improvements in glycemic control over a half-dozen weeks is very likely. This says nothing about the long-term effect of the diet though. To know the long-term effect of a diet, restricting the sample size down to a more manageable number so that each patient can be followed up frequently and consistently throughout the study duration can help. If not, having a long study duration will often yield no explanation about the long-term effects. This is because of the likelihood that people will stop adhering to the prescribed diet increases with time. Typically, people last about six months on a diet – even less if the regime is really strict or the eating pattern differs from their usual pattern [222]. Designing a diet that is easier to adhere to (e.g., a diet that is satiating, tastes good, and is easy to follow) can help patients' adherence over the long-term. With that in mind, implementing satiating and easy to follow diets into long-term studies could make the respective studies more relevant.

The confounding effect of low-to-moderate intensity exercise included in some studies could be a weakness. Exercise-focused studies were excluded from this analysis due to the effect of exercise on glycemic control, since the exercise used in these studies were generally strength training. Some of the included studies in this analysis incorporated moderate-intensity exercise into the intervention. These were not excluded since moderate-intensity exercise generally consisted of brisk walking for 30 minutes every other day. It is possible that even walking can be a potent therapy for very sick patients. However, excluding studies because the intervention includes brisk walking will limit the studies available for analysis. One can even argue that walking is part of everyday life for even very sick patients, and as such not a confounding factor since patients going on a diet will have walking incorporated into their routine. A sensitivity analysis could be performed to investigate this, but that was unfortunately not an idea at the time.

Even though studies with small sample sizes are better suited for measuring the efficacy of a diet, they could also be a weakness. Studies with smaller sample sizes are easier to conduct, which means more of them are going to be published, hence there will be more studies with interesting results and the risk of publication bias increases. However, I think most of the studies in this analysis has a good sample size respective to their study designs, and I did not choose to limit the sample size when screening for studies. Funnel Plot also shows a decent symmetry. I don't think this is an issue in this analysis, but it's still worth mentioning. On the other hand, I only searched PubMed and found only English articles. "Negative" studies with

uninteresting results can end up being published in obscure journals not indexed in major databases, or in gray literature, which results in studies not being identified by the search [62].

Not citing each study that appeared to meet the inclusion criteria, but was excluded anyway due to other reasons, is a weakness that was unfortunately discovered too late in the thesis project. The reasons for excluding these studies were reported in the flow-diagram (Figure 1), but citations for each study are missing which limits transparency.

Last but not least, the inexperience of the author is a weakness as I have not done a study like this before, especially of this type and magnitude. A meta-analysis has several pitfalls which has to be avoided. Even with plenty of help from a supervisor and several articles, avoiding all the pitfalls as a novice is a difficult task indeed.

One strength of this analysis is the inclusion of significantly different studies with varying diet designs, although it could also be seen as a weakness. Indeed, this analysis has a high heterogeneity between studies (main analysis: I^2=73%, P < 0.00001). The sensitivity analysis controlling for adherence reduced this heterogeneity by a meager 3% (I^2=70%, P < 0.00001). The cause of this variability is likely the large number of different studies included in the analysis, and the confidence interval (horizontal lines in the forest plot) have decent overlap with the exception of the few stand-out studies. The different effects produced by each study likely stems from the variable study designs and diets, and not chance [200]. For better or worse, including such a diverse range of studies makes it possible to identify common factors that contribute to significant results or a lack thereof. An example of this is the impact of diet quality on glycemic control. An observation made in this analysis was that food of high quality (e.g., minimally processed) were present in the majority of studies achieving significant reductions in HbA1c. Other factors such as patient adherence and diet design also impacted this, either beneficially or adversely. Still, the majority of the studies achieving significantly large HbA1c reductions had a strong association with high diet quality. Studies with the greatest reductions in HbA1c had other factors present too, such as good adherence and/or good diet design (e.g., low-carbohydrate diet with < 20E% from carbohydrates). This might in part explain their success compared to other studies. Including studies with different diets can also promote non-polarization since the focus is not on which diet is best, but rather how important the food quality is. A war of which diet is the best diet for losing weight and improving glycemic control have existed for a long time now, and this analysis shows that

different diets can have profound impact on your metabolic, glycemic, and cardiovascular health.

Another strength can be the rigorous and thorough appraisal of each included study. As part of the screening process, each study has been through a CASP checklist for educational purposes, a diet design and composition evaluation, and carefully reviewed multiple times. A GRADE-evaluation was also used on the outcome, assessing if the weaknesses at study level impacts the outcome evidence. More time than necessary has been spent on reviewing each study because of different issues appearing throughout the master thesis process. However, extra time spent on reviewing study after study is time well spent as long as delays are avoided.

Employing a special focus on dietary adherence in this analysis could be a strength. A lack of adherence to the prescribed diet as a common problem in nutritional epidemiology has been mentioned previously in this thesis. Taking measures to attenuate this problem as much as possible without compromising the integrity of this analysis can help reveal the true effect of a dietary intervention. Nutrition research, especially observational epidemiology, is comprised of several confounding and limiting factors that makes it hard to establish true effects. As mentioned before, not controlling for adherence has its benefits as well, such as establishing how hard it is to follow a specific diet. Whether controlling for adherence is a strength or a weakness might depend on the perspective you take.

Implications for practice and policy: Findings from this analysis indicates that several diets with variable designs can have significant and profound impact on glycemic control in patients with T2DM and MetS. If these diets can be adhered to long enough, then remission is very likely. The common factor among these successful diets seems to be whole foods or the elimination of UPF and processed food. Medical and general practices that specialize in treatment of diabetics can therefore choose what diet works best for the patient. Choosing a diet that is similar to previous eating patterns, similar macronutrient content, retention of specific foods that the patient really likes and so on can increase the likelihood that the patient adheres to the prescribed diet.

5. Conclusion

This meta-analysis of 51 RCT's studying the effects of diet on glycemic control found that an intervention diet (typically low-carbohydrate or very-low carbohydrate ketogenic diets, high-fiber diets such as the paleolithic diet, or low-GI/GL diets) was more efficacious at improving glycemic control in patients with T2DM or MetS than comparator diets (typically low-fat, calorie-restricted, diabetes guidelines-inspired diets). A recurring factor in the diets producing good results seems to be the elimination of processed food, especially processed carbohydrates. Additionally, studies who took special measures to improve adherence saw a significantly greater improvement in glycemic control compared to the main analysis. A full (HbA1c < 5.7%) or partial (HbA1c < 6.5%) remission of T2DM was observed in 17 out of the 51 included studies, where most of the patients achieving remission was prescribed the intervention diet. Many of the included studies did not achieve remission because of high HbA1c values at baseline, despite large and significant glycemic control improvements. Had these studies continued for longer with the same level of motivation and adherence, the probability of achieving remission would be high. A large majority of the included studies also saw significant reductions in cardiovascular parameters, suggesting that improving glycemic control through diet also decreases the risk of cardiovascular diseases such as coronary artery disease and heart attacks. **Based on observations made in this meta-analysis, reversing T2DM and prediabetes with diet is both possible and practicable even with high HbA1c values. Dietary interventions with strict follow-up and high-quality food is a tool that should be used more frequently to treat metabolic abnormalities in general, but especially in this patient population.**

6. Other Information

Acknowledgements: This meta-analysis was not registered before implementation. Protocol and other relevant information therefore does not exist. This meta-analysis is a master thesis in the Public Health Nutrition study course from OsloMet (Oslo Metropolitan University, Norway). The review, it's objectives, data collection and analysis were developed, written and completed by one author. The author had help of a study supervisor for answering questions and follow-up possibilities. No funding or conflict of interests were present.

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8. Appendixes

Appendix 1: Completed search string used in PubMed to identify potential eligible studies.

("type 2 diabetes"[Title] OR "metabolic syndrome"[Title] OR t2d[Title] OR mets[Title] OR NAFLD[Title] OR hyperinsulin*[Title] OR "impaired fasting glucose"[Title] OR "impaired glucose tolerance"[Title]) AND (fasting[Title] OR ketogenic*[Title/abstract] OR LCHF[Title/abstract] OR LC[Title/abstract] OR TRF[Title/abstract] OR "time-restricted feeding"[Title/abstract] OR "low-carb"[Title] OR IF[Title/abstract] OR "low GI"[Title] OR "low glycemic index"[Title] OR "low glycemic load"[Title] OR "whole foods"[Title/abstract] OR "low glycemic"[Title] OR "carbohydrate-restriction"[Title] OR "glycemic load"[Title] OR diet*[Title]) NOT (dapag*[Title] OR thyroid[Title] OR magnesium[Title] OR dulaglu*[title] OR metformin[title] OR cinnamon[Title] OR gestation*[Title] OR DNA[Title] OR ginseng[Title] OR curcumin[Title] OR fads[Title] OR probiotic*[Title] OR telecoaching[Title] OR psyllium[Title] OR alirocumab[title] OR yogurt[Title] OR pemafibrate[title] OR selen*[Title] OR cocoa[Title] OR arthritis[Title] OR vinegar[Title] OR polycystic[Title] OR gastric*[Title] OR degludec[title] OR glargine[title] OR psoriasis[title] OR luseogliflozin[title] OR ramadan[title] OR ipragliflozin[title] OR pioglitazone[title] OR liraglutide[title] OR simvastatin[title] OR atorvastatin[title] OR herbal[title] OR extract[title] OR "vitamin d"[title] OR dorzagliatin[title] OR "Ganoderma lucidum"[title] OR pharmacokinetic*[title] OR efpeglenatide[title] OR colchicine[title] OR sitagliptin[title] OR cardamom[Title] OR juice[title] OR risperidone[title] OR olanzapine[title] OR exenatide[title] OR lixisenatide[title] OR "cod protein hydrolysate"[title] OR ginger[title] OR bariatric[title]) **Filters:** RCT, Humans. **Results:** 652. **Date:** 1/8-2021.

Appendix 2: Completed PRISMA checklist for meta-analyses and systematic reviews.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	NA
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1 & 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 11 Sup.Material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11 & 12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 12 & 13
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 12-14
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 12 Page 14 (for missing data)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 13
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 13
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Inclusion and Exclusion criteria (item #5)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 14
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 13-14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 13 & 14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 13 & Sup.Material
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 16
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 16
Study characteristics	17	Cite each included study and present its characteristics.	Page 17-29
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 30 & 31
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 32-34
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 32
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 32-34
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 32 & 34
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 30
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 32
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 35 & 36
	23b	Discuss any limitations of the evidence included in the review.	Page 44
	23c	Discuss any limitations of the review processes used.	Page 44-46
	23d	Discuss implications of the results for practice, policy, and future research.	Page 48
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 48

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 3: Completed PRISMA checklist for abstract.

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	No
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

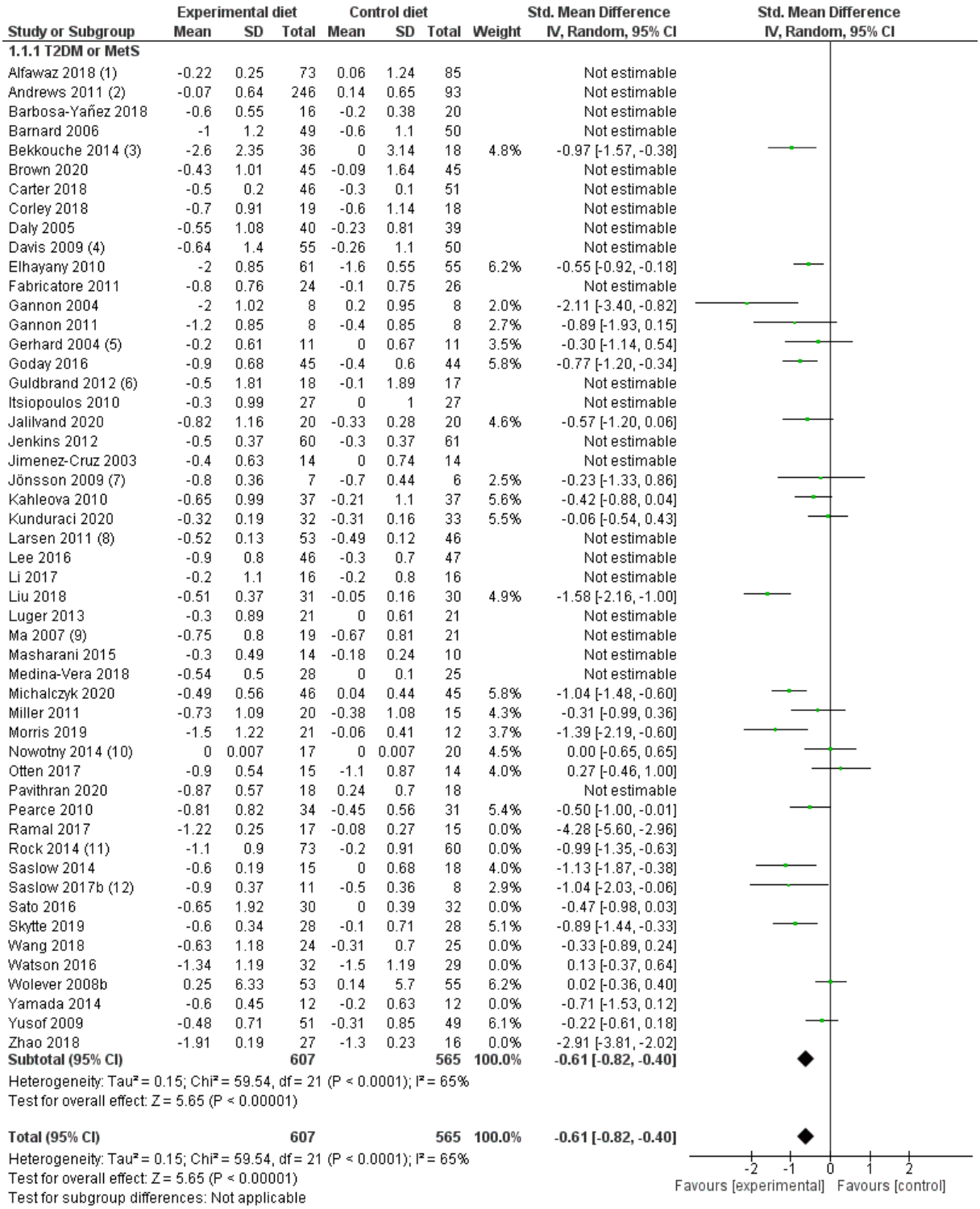
For more information, visit: http://www.prisma-statement.org/

Appendix 4: GRADE-approach assessment.

Factors	Assessment
Individual Study Limitations (Risk of Bias)	**No change.** 13/51 included studies had a potentially high risk of bias. Most of these were of minimal importance relative to the results, but had to be reported in the risk of bias summary for transparency. Only 2 studies had a serious risk of bias: Saslow et al. (2017) (incomplete outcome data – attrition bias) and Jönsson et al. (2009) (carry-over effects were reported, which made me use the first period of this cross-over study only, hence the difference in baseline values and low sample size). Most of the data in this analysis comes from studies with a low risk of bias, and no decrease in the level of certainty in the evidence is warranted (Guyatt, G. H., Oxman, A. D., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., . . . Schünemann, H. J. (2011). GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *Journal of Clinical Epidemiology, 64*(4), 407-415. doi:10.1016/j.jclinepi.2010.07.017).
Inconsistency of Results (Heterogeneity in meta-analysis)	**No change.** As stated in the "Strengths and Weaknesses" chapter, this meta-analysis had a substantial heterogeneity between studies (I^2=73%, P < 0.00001). The cause of this is likely the large number of different studies included in the analysis, as the confidence intervals (horizontal lines in the forest plot for each study) have decent overlap except for the few studies that had large HbA1c reductions, and all studies except two (and the ones with non-significant results) fall to the left side of the vertical line in the forest plot (favors experimental). The results of dietary interventions rely heavily on adherence and a good diet design, both of which can vary substantially between studies. The heterogeneity in this analysis is therefore, all things considered, likely not that impactful. The different effect sizes produced by each study likely stems from variable study designs and diets, and not chance, and is as such not enough to warrant a decrease in the certainty of the evidence in my opinion (GRADE guidelines: 7. Rating the quality of evidence—inconsistency Guyatt, Gordon H. et al. Journal of Clinical Epidemiology, Volume 64, Issue 12, 1294 – 1302. DOI: https://doi.org/10.1016/j.jclinepi.2011.03.017).

Indirectness of Evidence	**No change.** This meta-analysis includes dietary intervention RCT's of patients with T2DM or MetS (which means T2DM or prediabetes as an inclusion criteria). The population of interest and those who have participated in the studies are similar. Interventions are different in terms of setting (country) and diets, but still applicable to the population of interest and the research question. The outcome (HbA1c) is also applicable, and no surrogate markers were used as an outcome. Intervention and comparator diets are a direct comparison, however as stated in the meta-analysis, the purpose of this thesis is to evaluate the efficacy of any diet in reversing the diabetic condition. A comparison is not necessarily needed (GRADE guidelines: 8. Rating the quality of evidence—indirectness Guyatt, Gordon H. et al. Journal of Clinical Epidemiology, Volume 64, Issue 12, 1303-1310. DOI: https://doi.org/10.1016/j.jclinepi.2011.04.014).
Imprecision (Small sample size, wide CI's)	**No change.** Recommendations would not be altered if the lower and upper Confidence Intervals represented the true effect, as it is sufficiently narrow (SMD, -0.61; 95% CI, -0.76 to -0.47; $p < 0.00001$). This meta-analysis also includes 51 studies with a total of 3281 patients, and as such does not contain a small sample size (GRADE guidelines 6. Rating the quality of evidence—imprecision Guyatt, Gordon H. et al. Journal of Clinical Epidemiology, Volume 64, Issue 12, 1283 - 1293. DOI: https://doi.org/10.1016/j.jclinepi.2011.01.012).
Publication Bias	**No change.** Funnel Plot shows a decent symmetry with the exception of three studies that got large mean reductions due to high HbA1c baseline values and effective diets. Using Funnel Plots to assess the risk of publication bias is helpful, but they are distressingly prone to error. There are a number of small studies in this analysis that can increase the risk of publication bias, however I would say the majority of included studies have an acceptable sample size given the study designs. Conflict of Interest and suspicious funding were not reported with the exception of a few studies (e.g., Pearce 2010 focused the intervention on eggs and received funding from the largest marketer of eggs in Australia). Most of the funding and grants were from research and diabetes organizations. (GRADE guidelines: 5. Rating the quality of evidence—publication bias Guyatt, Gordon H. et al. Journal of Clinical Epidemiology, Volume 64, Issue 12, 1277 - 1282. DOI: https://doi.org/10.1016/j.jclinepi.2011.01.011).

Appendix 5: Forest Plot for association between glycemic control and diet in patients with T2DM and MetS in studies excluding insulin therapy.



Appendix 6: Graph of the Risk of Bias summary.