GLYCEMIC DIETARY PREDICTORS OF REMISSION OF TYPE 2 DIABETES

EVALUATING DAILY DIETARY GLYCEMIC LOAD, GLYCEMIC INDEX, AND CARBOHYDRATE INTAKE AS POTENTIAL PREDICTORS OF DIABETES REMISSION IN ADULTS WITH TYPE 2 DIABETES

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Abstract

There is growing evidence that type 2 diabetes remission can be achieved with non-surgical interventions. However, it remains unclear which factors are important predictors of diabetes remission. We conducted analyses on 304 individuals with type 2 diabetes in the REMIT trials to explore whether glycemic dietary indices are important independent predictors of diabetes remission. Diabetes remission was defined as glycemic levels returning to normal ($HbA_{1c} < 6.5\%$) without the need for glucose-lowering medications for at least 3 months.

Daily dietary glycemic load (GL, primary research question), glycemic index (GI), and carbohydrate intake (g) at 12 weeks or as a change from baseline to 12 weeks, were not associated with diabetes remission. Higher daily carbohydrate intake (% of daily energy intake) at 12 weeks was associated with lower odds of diabetes remission when comparing the highest quartile to the lowest quartile. The adjusted odds ratio (OR) of diabetes remission when comparing the highest quartile to the lowest was 0.289 (95% CI 0.124-0.673, p = 0.004). The change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks was also associated with diabetes remission, after adjusting for the baseline value. The adjusted OR of diabetes remission per 5% increase in daily carbohydrate intake from baseline to 12 weeks was 0.750 (95% CI 0.587-0.956, p = 0.020).

In summary, daily dietary GL, GI, and carbohydrate intake (g) were not statistically significant predictors of diabetes remission in our study. However, higher daily carbohydrate intake (% of daily energy intake) at 12 weeks and increasing daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks both predicted lower odds of diabetes remission.

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List of Abbreviations

ACME	average causal mediation effect
ALT	alanine transaminase
$AUC_{2hr\text{-}glucose}$	area under curve for 2-hour blood glucose profile
AVBCHO	available carbohydrate
BMI	body mass index
CI	confidence interval
CNF	Canadian Nutrient File
DIADEM-1	Diabetes Intervention Accentuating Diet and Enhancing Metabolism
DiRECT	Diabetes Remission Clinical Trial
FFQ	food frequency questionnaire
FFQ-CN	Chinese food frequency questionnaire
FFQ-EC	European-Caucasian food frequency questionnaire
FFQ-SA	South Asian food frequency questionnaire
FPG	fasting plasma glucose
G	grams
GI	glycemic index
GL	glycemic load
HbA_{1c}	hemoglobin A1C
HDL	high-density lipoprotein
IPAQ	international physical activity questionnaire
IQR	interquartile range
Look AHEAD	Look Action for Health in Diabetes
OR	odds ratio
Q1, Q2, Q3, Q4	quartile 1, quartile 2, quartile 3, quartile 4
REMIT	Remission Evaluation of Metabolic Interventions in Type 2 diabetes
RD	risk difference
RR	relative risk
SD	standard deviation
SSB	sugar-sweetened beverages
T2DM	type 2 diabetes mellitus
VIF	variance inflation factor
2-hour PG	2-hour plasma glucose

1. Introduction

Type 2 diabetes mellitus (T2DM) has traditionally been considered a chronic and progressive disease that cannot be cured[1]. It is a complex metabolic disease that affects millions of people across the world. The global presence and chronic nature of the disease place a heavy toll on both the individual and public health systems[2]. The management of T2DM will often require lifelong treatment combining pharmacological interventions and lifestyle modifications[1,3]. Consequently, it is desirable to identify long-term and sustainable solutions in diabetes therapies. Recent evidence suggests that the T2DM condition may be reversible and remission of T2DM can be achieved. Remission of T2DM is defined as glycemic levels returning to a normal healthy range for at least 3 months without the need for any diabetes medications[4-6].

Although surgical interventions find the largest success in inducing diabetes remission, non-surgical lifestyle interventions promoting changes in diet and exercise can also influence short- and long-term outcomes of diabetes remission[4]. Individuals adhering to carbohydrate-restricted diets have shown improvements in various health outcomes including diabetes remission[7-9]. Regulating the amount of carbohydrates consumed in the diet may be important for diabetes remission, but the quality of carbohydrates consumed should also be considered as well. The glycemic index is a measure of carbohydrate quality that is used to describe how fast a carbohydrate-containing food item can raise blood glucose levels[10,11]. The glycemic load is a measure of carbohydrate quality but also takes into consideration the amount of carbohydrates in the food item as well[11]. The glycemic load describes both how much and how fast a carbohydrate-containing food item can raise blood glucose levels[11]. However, the relationships between the overall glycemic index and glycemic load of the diet with diabetes remission are not

known. We hypothesized that higher measures of dietary glycemic index and glycemic load will decrease the likelihood of diabetes remission. The data obtained from the REMIT trials provided the opportunity to conduct analyses and test this hypothesis. A better understanding of the relationships between the quantity and quality of dietary carbohydrates with diabetes remission can provide more insight into new predictors and approaches for inducing sustained remission of diabetes.

2. Background Information

2.1. Epidemiology and etiology of type 2 diabetes

There are an estimated 529 million people worldwide with diabetes and approximately 96% of these cases are type 2 diabetes (T2DM)[12]. Projections for the next few decades estimate that the global prevalence will rise to 578 million by 2030 and 700 million by 2045[2]. Globally, diabetes mellitus is also one of the top 10 causes of mortality and the second largest source of reducing health-adjusted life expectancy[1,13].

T2DM manifests when the processes that are essential for glucose homeostasis become dysfunctional. In healthy individuals, the molecular and physiological mechanisms of the production, secretion, and responsiveness to insulin are tightly regulated. In patients with T2DM, the beta cells fail to adequately release insulin in response to glucose, and other tissues do not properly respond to insulin[14]. As beta cell function and insulin sensitivity continue to deteriorate, the body experiences more intensive states of hyperglycemia which characterizes the pathogenesis of T2DM[14,15]. Chronic hyperglycemia can also damage the beta cells via the effects of glucose toxicity in the pancreas, which further disrupts beta cell function and exacerbates the condition[16].

There are many underlying genetic and environmental factors that play a role in altering glucose homeostasis and contribute to the development of T2DM[15]. Ethnicity and family history of T2DM are two genetic factors that can predispose certain individuals or groups to a higher risk of disease[15,17]. Environmental and lifestyle factors can also influence the development of T2DM as well. Adhering to poor dietary habits and a sedentary lifestyle can decrease insulin sensitivity and increase weight gain[17]. In individuals who are obese or overweight, the accumulation of fat in important tissues can give rise to lipotoxicity and inflammation[18,19]. This

can damage the beta cells of the pancreas and promote insulin resistance in the liver and peripheral tissues[18,19]. Overall, the complex interplay of both genetic and environmental factors collectively contributes to beta cell dysfunction and insulin resistance, which are hallmarks in the development of T2DM.

2.2. Diagnosis of type 2 diabetes, current approaches to treatment, and associated complications

Type 2 diabetes is a chronic and progressive disease that is characterized by elevated levels of blood glucose for prolonged periods[20]. Diagnosis is typically made by a glycated hemoglobin A_{1c} (HbA_{1c}) test where HbA_{1c} levels above 6.5% will indicate diabetes[20]. Fasting plasma glucose and glucose tolerance tests can also be used to make the diagnosis, but HbA_{1c} levels provide a more consistent indicator of your average blood glucose levels in the last two or three months[20].

The current approaches to treating the T2DM condition are multifaceted that combine a variety of therapeutic strategies to maintain adequate glycemic control and prevent complications. These can include a combination of pharmacological interventions and lifestyle modifications[21]. Ultimately, the types of therapies used are tailored to the individual according to their needs, preferences, and health condition[21].

Over time, if the management of the diabetes condition is inadequate, T2DM can contribute to the development of many short and long-term complications. Prolonged periods of high blood sugar levels can damage vasculature and disrupt circulation which leads to cardiovascular disease, stroke, renal disease, neuropathies, retinopathies, and other serious health concerns[22,23].

2.3. Criteria for remission of type 2 diabetes and its significance in diabetes care

Type 2 diabetes has historically been considered a progressive disease that cannot be reversed. However, there is increasing evidence that some patients with T2DM can achieve sustained normoglycemia, even after discontinuation of glucose-lowering medications. This may be partly because of the newer types of interventions developed for diabetes therapy and research. Identifying new strategies or approaches that can reliably induce drug-free normoglycemia in patients with T2DM may be critical to lessen the long-term negative impacts that diabetes has on the global scale. In response, new criteria have been established to describe and objectively measure these outcomes. Remission of T2DM is defined as HbA_{1c} levels < 6.5% after the discontinuation of glucose-lowering medications for at least 3 months[4-6]. If HbA_{1c} values cannot be used or are considered unreliable, alternative methods for adjudicating diabetes remission may be applied. Secondary criteria for diabetes remission include FPG < 7 mmol/L or 2-hour plasma glucose (2-hour PG) < 11 mmol/L following an OGTT[4-6]. However, the use of HbA_{1c} levels is strongly preferred because there are several limitations with these secondary options, such as difficulties with sample collection and the high variability between repeated measurements[20].

2.4. Evidence on interventions inducing remission of type 2 diabetes

There are a few types of interventions that have demonstrated success in inducing remission in patients with T2DM. These interventions can be broadly classified as surgical, pharmacological, and lifestyle interventions, or combinations of the three.

2.4.1. Effects of bariatric surgery on diabetes remission

Bariatric surgery is a treatment option that is considered in patients with obesity and obesity-related diseases. The primary goal of bariatric surgery is inducing sustained weight loss,

which can reach up to 75% as early as 1 to 2 years after surgery[24]. However, bariatric surgery has demonstrated other health benefits including improvements in cardiovascular risk factors and diabetes remission in patients with obesity and T2DM[25-28].

In a systematic review and meta-analysis conducted by Sheng *et al*.[25], pooled data from 9 observational studies show that patients who underwent bariatric surgery had fewer microvascular (RR = 0.37, 95% CI = 0.30-0.46) and macrovascular complications (RR = 0.52, 95% CI = 0.44-0.61), lower mortality (RR = 0.21, 95% CI = 0.209-0.213), and a higher rate of diabetes remission (RR = 5.90, 95% CI = 3.75-9.27) when compared to patients receiving non-surgical therapies. In another meta-analysis, Khorgami *et al*.[26] compared the effects of bariatric surgery versus medical management on remission of T2DM. In 7 randomized controlled trials, remission was observed in 52.5% of patients with bariatric surgery compared to only 3.5% of patients receiving medical management ($p<0.001$). The evidence suggests that bariatric surgery is associated with a greater likelihood of diabetes remission when compared to alternative therapies. However, bariatric surgery is an invasive procedure that should only be considered after other treatment methods have been exhausted.

2.4.2. Effects of lifestyle and pharmacological interventions on diabetes remission

Alternative non-surgical approaches that emphasize lifestyle changes and/or weight loss have also shown beneficial effects toward achieving diabetes remission.

In the Look AHEAD trial[29], participants with T2DM were recruited and randomized to either an intensive lifestyle intervention targeting 7% weight loss with dietary changes and increased physical activity (n = 2241), or a diabetes support and education control condition (n = 2262). Exploratory analyses indicated that the intensive lifestyle intervention increased the

likelihood of partial remission in patients with T2DM at year 1 (11.5%) and year 4 (7.3%) when compared to the control group (2% at both years 1 and 4)[30].

In the DiRECT trial[31], participants were randomized to a weight management program (n = 157) or standard care (n = 149). The intervention incorporated total diet replacement, withdrawal of antidiabetic drugs, and structured support for long-term weight loss. Diabetes remission was observed in 46% of participants in the intervention group compared to only 4% in the control group. Post-hoc analyses found that remission was achieved in 64% of participants who maintained at least 10 kg of weight loss and in 85% of participants who maintained at least 15 kg of weight loss[32].

In the DIADEM-I trial[33], individuals of Middle Eastern and North African descent with T2DM were randomized to a 12-week intervention comprised of a low-energy diet and physical activity targeting weight loss (n = 70) or 12 weeks of usual medical care (n = 77). Diabetes remission was observed in 61% of participants in the intervention group compared to only 12% in the control group with an OR = 12.03 (95% CI, 5.17-28.03).

Goldenberg *et al.*[8] conducted a systematic review and meta-analysis of 23 randomized controlled trials with 1357 participants investigating the efficacy and safety of low-carbohydrate and very-low-carbohydrate diets on remission of T2DM. At 6 months, patients adhering to low-carbohydrate diets achieved higher rates of diabetes remission (57%) when compared to the control diet (31%) (RD = 0.32, 95% CI = 0.17-0.47). Similar effects were observed in a randomized controlled trial by Esposito *et al.*[34] when participants were randomized to a low-carbohydrate Mediterranean diet (LCMD) or a low-fat control diet. In patients with T2DM, the LCMD lowered HbA_{1c} levels and increased the likelihood of diabetes remission (14.7% vs 4.1% at year 1 and 5.0% vs 0% at year 6).

The REMIT trials[35,36] are a group of randomized controlled trials that investigated the effects of different intensive metabolic interventions on diabetes remission. In the REMIT-dapa and REMIT-sita trials, although the effects of the intervention on remission were not statistically significant in primary analyses, there was evidence that patients receiving short-term intensive treatment with drug therapy and lifestyle changes could achieve sustained diabetes remission.

In summary, diabetes remission is a practical target in both surgical and non-surgical diabetes therapies. Bariatric surgery is an effective approach to inducing diabetes remission, but it is an invasive procedure that is not recommended for every patient. Lifestyle and/or pharmacological interventions may also induce diabetes remission, but the amount of evidence is limited, and the underlying mechanisms are not well understood.

2.5. Potential mechanisms of diabetes remission

Although the exact mechanisms of diabetes remission are unclear, a few have been proposed according to the evidence and our understanding of the etiology of T2DM.

2.5.1. Eliminating the effects of glucose toxicity

T2DM is characterized by persistently high levels of blood glucose. Chronic hyperglycemia can promote glucose toxicity and damage various tissues in the body[16,37,38]. Prolonged exposure to environments of high glucose can impair the function of pancreatic islet beta cells and reduce their capacity to secrete insulin[16,38]. Glucose toxicity can also affect peripheral tissues, such as adipose and skeletal muscle, by reducing insulin sensitivity[16,38]. Altogether, glucose toxicity further perpetuates the cycle of hyperglycemia and insulin resistance, which exacerbates the condition[16,38]. By reducing blood glucose levels and limiting

the effects of glucose toxicity, it may be possible to restore beta cell function and eventually help achieve diabetes remission.

2.5.2. Energy restriction and weight loss

The majority of patients with T2DM are also overweight or obese. Excess weight potentiates the development of T2DM by increasing fat deposition in various tissues such as the liver and pancreas[18,19,39]. Fat accumulation damages these tissues by inducing inflammation and through the effects of lipotoxicity[40]. Fatty liver can impair glucose metabolism and promote insulin resistance while ectopic fat in the pancreas can lead to decreasing beta cell function[40]. Altogether, these processes contribute toward the development of T2DM.

However, there is evidence that the normalization of hepatic insulin sensitivity and beta cell function can be restored by minimizing the effects of fat accumulation. As observed in patients with T2DM undergoing bariatric surgery, dietary interventions, or weight loss interventions, reductions in caloric intake can lead to substantial weight loss and improve insulin sensitivity[24-31,41]. The underlying factors that cause T2DM seem to be reversible by restricting energy intake with the goal of achieving sustained weight loss.

The success of diabetes remission seems to be linked to the extent of weight loss, where intensive weight loss of up to 15% can maximize benefits among patients with T2DM[31,42,43]. However, diabetes remission can also occur before substantial weight loss is achieved as evident in patients after receiving bariatric surgery[27]. This suggests that mechanisms of diabetes remission are quite complex, and some may be independent of weight loss. While the mechanisms described above provide some insight into understanding T2DM and diabetes remission, the exact mechanisms and predictors of diabetes remission are not well established.

Thus, there is a need to further explore how different lifestyle interventions or factors influence the likelihood of remission in individuals with T2DM.

2.6. Importance of diet, body weight, and carbohydrate intake on diabetes health

Although using drug therapies is an effective approach to managing hyperglycemia, engaging in healthy lifestyle behaviors can also strongly influence glycemic control. Current clinical guidelines recommend patients with T2DM follow a healthy and balanced diet to improve their physiological and nutritional health[3]. Eating a healthy diet has numerous health benefits that become particularly important in the prevention and treatment of metabolic diseases such as T2DM[3]. Since there is limited evidence in support of a single type of diet, dietary recommendations are often individualized based on the patient's treatment and nutritional goals. However, some of the primary considerations when making these dietary recommendations involve energy restrictions and macronutrient distributions.

Obesity and excess body weight have been strongly linked to insulin resistance and the development of T2DM[19,44]. Thus, weight management is an important factor in preventing and managing T2DM, especially because a large majority of patients with T2DM are also overweight or obese[44]. In the Look AHEAD study[29,45], an intensive lifestyle intervention designed to restrict caloric intake and induce sustained weight loss was able to achieve weight loss and significant improvements in HbA_{1c} levels in individuals with T2DM. Secondary analyses of data from the Look AHEAD study also found that the extent of weight loss was associated with improvements in cardiovascular risk factors such as blood pressure, HDL cholesterol, and triglycerides[43]. Other studies have found that similar energy-restrictive approaches can reduce the risk of developing T2DM in individuals at high risk[46,47]. In individuals already with T2DM, restricting energy intake can also increase insulin sensitivity and potentially normalize beta cell function[41,48].

Overall, energy restriction targeting modest weight loss between 5-10% can help individuals achieve significant improvements in glycemic control, insulin sensitivity, and cardiovascular health[44,48-51].

The distribution in the consumption of macronutrients has also been considered in the management of diabetes. High-fat consumption may contribute to insulin resistance and indirectly elevate blood glucose levels, but overall, the consumption of protein and fat have minimal effects on blood glucose[3]. Carbohydrates have the largest and quickest impact on the postprandial glycemic response[3]. However, there is conflicting evidence on how carbohydrate-restricted diets may influence glycemic control and other important health factors.

Some studies support the idea that carbohydrate-restricted diets can improve health outcomes in individuals with T2DM. Ajala *et al*.[7] conducted a systematic review and meta-analysis of 3073 participants across 20 randomized controlled trials on the effects of various diets on cardiometabolic outcomes in patients with T2DM. Improvements in glycemic control were observed when individuals consumed low-carbohydrate, low-GI, high-protein, or Mediterranean diets in comparison to control diets. Higher weight loss was also observed with the low-carbohydrate and Mediterranean diets as well. The low-carbohydrate diets included in these studies consisted of restricting carbohydrate intake to 20-60 g per day ranging from 13-45% of daily energy intake. Wheeler *et al*.[52] conducted a separate systematic review of 11 randomized controlled trials examining the effects of low carbohydrate intake on various outcomes in individuals with T2DM. Significant improvements in markers of glycemic control (HbA_{1c}, FPG, 24-hour blood glucose) and insulin sensitivity (24-hour insulin, fasting insulin levels) were both observed. Very-low and moderately low-carbohydrate diets were included in

these studies which consisted of restricting carbohydrate intake to 21-70 g per day ranging from 30-40% of daily energy intake.

In contrast, other studies have found that low-carbohydrate diets do not have any effects on diabetes-relevant outcomes when compared to control diets. In reviews by Van Wyk *et al*.[53] and Dyson[54], both studies found no differences in glycemic control or weight loss when comparing low-carbohydrate and high-carbohydrate diets consumed by individuals with T2DM. Noto *et al*.[55] also found that the risk of incident T2DM was not significantly different between healthy populations consuming low-carbohydrate and high-carbohydrate diets as well. The inconsistent evidence of the effects of carbohydrate-restricted diets on important outcomes in diabetes health justifies the need for further investigation.

2.7. Importance of considering the quality of dietary carbohydrates

The study of the effects of dietary carbohydrates on health and disease has been increasingly popular. Dietary and nutritional recommendations have traditionally focused on the quantity of carbohydrates consumed in the diet[3]. However, this outlook fails to consider the varying health effects of different types of carbohydrates. The three main types of carbohydrates are starches, sugars, and fiber[3]. Within these groupings, they can be broken down even further into other categories such as whole and refined grains, natural and added sugars, and more[3]. These types of carbohydrates can also be broadly defined as good or bad, depending on how it influences blood glucose levels after consumption[56]. Whole grains, fruits, and vegetables are generally considered good carbohydrates because they contain a lot of fiber, vitamins, and minerals, and do not raise blood glucose levels too much[3,57]. In contrast, refined grains, processed sugars, and artificially sweetened beverages are often labeled as bad carbohydrates because they are digested quickly and cause spikes in blood glucose levels[3,57]. Thus, it may be

important to also consider the effects of the quality of carbohydrates on different health outcomes, especially when we evaluate the pathophysiological processes of metabolic diseases such as T2DM.

2.7.1. Measures of carbohydrate quality

The glycemic index (GI) and glycemic load (GL) are two emerging indicators of the quality of carbohydrates in different food sources. The GI is a measure of carbohydrate quality that describes how fast a carbohydrate-containing food item can raise blood glucose levels[10,11,58]. The GL is also a measure of carbohydrate quality but takes into consideration the quantity of carbohydrates in those food items as well[11,58]. The GL describes both how much and how fast a food item can raise blood glucose levels.

The GI is calculated as the percent of the area under the curve for the 2-hour blood glucose profile ($AUC_{2hr\text{-}glucose}$) after consumption of a certain food item compared to a reference food of either pure glucose or white bread[59]. To standardize the comparisons, the food item of interest and the reference food must both contain an equal quantity of available carbohydrates (typically 50 g). The reference food is assigned a GI value of 100, and all other food items are assigned GI values between 0 to 100. Accordingly, the GI provides a ranked scale of any carbohydrate-containing foods based on how fast it raises blood glucose levels relative to the reference food. Using the glucose scale, a GI $\leq$ 55 is typically considered low, 56-69 is medium, and $\geq$ 70 is high[60].

$$Glycemic\ Index = \frac{AUC\ of\ 2\ hour\ blood\ glucose\ after\ consuming\ food\ item}{AUC\ of\ 2\ hour\ blood\ glucose\ after\ consuming\ reference\ food} * 100$$

The GL is calculated by multiplying the GI of a food item by the amount of available carbohydrates (AVBCHO) in a serving, divided by 100. The GL is a useful measurement as it

takes into consideration both the quality and the quantity of carbohydrates in a particular food item. It provides a better representation of the actual impact that food items have on blood glucose levels. The GL and AVBCHO are expressed per serving of a food item in the following calculation.

$$GL = \frac{GI * AVBCHO}{100}$$

Using the GI and GL of common food items, we can also calculate the overall GI and GL of an individual's diet. The dietary GI provides an overall measure of the quality of carbohydrates consumed in the diet while the dietary GL provides an overall measure of both the quality and quantity of carbohydrates consumed in the diet.

2.7.2. Current evidence of the relationships between measures of carbohydrate quality and diabetes health

Livesey *et al.*[61] conducted a systematic review of 26 prospective cohort studies that investigate the associations between GI and/or GL with incident T2DM. Of the 10 studies that used valid dietary instruments, high GI diets increased the risk of developing T2DM with a risk ratio (RR) of 1.27 ($p < 0.001$). Similar effects on incident T2DM were observed but in high GL diets with a RR of 1.26 ($p < 0.001$). Overall, diets with high GI or GL are associated with an increased risk of developing T2DM in healthy populations of men and women.

Thomas *et al.*[62], Opperman *et al.*[63], and Brand-Miller *et al.*[64] conducted reviews and meta-analyses of randomized controlled trials exploring the effects of low-GI on HbA_{1c} and other health outcomes in patients with T2DM. Low-GI diets were consistently able to reduce HbA_{1c} when compared to conventional or high-GI diets, suggesting that low-GI diets have an important effect on glycemic control.

Chiavaroli *et al*.[65] conducted a systematic review summarizing the literature on the effects of low glycemic index or glycemic load diets on glycemic control and other risk factors in diabetes. The review included 1617 participants across 27 randomized controlled trials. When comparing low GI/GL diets with high GI/GL control diets, small improvements in glycemic control (HbA_{1c} and fasting plasma glucose) were observed over a median follow-up of 12 weeks. Low GI/GL diets led to a reduction in HbA_{1c} by -0.31% ($P<0.001$) and fasting plasma glucose by -0.36 mmol/L ($P<0.001$) when compared to high GI/GL diets.

Overall, the evidence on the relationships between dietary GI and GL with diabetes health suggests these are two dietary variables that are important to consider when managing the progression of T2DM. Decreasing the GI and GL in the diets of healthy patients and adults with T2DM may be an effective strategy to improve glycemic control and physiological health.

2.8. Dietary assessment tools to measure intake of foods and beverages

There are several dietary assessment tools that can be used to measure the dietary intake of individuals. The main instruments used in research include food frequency questionnaires (FFQ), 24-hour recalls, food records, and screening tools[66,67]. Each dietary assessment tool can obtain detailed information about food and beverage consumption over a specified period of time, but there are different advantages and disadvantages associated with their use. The choice of dietary assessment will ultimately depend on the research questions, the goals of the study, and the study sample.

The 24-hour dietary recall is an informal interview to capture dietary intake in the last 24 hours[66-67]. In addition to collecting detailed information about the food and beverage items consumed in the last 24 hours, researchers can also collect other information such as methods of food preparation, time and location of consumption, and activities during meals[66].

Food records are comprehensive assessments where respondents are asked to record all food and beverage items consumed over a span of several days[66,67]. Both the 24-hour dietary recall and food records are useful because there are no limits to the number and types of items that respondents can report[66-67]. However, these assessments can only capture short-term dietary intake and patterns up to a few days at a time, which may not reflect the respondent's usual dietary habits[66-67].

FFQs are a more cost-effective approach that can capture dietary intake over a longer period of time[66-67]. Respondents are asked to report the frequency and often the portion size of their consumption for each item in the FFQ[66-67]. However, the FFQ is more susceptible to systematic error and is limited by the specific items included in the questionnaire[66-67]. Completion of the FFQ can also be burdensome for the respondents as well.

Screening tools are typically used when more specific information about dietary behaviors or the consumption of nutrients or food groups is required[66-67]. These screeners are convenient when a narrow scope of information is needed because they provide a fast and inexpensive method of collecting detailed information[66-67].

3. Rationale and objectives of this thesis

The goal of this thesis is to explore how the consumption of dietary carbohydrates can affect the likelihood of remission of type 2 diabetes. Our primary focus is to assess how the quantity and quality of carbohydrates influence diabetes remission, by using measures such as glycemic index, glycemic load, and overall carbohydrate consumption. We are also interested in identifying whether specific types or sources of dietary carbohydrates may relate to remission as well. A better understanding of these relationships may help elucidate some of the mechanisms involved in inducing diabetes remission and how the consumption of dietary carbohydrates plays a role in these processes.

The REMIT trials[35-36] provide a great opportunity to explore these relationships in more detail. There are currently 3 completed randomized controlled trials that studied the effects of intensive metabolic interventions versus standard diabetes care on the outcome of diabetes remission. In addition, the REMIT trials also captured detailed information about dietary intake throughout the trials via food frequency questionnaires. Therefore, using the data from the REMIT trials, we conducted analyses to explore the relationships between dietary glycemic load, glycemic index, and other carbohydrate-related variables with remission of T2DM.

4. Hypothesis and research questions

4.1. Hypothesis

We hypothesized that in patients with type 2 diabetes, a higher daily dietary glycemic load (highest vs lowest quartile) measured at 12 weeks will decrease the likelihood of remission of diabetes at 24 weeks after randomization.

4.2. Primary research question

Among adults with type 2 diabetes who participated in the REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi trials, does a higher daily dietary glycemic load (highest vs lowest quartile) measured at 12 weeks decrease the likelihood of remission of diabetes at 24 weeks after randomization?

4.3. Secondary research questions

Among adults with type 2 diabetes who participated in the REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi trials…

1) Dietary glycemic load
   - Does decreasing daily dietary glycemic load measured from baseline to 12 weeks increase the likelihood of remission of diabetes at 24 weeks after randomization?
2) Dietary glycemic index
   - Does a higher daily dietary glycemic index measured at 12 weeks decrease the likelihood of remission of diabetes at 24 weeks after randomization?
   - Does decreasing daily dietary glycemic index measured from baseline to 12 weeks increase the likelihood of remission of diabetes at 24 weeks after randomization?
3) Carbohydrate intake

- Does a higher daily intake of carbohydrates (total grams and % of total daily energy intake) measured at 12 weeks decrease the likelihood of remission of diabetes at 24 weeks after randomization?
- Does decreasing daily intake of carbohydrates (total grams and % of total daily energy intake) measured from baseline to 12 weeks increase the likelihood of remission of diabetes at 24 weeks after randomization?

4) Starchy foods
   - Does a higher daily consumption of starchy foods measured at 12 weeks decrease the likelihood of remission of diabetes at 24 weeks after randomization?
5) Sugar-sweetened beverages
   - Does a higher daily consumption of sugar-sweetened beverages measured at 12 weeks decrease the likelihood of remission of diabetes at 24 weeks after randomization?
6) Sweets
   - Does a higher daily consumption of sweets measured at 12 weeks decrease the likelihood of remission of diabetes at 24 weeks after randomization?
7) Dietary fiber
   - Does a higher daily intake of dietary fiber measured at 12 weeks increase the likelihood of remission of diabetes at 24 weeks after randomization?

4.4. Tertiary research questions

If we found statistically significant relationships between the predictor and outcome variables of interest described above (e.g. change in glycemic load, change in carbohydrate

intake), mediation analyses were planned to be conducted to explore the mediating role of weight loss in these relationship(s). They were meant to answer the following research question:

1) Is the effect of the change in a dietary variable of interest measured from baseline to 12 weeks on remission of diabetes at 24 weeks mediated by percent weight loss from baseline to 12 weeks?

4.5. Exploratory research questions

1) Are the relationships between dietary variables of interest and remission similar in the intervention group and the control group?
2) Are the relationships between dietary variables of interest measured at 12 weeks (e.g. glycemic load, carbohydrate intake) and remission measured at 24 weeks similar after adjusting for total daily caloric intake measured at 12 weeks (i.e. is total daily caloric intake a confounder of the observed relationships)?
3) Will the relationships between dietary variables of interest and remission change after isolating the effects of the dietary variables from physical activity and the drug effects as the other components of the studied interventions?

5. Methods

In this thesis, analyses were conducted using the data collected from 3 completed REMIT trials (REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi). A total of 416 adults with type 2 diabetes participated in the 3 trials.

5.1. REMIT trials

5.1.1. Study designs and population

The REMIT trials[35,36] are a group of multicenter, open-label, parallel, randomized controlled trials that investigated whether metabolic interventions combining short-term intensive medical therapy and lifestyle modifications can increase the likelihood of remission in adults with early type 2 diabetes. There are currently 3 completed trials (REMIT-dapa, REMIT-sita, REMIT-iGlarlixi) and 1 ongoing trial (REMIT-iDegLira) that have been conducted at multiple sites across Canada since 2015. The primary difference between the REMIT trials involves the choice of diabetes medications administered to participants in the intervention group. The REMIT trials used the following diabetes medications of interest in their interventions: dapagliflozin, metformin, and insulin glargine in REMIT-dapa; sitagliptin, metformin, and insulin glargine in REMIT-sita; insulin glargine/lixisenatide and metformin in REMIT-iGlarlixi; and insulin degludec/liraglutide and metformin in REMIT-iDegLira.

Eligible patients that were recruited include men and women between the ages of 30 to 80 years old diagnosed with type 2 diabetes mellitus within the last 5 to 8 years (depending on the trial), a body mass index (BMI) $\geq$ 23 kg/m^2, and glycated hemoglobin A_{1c} (HbA_{1c}) levels within certain ranges depending on the number of current glucose-lowering agents used.

Patients were excluded from the study if there was current use of insulin therapy, known hypersensitivities to any of the medications used in the trials, history of hypoglycemia unawareness or severe hypoglycemia requiring assistance, history of excessive alcohol intake, prior/planned bariatric surgery, or current/planned pregnancy for the duration of the trial. Patients with a previous history of cardiovascular disease, end-stage renal disease or renal dysfunction, lactic acidosis or diabetic ketoacidosis, disease that required systemic glucocorticoid treatment, active liver disease or alanine transaminase levels (ALT) ≥ 2.5 times the upper limit of normal were also excluded from the trials.

The specific criteria varied between each REMIT trial. A full list of inclusion and exclusion criteria is provided in the Appendix: Supplementary Table 1. All previous and current REMIT trials were approved by research ethics boards at all sites and all participants provided written informed consent.

5.1.2. Trial procedures and treatments

Eligible participants were randomized to either the intervention group (comprised of 12 weeks of intensive metabolic therapy and subsequent 52 weeks of follow-up) or the control group (comprised of 12 weeks of standard diabetes care and subsequent 52 weeks of follow-up).

Participants allocated to the intervention group were asked to discontinue their current glucose-lowering drugs at randomization. They entered a 12-week induction phase which included intensive glucose-lowering medical therapy with basal insulin, metformin, and the REMIT trial's unique drug of interest. Participants were also counseled on lifestyle modifications which involve reducing caloric intake to achieve ≥ 5% weight loss by 24 weeks, increasing moderate-intensity physical activity to ≥ 150 minutes per week by 12 weeks, and regularly measuring

capillary glucose levels at least twice daily. Coaching sessions were also frequently provided with individualized goal setting and assessment of barriers to further reinforce the participant's personalized lifestyle modifications.

Participants allocated to the control group were asked to continue using their prescribed glucose-lowering medications and visit their usual diabetes care providers according to the Canadian Diabetes Association (CDA) Clinical Practice Guidelines in 2013[60]. Participants were similarly encouraged to regularly visit research staff throughout the trial to review glucose self-monitoring, management of hypoglycemia, and the importance of a healthy diet and physical activity.

5.1.3. Study timeline and data measurements

After 12 weeks of the intervention or standard diabetes care, participants were followed for 52 weeks with follow-up visits at 12, 24, 36, 48, and 64 weeks after randomization. Important participant characteristics were measured at baseline and/or follow-up, which include height, weight, fasting plasma glucose, and six-point glucose profiles. HbA_{1c} levels were also measured at baseline (0 weeks), 12, 24, 36, 48, and 64 weeks after randomization. The HbA_{1c} levels at 12 weeks were assessed to determine whether participants could discontinue the use of glucose-lowering medications. If participants presented with $HbA_{1c} < 7.3\%$, they were asked to stop taking glucose-lowering medications. If participants presented with $HbA_{1c} \geq 7.3\%$, they were advised to continue diabetes medication use and reach out to their usual diabetes care providers for further diabetes care.

The primary outcome varied across the REMIT trials but in these analyses, the outcome selected was measured the same way in all trials. Diabetes remission at 24 weeks after

randomization (12 weeks after diabetes medications were discontinued) was defined as HbA_{1c} levels < 6.5% without the use of any glucose-lowering medications for at least 12 weeks. The outcome of diabetes remission is a binary variable that records whether remission was achieved or not in each participant at every follow-up visit. This definition of remission meets the current diabetes remission definition by the Canadian Diabetes Association Clinical Practice Guidelines[4]. Diabetes remission was also measured at follow-up at 36, 48, and 64 weeks after randomization. Participants who did not meet the criteria for remission were considered to have experienced diabetes relapse. Participants who missed a follow-up visit were classified with the same remission status as their subsequent visit. If there was no subsequent visit, it was assumed that a diabetes relapse had occurred.

Participants were also asked to complete both physical activity and food frequency questionnaires at baseline, 12, 24, and 64 weeks after randomization.

5.2. Methodological considerations

5.2.1. Food frequency questionnaire

The food frequency questionnaire (FFQ) is a dietary assessment tool that helps estimate food and beverage intake over a specific period of time. In the REMIT trials, participants were asked to report the food and beverage items they consumed in the last 3 months. The FFQ includes a detailed list of commonly consumed items with pre-determined portion sizes and response options for the frequency of consumption. The FFQ is a self-reported questionnaire where individuals are asked to recall the amount and frequency at which they consume different types of foods. The average daily amount of consumed food items is calculated by translating food frequency responses into a per-day value and multiplying by the serving size responses:

0.5x, 1x, and 1.5x for small, average, and large serving sizes, respectively. As a result, we can obtain the individual's average daily consumption of each item in the FFQ.

The FFQs used in the REMIT trials were validated and previously used in the SHARE and CAHHM studies[68,69]. There are 3 different versions of the FFQ that were tailored to account for food items commonly consumed in the diets of different ethnic groups. These include the FFQ-European Caucasian (FFQ-EC), FFQ-South Asian (FFQ-SA), and FFQ-Chinese (FFQ-CN). For the purposes of the current analyses, we decided to only include participants who completed the FFQ-EC since very few participants (<5%) completed the FFQ-SA and FFQ-CN. There are also a lot more mixed dishes in South Asian and Chinese diets, which makes it more difficult to estimate the nutritional intake and glycemic index of certain food items in the FFQ-SA and FFQ-CN. By using a single version of the FFQ, we gain more precision in estimating dietary intake and avoid introducing more statistical noise to the dataset.

In the REMIT trials, there were slight modifications made to the FFQ-EC which include the addition of 9 miscellaneous food items that were not previously used in the validated FFQ plus several questions related to the use of processed foods. These were added at the end of the questionnaire. We decided to remove these items from the nutrient calculations and analyses and only include the food items used in the validated questionnaires. There was also a section in the REMIT FFQs that allowed participants to manually write in their consumption of miscellaneous food items that may not have been listed in the FFQ. These manually reported items were also omitted to ensure the nutrient calculations and estimations remained consistent across all participants who completed the FFQs.

5.2.2. Nutrient composition matrix

Based on the user responses to the FFQ-EC, we can also estimate the dietary and nutritional profile of each participant using a nutrient composition matrix. The nutrient matrix used in the analyses was developed based on the information provided by the Canadian Nutrient File (CNF)[70]. The CNF database provides an updated and detailed breakdown of the amount of different macronutrients and micronutrients found in common food and beverage items in Canada[70]. Examples include the number of calories, carbohydrates, protein, fat, dietary fiber, vitamins, and minerals found in each item. By combining the nutrient composition breakdown of food items with an individual's responses to the FFQ, we can estimate the total daily intake of macronutrients (carbohydrate, protein, and fat intake), micronutrients (vitamins and minerals), and other dietary factors (caloric intake) for each individual.

For example, according to the CNF[70], one slice of commercial white bread contains 94 kcals of energy, 17.72 g of carbohydrates, 28 mg of calcium, and 5.3 mg of choline. If an individual reports that they consume 2 slices of white bread per day, then the daily nutritional value obtained by this individual from consuming white bread is 188 kcals, 35.44 g of carbohydrates, 56 mg of calcium, and 10.6 mg of choline. These estimations are repeated and summed for every item in the FFQ.

5.2.3. Calculating the glycemic index and glycemic load of the individual's diet

To calculate the overall glycemic index (GI) and glycemic load (GL) of the diet, the GI and GL of items in the FFQ-EC are required. We obtained the GI values for all food items in the FFQ-EC from publications, databases, or online sources using glucose as the reference food[71-82]. The glucose scale is based on a GI of 100 for pure glucose. If one source reported multiple GI values for the same food item, we calculated and used the mean of the GI values. We relied on more credible sources such as publications and databases to find most of the GI values but turned

to online sources or websites to find GI values for less common items. If no data were provided, the GI for a similar food item was used. We were unable to find the GI value for non-dairy creamer in coffee/tea in the FFQ, so we proceeded to use the GI value for coffee creamer in coffee/tea instead.

The GL for one serving of each item in the FFQ-EC was calculated using the following formulas (where available carbohydrates (AVBCHO), total carbohydrates, and dietary fiber are expressed per serving):

$$AVBCHO = Total\ carbohydrates - Dietary\ fiber$$

$$GL\ per\ serving = \frac{AVBCHO * Glycemic\ Index}{100}$$

The dietary GL and dietary GI for an individual were calculated using their responses to the FFQ (where GL of consumed item, number of medium-size servings, dietary GL, dietary GI, and dietary AVBCHO are expressed in daily values):

$$GL\ of\ consumed\ item = GL\ per\ serving * number\ of\ medium\ size\ servings\ consumed$$

$$Dietary\ GL = sum\ of\ GL's\ for\ all\ consumed\ items$$

$$Dietary\ GI = \frac{Dietary\ GL}{Dietary\ AVBCHO} * 100$$

5.3. Analytical considerations

5.3.1. Missing data and applying data restrictions

Of the 416 participants across the 3 REMIT trials, 74 participants were excluded from analyses because they were missing FFQ data completely at baseline or 12 weeks, or any important baseline variables. Seventy-two participants were missing FFQ data completely at

either baseline or 12 weeks. Two participants were missing fasting plasma glucose measurements at baseline. Thus, there was available data for 342 participants which were considered for the analyses.

We also placed restrictions on the dataset to remove any participants who may have misreported their dietary intake and/or consumed extreme diets that are not representative of individuals with diabetes. Participants were excluded from analyses if their daily caloric intake estimated from their responses to the FFQ was unusually high or low (males with less than 800 kcal or greater than 4200 kcal, females with less than 500 kcal or greater than 3500 kcal). Participants were also excluded if their daily carbohydrate intake was unusually high or low (less than 50 g or more than 400 g). Twenty-nine participants reported a daily caloric intake outside the accepted range at baseline or 12 weeks, and another 9 participants reported daily carbohydrate intake outside the accepted range at baseline or 12 weeks. A total of 38 participants were excluded according to these data restrictions. We also planned to exclude participants if they did not respond to enough items on the FFQ (less than 90% of the items on the FFQ). This was planned to remove participants who had attempted the questionnaire but provided incomplete responses which may not accurately reflect their dietary intake. However, no participants who attempted the FFQ had responded to less than 90% of the items on the questionnaire.

Overall, we analyzed data taken from 304 participants across 3 completed trials (REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi). These participants completed the FFQ at baseline (0 weeks) and 12 weeks and had data on their remission status at 24 weeks. A detailed consort diagram of the missing data and data restrictions is shown in Figure 1. All analyses were conducted using SAS software version 9.4 (2013).

5.3.2. Descriptive analyses and data exploration to identify high-leverage points

Prior to creating any statistical models, descriptive analyses were performed on the baseline characteristics of the study participants and all variables planned to be included in the regression models. This includes age, sex, ethnicity, BMI, duration of diabetes, use of glucose-lowering medications, FPG at baseline, HbA_{1c} at baseline, assigned treatment group, daily caloric intake at baseline, daily dietary GL at baseline, daily dietary GI at baseline, and daily carbohydrate intake at baseline. We also planned to compare these variables between those who achieved and did not achieve diabetes remission. Categorical variables were described using frequency tables with percentages and compared using a chi-squared test of independence. Continuous variables were described using means with standard deviations and compared using a two-sample t-test.

In addition, we explored the dataset and identified any high-leverage points (outliers with respect to the independent variable) using boxplots for each dietary predictor variable. Data points were considered high-leverage points if the value of the dietary independent variable was more than 1.5x the interquartile range (IQR) above the third quartile or below the first quartile. If high-leverage points were identified, sensitivity analyses were conducted with and without the high-leverage points in each regression model.

5.3.3. Comparing the distributions of the dietary variables between two time points separately in individuals who achieved and did not achieve diabetes remission

We wanted to compare the distributions of each dietary predictor variable measured at baseline to the same variable measured at 12 weeks. The paired samples t-test was used to compare the baseline to the 12-week values of the following dietary predictor variables: daily

dietary GL, daily dietary GL, and daily carbohydrate intake (in g and % of daily energy intake). The comparisons were conducted exclusively and separately in participants who achieved and did not achieve diabetes remission at 24 weeks after randomization. This was done to further explore how these dietary predictor variables may change across time points depending on remission status and also to provide a better understanding of the data.

5.3.4. Regression models

Regression models were created to explore the relationship between the following dietary predictor variables and the outcome of diabetes remission: daily dietary GL, daily dietary GI, daily carbohydrate intake (in total g and % of energy intake), daily dietary fiber intake, daily consumption of starchy foods, daily consumption of sugar-sweetened beverages, and daily consumption of sweets.

5.3.5. Selection of time points for the predictor and outcome variables

The outcome used in the current analyses was remission of diabetes at 24 weeks after randomization. As used in the REMIT trials, the outcome of diabetes remission occurred in participants who presented with HbA_{1c} levels < 6.5% at follow-up after discontinuing glucose-lowering medications for at least 12 weeks. Participants who met the criteria for diabetes remission at their follow-up visit were coded as '1'. Participants who did not meet the same criteria were coded as '0'. Since the outcome at 24 weeks was recorded as a binary variable of either achieving remission or not, we performed logistic regression analyses to model these relationships.

In the REMIT trials[35,36], diabetes remission was measured at 24, 36, 48, and 64 weeks after randomization during follow-up visits for each participant. Therefore, we had the option of

selecting the time point of the outcome in the thesis analyses. We decided to use the outcome of remission measured at 24 weeks because the 24-week visit is the earliest time point at which remission was recorded. It is also the time point closest to the intervention period and when diabetes remission was recorded most frequently.

Participant data for all dietary predictor variables were derived from the FFQs that were administered in the REMIT trials. Participants were asked to complete the FFQ at baseline, 12, 24, and 64 weeks after randomization. Thus, we also had the option of selecting from multiple time points to express the FFQ-derived predictor variables. We decided to look at each dietary variable measured at 12 weeks and the change in the variable from baseline to 12 weeks. This was because we believed that both the baseline value and the dietary changes the participant makes during follow-up are important for the outcome of remission. For each dietary predictor variable, we created separate regression models for the variable measured at 12 weeks and the change in the variable from baseline to 12 weeks to reflect both considerations. We selected the 12-week follow-up time point for both of these models to ensure the measurement of the predictor variables occurred before the outcome was measured.

5.3.6. Selection of the covariates to adjust for in the models

The following covariates were included and adjusted for in the final regression models: age, sex, ethnicity, duration of diabetes, baseline FPG, use of diabetes medications at baseline, and assigned treatment group.

Age, sex, and ethnicity are important demographic variables that are commonly adjusted for in epidemiological analyses. Age was a continuous variable expressed in years. Sex was a categorical variable and assigned dummy code as “0” for females and “1” for males. Ethnicity

was a categorical variable and was recorded using 11 different categories. For the analyses, ethnicity was assigned a dummy code as "0" if they were not European-Caucasian and "1" if they were European-Caucasian.

Duration of diabetes, baseline FPG, and the use of diabetes medications at baseline are unique baseline variables that reflect the health status and severity of the diabetes condition in patients with type 2 diabetes. These variables are implicated as important predictors of health outcomes relevant to diabetes[83-86]. Thus, they should be accounted for when assessing the independent effects of dietary variables on diabetes remission. Duration of diabetes was a continuous variable measured at baseline as the number of months since their diagnosis of diabetes. FPG was also a continuous variable measured at baseline in mmol/L. The use of diabetes medications at baseline was a categorical variable and assigned a dummy code as "0" for not taking any diabetes medications and "1" for taking diabetes medications.

Because the data come from participants enrolled in randomized clinical trials, it is also important to consider how the differential effects of the treatments used in the intervention and control arms may affect the outcomes in the analyses. In each REMIT trial[35-36], similar 12-week intensive metabolic therapies were administered to participants of the intervention groups. In contrast, participants in the control arms received 12 weeks of standard diabetes care. They also on their own tried to make lifestyle changes. Consequently, when creating the regression models, we adjusted for the treatment group to explore if the dietary variables are independent determinants of remission after accounting for the effects of the study interventions on remission. The treatment group was a categorical variable and assigned a dummy code as "0" for the control group and "1" for the intervention group.

5.3.7. Proposed regression models

To model the probability of achieving the categorical outcome of diabetes remission, logistic regression models were created. The analyses conducted can be split into 2 sets of models that evaluate: 1) relationships between dietary variables measured at 12 weeks and diabetes remission at 24 weeks and 2) relationships between change in dietary variables from baseline to 12 weeks and diabetes remission at 24 weeks. In these models, we adjusted for age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, and treatment group. All proposed regression models are described in Tables 1 and 2.

5.3.8. Exploring the potential role of weight loss as a mediator of the significant relationships between dietary variables and diabetes remission

When we evaluate the associations between variables related to the diet and diabetes remission, it may be necessary to consider how weight loss influences these relationships. Previous evidence has suggested that diabetes remission may be closely linked to weight loss[4,30,42]. We also understand that the diet can strongly influence changes in body weight[44,50]. Thus, if there exists a relationship between the dietary variables of interest and diabetes remission, we must account for the possibility that the effects of the independent variables on the outcome could operate through a third variable of weight change.

We decided a priori to assess whether the extent of weight loss mediates any of the observed relationships in the analyses. If there were statistically significant relationships between a dietary variable and diabetes remission, we planned to conduct mediation analyses to explore the role of percent weight loss from baseline to 12 weeks as a potential mediator. We restricted the mediation analyses to models that investigated the change in dietary variables from baseline to 12 weeks and not the dietary variables fixed at 12 weeks. This was done to ensure both the independent variable and the mediating variable are expressed across the same time points.

To analyze mediation, we followed Baron and Kenny's stepwise approach to model building in mediation analyses[87]. This approach involves 3 steps of model building that were considered for each statistically significant independent variable.

1. Create a model predicting the outcome (Y) using the independent variable (X) and other covariates. Assess the significance of the beta coefficient (b1) for the independent variable. If b1 is significant, we can proceed with step 2. Otherwise, there is no relationship between X and Y and no mediation.

$$Y = b0 + b1\ (X) + e$$

2. Create a model predicting the mediating variable (M) using the independent variable (X) and other covariates. Assess the significance of the beta coefficient (b2) for the independent variable. If b2 is significant, we can proceed with step 3. Otherwise, there is no relationship between X and M, and no mediation (M is simply a third variable that may or may not be associated with Y).

$$M = b0 + b2\ (X) + e$$

3. Create a model predicting the outcome (Y) using both the independent variable (X) and the mediating variable (M) and other covariates. A mediation effect may exist if the relationship between X and Y disappears or weakens after including M in the model (i.e. if b4 is not significant or smaller than b1). This can be tested using the Sobel test (or Preacher and Hayes bootstrapping approach).

$$Y = b0 + b4\ (X) + b3\ (M) + e$$

The Preacher and Hayes bootstrapping approach helps test if a mediation effect is present[88]. Bootstrapping assesses whether the average causal mediation effect (ACME) is different from zero. The ACME is also referred to as the mediation effect or the indirect effect. The ACME can be calculated in two ways: 1) the total effect minus the direct effect (b1 – b4) or 2) the product of the beta coefficients for X in step 2 and M in step 3 (b2*b3). Testing the significance of the ACME determines whether there is no mediation effect (not significant), partial mediation (not significant but ACME is non-zero), or full mediation (significant)[87-89].

5.3.9. Comparing the relationships of interest separately in individuals randomized to the intervention group and control group

We proposed to test for an interaction effect between the treatment group and the dietary predictor variables of interest (dietary GL, GI, and carbohydrate intake) both at 12 weeks and as a change from baseline to 12 weeks with respect to diabetes remission. The purpose of testing for this interaction was to assess whether the relationships of interest are similar across the two treatment groups. By adding an interaction term to each of these models, we can identify if the treatment group may act as an effect modifier of these relationships. If the interaction term was statistically significant, effect modification is present, and we proceeded to interpret the results stratified by the treatment group and ignore the overall relationship.

However, it is important to understand that testing for interaction often requires large sample sizes and adequate statistical power. We recognized that in our analyses, an interaction effect may not be detected even if it was truly present. Thus, we planned to present both the main effects and the effects stratified by treatment group, unless a statistically significant interaction was observed.

5.3.10. Exploring daily caloric intake as a potential confounder of the relationships between dietary predictor variables and diabetes remission

In separate models, we wanted to explore whether daily caloric intake measured at 12 weeks may be a confounder of the relationships highlighted in the proposed models. This is because we expected that many dietary variables go hand in hand with daily caloric intake. For example, individuals who consume larger amounts of carbohydrates per day are naturally increasing their daily caloric intake. Thus, it is important to understand whether the effects on diabetes remission can be attributed to the carbohydrate-related variable itself or simply due to changes in daily caloric intake. In these models, we included a statistical adjustment for the daily caloric intake derived from the FFQ measured at 12 weeks. We restricted these models to dietary variables measured only at 12 weeks to ensure both the independent variable and potential confounding variable are expressed at the same time point.

5.3.11. Considering potential over-adjustment when adjusting for the treatment group

Although we adjusted for the treatment group in most of the regression models, we believe this may not precisely help assess the relationship between our dietary variables and the outcome. This is because the treatments in the intervention groups are comprised of many components, including a dietary component. In addition to medical therapy and increased physical activity, participants were also counseled with individualized dietary recommendations and caloric restrictions targeting ≥ 5% weight loss by 24 weeks. In this case, adjusting for the treatment group may bury some of the important remission-related effects attributed to the dietary variables of interest. Therefore, in separate exploratory models, we decided to investigate whether adjusting for only the non-dietary components of the intervention rather than the

treatment group altogether will change the observed relationships between our independent and dependent variables.

We proposed that one way to isolate the effects of the dietary variables of interest will be adjusting for (i) the fasting capillary glucose measured twice during week 12 while on diabetes medications which mostly reflects the response to glucose-lowering therapy and adjusting for (ii) total physical activity. Fasting capillary glucose was a continuous variable measured in mmol/L. Total physical activity was measured in minutes per week by the International Physical Activity Questionnaire (IPAQ) at 12 weeks. This approach may help address and adjust for the drug and physical activity components without burying the effects of the dietary component of the study interventions.

5.3.12. Adjusting for the baseline value of the dietary predictor variables in separate sensitivity analyses

As mentioned previously, we selected the dietary variables measured at 12 weeks as our independent variables of interest in the regression models. Because these variables were measured both at baseline and follow-up, we also considered adjusting for the baseline values in our models.

When adjusting for the baseline value, the beta-coefficient for the follow-up value would reflect the independent contribution of this value on the outcome, after accounting for potential differences at baseline. Adjusting for the baseline value would remove its effect on the outcome by keeping it constant. This would be appropriate if we were uninterested in how the values of the independent variables at baseline may affect the outcome. However, we believe that both the baseline value and any changes to the diet from baseline to 12 weeks are important for the

outcome of diabetes remission. Thus, in both the models assessing the dietary variables at 12 weeks and the change in dietary variables from baseline to 12 weeks, we decided not to adjust for the baseline value of the predictor variable in initial analyses. This allows us to investigate the relationships between the dietary variables and the outcome, which captures how potential differences at baseline may influence the outcome.

Separate sensitivity analyses were conducted to test whether the results are robust to the adjustment for the baseline values of each dietary variable. In these models, the results of adjusting and not adjusting for the baseline values are presented for both the dietary variables measured at 12 weeks and the change in dietary variables from baseline to 12 weeks.

5.3.13. Testing the assumptions of logistic regression models

There are 4 assumptions to multivariable logistic regression models which are as follows: 1) the outcome is a binary variable, 2) observations are independent of one another, 3) there is a linear relationship between the continuous independent variables and the logit of the outcome variable, 4) the independent variables are not collinear.

Assumptions 1 and 2 can be evaluated by considering the relevant methodological components of the study, including the details of participant recruitment and outcome measurement.

Assumption 3 was evaluated using the Box-Tidwell test, which can be used to check if there is a linear relationship between the continuous independent variables and the logit of the outcome variable. This was done by adding an interaction term between the independent variable and the natural log of the independent variable to the model. Using the Wald test, we tested the statistical significance of the coefficient for the interaction term. A statistically significant

interaction term suggests there is evidence of a non-linear relationship between the independent variable and the logit of the outcome variable. In the event that a continuous independent variable is non-linearly associated with the logit of the outcome, we planned to implement data transformations or categorize the continuous variable to improve the fit of the model.

Assumption 4 was evaluated by calculating the variance inflation factors (VIF) for each independent variable in the regression model. The VIF is a measure of the amount of multicollinearity that exists between independent variables of a multivariable regression model. It estimates the degree to which the variance of a regression coefficient is inflated due to potential issues with multicollinearity. A VIF of 1 suggests the independent variable is not correlated with the other independent variables. Typically, a VIF greater than 10 indicates there are serious concerns of multicollinearity between the independent variables. In the event that two or more independent variables were highly correlated, we planned to remove collinear variables until the VIFs of each independent variable in the model were less than 10.

5.3.14. Interpreting the regression model output and statistical tests for goodness-of-fit

In this thesis, we conducted multivariable logistic regression analyses to estimate the probability of achieving a categorical outcome depending on the values of the independent variables. Beta coefficients were estimated for each independent variable included in the model. This was estimated using the maximum likelihood estimation (MLE) where different values of the coefficient are tested and optimized for the greatest fit of log odds. The beta coefficient represents the expected change in log odds of achieving the outcome for every unit change increase in a continuous independent variable or when changing categories in a categorical independent variable. By taking the antilog of the beta coefficient, we can describe the odds ratio that associates the independent variable with the outcome.

The Wald chi-squared test is a statistical test that was used to confirm whether the beta coefficients for the predictor variables in the model were equal to zero. The null hypothesis tested was that the beta coefficient is equal to zero. If the beta coefficient was statistically significant, we rejected the null hypothesis which suggests that the predictor variable has an independent effect on the outcome after accounting for all other covariates in the model.

To assess the goodness of fit of the regression models in our analyses, we used the Hosmer-Lemeshow test. Individuals were grouped into deciles of predicted probabilities and comparisons were made between the actual and predicted event rates. The null hypothesis tested was that the actual and predicted event rates are similar across 10 deciles. A statistically significant test rejects the null hypothesis and suggests the model is not a good fit for the data. If the Hosmer-Lemeshow test was found to be statistically significant, we planned to change the selection of the covariates included in the model.

6. Results

6.1. Characteristics of the study population included in analyses

6.1.1. Baseline characteristics of the study population

The baseline characteristics of the study population included in the analyses are described in Table 3. The mean age of the study participants is 56.8 years with a standard deviation (SD) of 9.6 years. There are 178 males (58.6%) and 274 European-Caucasians (90.1%). The mean body mass index (BMI) is 32.7 kg/m^2 with an SD of 5.9 kg/m^2. The mean duration of time since diabetes diagnosis is 29.5 months with a SD of 22.0 months. There were 275 participants taking diabetes medications at baseline (90.5%). The mean fasting plasma glucose (FPG) levels at baseline were 7.6 mmol/L with an SD of 1.8 mmol/L and the mean HbA_{1c} levels at baseline were 6.7% with an SD of 0.7%. There were 168 participants (55.3) and 136 participants (44.7) who were randomized to the intervention and control groups, respectively, in the 3 REMIT trials.

6.1.2. Dietary characteristics of the study population derived from the FFQ completed at baseline

A summary of the dietary characteristics of the study population as derived from the FFQ completed at the baseline visit is also provided in Table 3. The dietary variables are all expressed as daily values. The mean total caloric intake at baseline was 1813.5 kcal/day with an SD of 632.4 kcal. The mean daily dietary glycemic load and glycemic index at baseline were 84.5 GL units (SD, 36.3) and 45.5 GI units (SD, 5.8), respectively. The mean daily carbohydrate intake at baseline was 202.6 g (SD, 72.1 g). It contributes to 45.1% (SD, 7.3%) of the average daily energy intake.

6.1.3. Comparing baseline characteristics and dietary variables at baseline between participants in the remission and non-remission groups

Out of the 304 participants included in the analyses, 81 (26.6%) achieved diabetes remission at 24 weeks. Diabetes remission was defined as achieving HbA_{1c} levels < 6.5% and having discontinued any glucose-lowering medications for at least 12 weeks. Baseline characteristics and certain dietary variables derived from the FFQ at both baseline and 12 weeks were compared between participants who achieved and did not achieve diabetes remission at 24 weeks after randomization (Table 3, Figures 2 and 3).

In comparison to the non-remission group, participants who achieved remission had a lower FPG (6.7 vs 8.0 mmol/L), a lower HbA_{1c} (6.2 vs 6.9%), and a shorter duration of diabetes (21.7 vs 32.3 months) at baseline. Participants who achieved remission also consumed a lower amount of carbohydrates expressed as a percentage of daily energy intake (43.5 vs 45.6%) at baseline. Comparisons of other baseline characteristics and dietary variables at baseline listed in Table 3 were not found to be statistically significant.

6.1.4. Comparing the baseline with the 12-week distributions of each dietary variable separately for participants in the remission and non-remission groups

The distributions of the dietary variables of interest at baseline were also compared to the same variables at 12 weeks separately in those who achieved and did not achieve diabetes remission at 24 weeks after randomization (Figures 2 and 3). In participants who achieved remission, daily dietary GL (66.4 vs 81.0 GL units), daily dietary GI (43.5 vs 45.1 GI units), and daily carbohydrate intake expressed in total grams (170.1 vs 200.5 g) were all lower at 12 weeks

compared to baseline. However, daily carbohydrate intake (% of daily energy intake) at baseline and 12 weeks was not significantly different.

Similarly, in participants who did not achieve remission, daily dietary GL (72.8 vs 83.0 GL units), daily dietary GI (44.5 vs 45.5 GI units), and daily carbohydrate intake expressed in total grams (183.9 vs 203.4 g) were lower at 12 weeks compared to baseline. But daily carbohydrate intake (% of daily energy intake) at baseline and 12 weeks was not significantly different.

6.2. Associations between daily dietary GL and GI with diabetes remission

6.2.1. Relationships between daily dietary GL and GI at 12 weeks with diabetes remission (Models A1 and A2)

In multivariable logistic regression analyses, the relationships between daily dietary GL and daily dietary GI at 12 weeks with diabetes remission at 24 weeks after randomization were assessed in 304 study participants. Both daily dietary GL and GI were categorized into quartiles and comparisons were made between quartiles of each variable with the lowest quartile as the reference (Q4 vs Q1, Q3 vs Q1, and Q2 vs Q1). The median values for the daily dietary GL are as follows: quartile 1, 41 (IQR, 30-46); quartile 2, 58 (IQR, 54-62); quartile 3, 78 (IQR, 74-83), quartile 4, 103 (IQR, 97-119). The median values for the daily dietary GI are as follows: quartile 1, 38 (IQR, 33-40); quartile 2, 44 (IQR, 42-45); quartile 3, 47 (IQR, 46-48), quartile 4, 50 (IQR, 49-52).

The results of the comparisons between quartiles are shown in Figure 4 – Panel A. The adjusted odds ratios of diabetes remission, 95% confidence intervals, and p-values are presented for quartiles 2, 3, and 4, in comparison to the reference quartile. There were no statistically

significant differences between quartiles for either daily dietary GL or GI at 12 weeks with respect to associations with diabetes remission at 24 weeks after randomization. However, there was a consistent direction of effects towards lower odds of diabetes remission with higher daily dietary GL at 12 weeks for each quartile comparison.

6.2.2. Relationships between daily dietary GL and GI at 12 weeks with diabetes remission assessed separately in intervention and control groups (Models B1 and B2)

When exploring the potential effect modification of the assigned treatment group on the relationships between daily dietary GL and GI at 12 weeks with diabetes remission, we found no evidence of an interaction effect as the interaction terms of these models were not statistically significant (results are not included). Although no effect modification was detected, the results of these models stratified by the treatment group are presented for exploratory purposes in Figure 4 – Panels B and C. There were no apparent differences in the odds ratios obtained in the intervention versus control groups.

6.2.3. Relationships between change in daily dietary GL and GI from baseline to 12 weeks with diabetes remission (Models C1 and C2)

Similarly, in multivariable logistic regression analyses, the relationships between the change in daily dietary GL and GI from baseline to 12 weeks with diabetes remission at 24 weeks after randomization were evaluated in 304 study participants. The change in daily dietary GL and GI were expressed as continuous variables using GL and GI units, respectively. These relationships are shown in Figure 5 – Panel A. The adjusted odds ratios of diabetes remission, 95% CIs, and p-values are presented for every 10 and 5 units increase in GL or GI, respectively, from baseline to 12 weeks. There were no statistically significant relationships between the

change in daily dietary GL or daily dietary GI from baseline to 12 weeks with diabetes remission at 24 weeks after randomization.

6.2.4. Relationships between change in daily dietary GL and GI from baseline to 12 weeks with diabetes remission assessed separately in intervention and control groups (Models D1 and D2)

Potential effect modification was also tested for the assigned treatment group on the relationships between the change in daily dietary GL and GI from baseline to 12 weeks with diabetes remission. The interaction terms of the models were not found to be statistically significant (results are not included). Although no effect modification was detected, the results of these models stratified by the treatment group are presented for exploratory purposes in Figure 5 – Panel B. There were no apparent differences in the odds ratios of remission obtained in the intervention and control groups for the change in daily dietary GL from baseline to 12 weeks. However, when exploring the relationship between change in daily dietary GI from baseline to 12 weeks with diabetes remission separately in the intervention and control groups, there was a statistically significant relationship only in the control group. The OR of diabetes remission in the control group was 0.610 (95% CI 0.375-0.985, p = 0.044) for every 5 GI units increase in daily dietary GI from baseline to 12 weeks.

6.2.5. Sensitivity analyses on excluding high-leverage points of daily dietary GL or GI from the dataset

We identified the following numbers of high-leverage points according to the dietary independent variable: 4, daily dietary GL at 12 weeks; 12, change in daily dietary GL from baseline to 12 weeks; 11, daily dietary GI at 12 weeks; 12, change in daily dietary GI from

baseline to 12 weeks). In separate sensitivity analyses, we compared the results after removing these high-leverage points from its corresponding regression model. The results of the sensitivity analyses are shown in Table 4. The results were robust with and without the removal of high-leverage points for each of the corresponding regression models.

6.2.6. Sensitivity analyses on adjusting for the baseline value of daily dietary GL or GI

The logistic regression models assessing the dietary predictors at 12 weeks and the change in dietary predictors from baseline to 12 weeks did not include adjustments for the baseline for the reasons described in section 5.3.12. We conducted sensitivity analyses to compare the robustness of the results after adjusting for the baseline value of daily dietary GL or GI. Models A1, A2, C1, and C2 were repeated for the 304 study participants after adjusting for the baseline value of daily dietary GL and GI, respectively. The results of the relationships between daily dietary GL at 12 weeks and the change in daily dietary GL from baseline to 12 weeks with diabetes remission remained robust after adjusting for the baseline value of daily dietary GL. Similarly, the results of the relationships between daily dietary GI at 12 weeks and the change in daily dietary GI from baseline to 12 weeks with diabetes remission remained robust after adjusting for daily dietary GI at baseline. The results of these sensitivity analyses are shown in Table 5.

6.2.7. Exploring the role of daily caloric intake as a potential confounder of the relationships between daily dietary GL or GI and diabetes remission (Models E1 and E2)

Daily caloric intake at 12 weeks was evaluated as a potential confounder of the relationships between dietary variables of interest and diabetes remission at 24 weeks after randomization. These relationships after adjustment for daily caloric intake are shown in Table 6.

The adjusted odds ratios of diabetes remissions, 95% CIs, and p-values are presented for quartiles 2, 3, and 4, in comparison to the reference quartile. After adjusting for daily caloric intake at 12 weeks, comparisons between quartiles of daily dietary GL or GI at 12 weeks when predicting diabetes remission at 24 weeks after randomization were not statistically significant. The beta coefficient for daily caloric intake was also not statistically significant, suggesting that daily caloric intake is not a confounder of the relationships between daily dietary GL and GI with diabetes remission in our analyses.

6.2.8. Evaluating the relationships between daily dietary GL and GI with diabetes remission after adjusting for non-dietary components of the studied interventions (Models F1 and F2)

The relationships between both daily dietary GL and GI at 12 weeks with diabetes remission were evaluated again but with adjustments for only the non-dietary components of the interventions, as opposed to the treatment group altogether. This includes adjusting for fasting capillary glucose at 12 weeks while on diabetes medications (to reflect the responses to glucose-lowering therapy) and total physical activity at 12 weeks measured by the international physical activity questionnaire (IPAQ). The adjustment for all other covariates remained the same. The results of these exploratory models are shown in Table 7. According to this approach for isolating the effects of the dietary variables on diabetes remission from the drug and physical activity components of the interventions, there were still no statistically significant relationships observed when comparing quartiles of daily dietary GL or GI at 12 weeks with respect to associations with diabetes remission at 24 weeks after randomization. However, the quartile comparisons still demonstrated a consistent direction of effects towards lower odds of diabetes remission with a higher daily dietary GL at 12 weeks.

6.3. Associations between daily carbohydrate intake with diabetes remission

6.3.1. Relationships between daily carbohydrate intake at 12 weeks with diabetes remission (Models A3 and A4)

The relationships between daily carbohydrate intake at 12 weeks with diabetes remission at 24 weeks after randomization were assessed in 304 study participants. In these models, daily carbohydrate intake was expressed both as a measure of total intake in grams and as a percentage of their daily energy intake. Both measures of carbohydrate intake were categorized into quartiles and comparisons were made between quartiles with the lowest quartile as the reference. The median values for daily carbohydrate intake (g) are as follows: quartile 1, 113 (IQR, 91-123); quartile 2, 149 (IQR, 141-163); quartile 3, 195 (IQR, 185-206), quartile 4, 253 (IQR, 231-289). The median values for daily carbohydrate intake (% of daily energy intake) are as follows: quartile 1, 37 (IQR, 35-39); quartile 2, 43 (IQR, 42-44); quartile 3, 47 (IQR, 46-48), quartile 4, 53 (IQR, 51-55).

The results of the comparisons between quartiles are shown in Figure 6 – Panel A. The adjusted odds ratios of diabetes remission, 95% CIs, and p-values are presented for quartiles 2, 3, and 4, in comparison to the reference quartile. Comparisons between quartiles of daily carbohydrate intake (g) at 12 weeks with respect to associations with diabetes remission at 24 weeks after randomization were not statistically significant. However, a comparison between the highest and lowest quartile (Q4 vs Q1) of daily carbohydrate intake (% of daily energy intake) at 12 weeks when predicting diabetes remission at 24 weeks after randomization was statistically significant. After adjusting for age, sex, ethnicity, baseline FPG, use of diabetes medications at baseline, and treatment group, the OR of diabetes remission when comparing the highest to lowest quartile of daily carbohydrate intake as a % of daily energy intake was 0.289 (95% CI

0.124-0.673, p = 0.004). Comparisons of the third or second quartile with the lowest quartile (Q3 vs Q1, Q2 vs Q1) of daily carbohydrate intake at 12 weeks were not statistically significant, however there was a consistent direction of effects towards lower odds of diabetes remission with a higher daily carbohydrate intake (% of daily energy intake).

6.3.2. Relationships between daily carbohydrate intake at 12 weeks with diabetes remission assessed separately in intervention and control groups (Models B3 and B4)

When exploring the potential effect modification of the assigned treatment group on the relationships between daily carbohydrate intake, in grams or percent of daily energy intake, at 12 weeks with diabetes remission, we found no evidence of an interaction effect. The interaction terms of these models were not statistically significant (results are not included). Although no effect modification was detected, the results of these models stratified by the treatment group are presented for exploratory purposes in Figure 6 – Panels B and C. There were no apparent differences in the odds ratios of remission obtained separately in the intervention and control groups for daily carbohydrate intake (g). However, when exploring the relationship between daily carbohydrate intake (% of daily energy intake) at 12 weeks separately in the intervention and control groups, there were statistically significant relationships only in the intervention group. The ORs of diabetes remission were 0.319 (95% CI 0.103-0.988, p = 0.048) when comparing quartile 2 to quartile 1, and 0.175 (95% CI 0.053-0.580, p = 0.004) when comparing quartile 4 to quartile 1 in this group.

6.3.3. Relationships between change in daily carbohydrate intake from baseline to 12 weeks with diabetes remission (Models C3 and C4)

The relationships between the change in daily carbohydrate intake from baseline to 12 weeks with diabetes remission at 24 weeks after randomization were evaluated in 304 study participants. The changes in daily carbohydrate intake were expressed as continuous variables both as a measure of total intake (g) and relative intake (% of daily energy intake). These relationships are shown in Figure 7 – Panel A. The adjusted odds ratios of diabetes remission, 95% CIs, and p-values are presented for every 100 g or 5% increase in daily carbohydrate intake from baseline to 12 weeks. There were no statistically significant relationships between the change in daily carbohydrate intake from baseline to 12 weeks, expressed in either grams or percent of daily energy intake, with diabetes remission at 24 weeks after randomization.

6.3.4. Relationships between change in daily carbohydrate intake from baseline to 12 weeks with diabetes remission assessed separately in intervention and control groups (Models D3 and D4)

Potential effect modification was also tested for the assigned treatment group on the relationships between the change in daily carbohydrate intake, in grams or % of daily energy intake, from baseline to 12 weeks with diabetes remission. Once again, the interaction terms of the models were not statistically significant (results are not included), which suggests an interaction effect was not detected between variables. Although no effect modification was detected, the results of these models stratified by the treatment group are presented for exploratory purposes in Figure 7 – Panel B. There were no apparent differences in the odds ratios of remission obtained in the intervention and control groups for a change in daily carbohydrate intake from baseline to 12 weeks.

6.3.5. Sensitivity analyses on excluding high-leverage points of daily carbohydrate intake from the dataset

We identified the following numbers of high-leverage points according to the dietary independent variable: 6, daily carbohydrate intake (g) at 12 weeks; 6, change in daily carbohydrate intake (g) from baseline to 12 weeks; 7, daily carbohydrate intake (% of daily energy intake) at 12 weeks; 5, change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks. In separate sensitivity analyses, we compared the results after removing these high-leverage points from its corresponding regression model. The results of the sensitivity analyses are shown in Table 4. The results were robust with and without the removal of these high-leverage points.

6.3.6. Sensitivity analyses on adjusting for the baseline value of daily carbohydrate intake

Sensitivity analyses were conducted to compare the robustness of the results after adjusting for the baseline value of daily carbohydrate intake. Models A3, A4, C3, and C4 were repeated for the 304 study participants after adjusting for the baseline value of daily carbohydrate intake in grams or as a percent of daily energy intake, accordingly. The results of the sensitivity analyses are shown in Table 5 and Figure 7 – Panel A. The results of the relationships between daily carbohydrate intake at 12 weeks and the change in daily carbohydrate intake from baseline to 12 weeks (both in grams) remained robust after adjusting for daily carbohydrate intake at baseline. Similarly, the results of the relationship between daily carbohydrate intake (% of daily energy intake) at 12 weeks remained robust after adjusting for the baseline value. However, when evaluating the relationship between the change in daily carbohydrate intake, as a percent of daily energy intake, from baseline to 12 weeks, the results became statistically significant after adjusting for the baseline value of daily carbohydrate intake (% of daily energy intake). The OR of diabetes remission was 0.750 (95% CI 0.587-0.956, p = 0.020) for every 5% increase in daily carbohydrate intake from baseline to 12 weeks. These results support the direction of effect

observed in the same model not adjusted for the baseline value where the OR of diabetes remission was 0.868 (95% CI 0.707-1.061, p = 0.168).

6.3.7. Mediation analyses to explore if the statistically significant relationship between change in daily carbohydrate intake and diabetes remission was mediated by percent weight loss

We conducted mediation analyses to explore if percent weight loss was a potential mediator of the statistically significant relationship between the change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks and diabetes remission at 24 weeks after randomization after adjusting for the baseline value of carbohydrate intake (% of daily energy intake). The results of the mediation analyses are shown in Table 8.

We followed Baron and Kenny's stepwise approach to model building and found that percent weight loss was not mediating the relationship[87]. In step 2 using their approach, the model predicting percent weight loss using the change in daily carbohydrate intake and other covariates was not found to be statistically significant (p = 0.055). The covariates adjusted in this model included age, sex, ethnicity, treatment group, and daily carbohydrate intake (% of daily energy intake) at baseline. According to Baron and Kenny's approach, since there was no relationship between the change in daily carbohydrate intake and percent weight loss, a mediation effect could not be calculated.

6.3.8. Exploring the role of daily caloric intake as a potential confounder of the relationships between daily carbohydrate intake and diabetes remission (Models E3 and E4)

The relationships between daily carbohydrate intake and diabetes remission after adjustment for daily caloric intake are shown in Table 6. The adjusted odds ratios of diabetes remissions, 95% CIs, and p-values are presented for quartiles 2, 3, and 4, in comparison to the

reference quartile. After adjusting for daily caloric intake at 12 weeks, comparisons between quartiles of daily carbohydrate intake (in total grams) at 12 weeks when predicting diabetes remission at 24 weeks after randomization were not statistically significant. The beta coefficient for daily caloric intake was also not statistically significant in the model, indicating that daily caloric intake does not appear to be a confounder of the relationships between daily carbohydrate intake (g) with diabetes remission.

A comparison between the highest and lowest quartiles (Q4 vs Q1) of daily carbohydrate intake at 12 weeks expressed as a percentage of daily energy intake was found to be a statistically significant predictor of diabetes remission at 24 weeks after randomization. After adjusting for age, sex, ethnicity, baseline FPG, use of diabetes medications at baseline, treatment group, and daily caloric intake at 12 weeks, the OR of diabetes remission when comparing quartile 4 to quartile 1 was 0.288 (95% CI 0.124-0.671, p = 0.004). However, these results were similar to the results of the models described in section 6.3.1, where daily caloric intake at 12 weeks was not adjusted for. Thus, the results of the comparison between the highest and lowest quartiles for daily carbohydrate intake expressed as a percent of daily energy intake were similar and remained statistically significant before and after adjusting for daily caloric intake at 12 weeks. The beta coefficient for daily caloric intake was also not statistically significant, suggesting that in this dataset, daily caloric intake is not a confounder of the relationships between daily carbohydrate intake (% of daily energy intake) and diabetes remission.

6.3.9. Evaluating the relationship between daily carbohydrate intake with diabetes remission after adjusting for non-dietary components of the studied interventions (Models F3 and F4)

The relationships between daily carbohydrate intake at 12 weeks with diabetes remission were also evaluated again but with adjustments for fasting capillary glucose on diabetes medications at 12 weeks and total physical activity at 12 weeks measured by the IPAQ, rather than the treatment group. These adjustments aim to account for the effects of the medical therapy and physical activity components of the interventions on the outcome. The adjustment for all other covariates remained the same. The results of these exploratory models are shown in Table 7. According to this approach for isolating the effects of the dietary variables on diabetes remission from the drug and physical activity components of the interventions, there were no statistically significant relationships when comparing quartiles of daily carbohydrate intake (g) in relation to diabetes remission. In contrast, there was a statistically significant relationship when comparing the highest quartile of daily carbohydrate intake (% of daily energy intake) with the lowest quartile with an OR of diabetes remission = 0.267 (95% CI 0.102-0.700, p = 0.007). Similar results were also observed when directly adjusting for the treatment group as stated in section 6.3.1, suggesting that the results from adjusting for the non-dietary components of the intervention did not affect our overall findings.

6.4. Associations between daily dietary fiber intake, daily consumption of starchy foods, sugar-sweetened beverages, and sweets with diabetes remission

The relationships between daily dietary fiber intake, daily consumption of starchy foods, sugar-sweetened beverages (SSB), and sweets at 12 weeks with diabetes remission at 24 weeks after randomization were modeled in 304 study participants. The results of these regression models are shown in Table 9. The adjusted odds ratios of diabetes remission, 95% CIs, and p-values are presented for quartiles 2, 3, and 4, in comparison to quartile 1 (reference).

6.4.1. Relationship between daily dietary fiber intake at 12 weeks with diabetes remission (Model G1)

Daily dietary fiber intake (g) was categorized into quartiles, and comparisons were made between quartiles with the lowest quartile as the reference. The comparisons between quartiles of daily dietary fiber intake at 12 weeks when predicting diabetes remission at 24 weeks after randomization were not statistically significant.

6.4.2. Relationship between daily consumption of starchy foods at 12 weeks with diabetes remission (Model G2)

Daily consumption of starchy foods, measured as the number of medium-sized servings per day, was categorized into quartiles, and comparisons were made between quartiles with the lowest quartile as the reference. The comparisons between quartiles of the daily consumption of starchy foods at 12 weeks when predicting diabetes remission at 24 weeks after randomization were not statistically significant.

6.4.3. Relationship between daily consumption of sugar-sweetened beverages at 12 weeks with diabetes remission (Model G3)

Daily consumption of SSBs, measured as the number of medium-sized servings per day, was also categorized into quartiles, and comparisons were made between quartiles with the lowest quartile as the reference. The comparisons between quartiles of the daily consumption of SSBs at 12 weeks when predicting diabetes remission at 24 weeks after randomization were not statistically significant.

6.4.4. Relationship between daily consumption of sweets at 12 weeks with diabetes remission (Model G4)

Daily consumption of sweets, measured as the number of medium-sized servings per day, was categorized into quartiles, and comparisons were made between quartiles with the lowest quartile as the reference. The comparisons between quartiles of the daily consumption of sweets at 12 weeks when predicting diabetes remission at 24 weeks after randomization were not statistically significant.

6.5. Testing the assumptions of logistic regression models

There are 4 assumptions to multivariable logistic regression models which are as follows: 1) the outcome is a binary variable, 2) observations are independent of one another, 3) there is a linear relationship between the continuous independent variables and the logit of the outcome variable, 4) the independent variables are not collinear.

In all the multivariable logistic regression models conducted, assumption 1 was met because the outcome of diabetes remission is binary. Participants were categorized as either achieving diabetes remission or failing to do so (diabetes relapse). Assumption 2 was met because the study design of the REMIT trials ensures that participants were recruited independently of one another. Assumption 3 was evaluated and met using the Box-Tidwell test. There were no statistically significant interaction terms between the continuous independent variables and their natural log, which suggests there are linear relationships between the continuous independent variables and the logit of the outcome variable. Assumption 4 was evaluated and met by calculating the variance inflation factors (VIF) for each independent variable in a regression model. The VIFs did not exceed a value greater than 10, which suggests multicollinearity was not present in any of the regression models.

7. Discussion

In this thesis, we wanted to assess how the quantity and quality of the carbohydrates consumed in the diet may influence the likelihood of diabetes remission. We hypothesized that patients with type 2 diabetes who consume a higher daily dietary glycemic load will have a lower likelihood of achieving diabetes remission at a later time point. By using data obtained from the REMIT trials, we conducted secondary analyses to test this hypothesis and explore the relationships between measures of the quantity and quality of carbohydrate intake with diabetes remission.

7.1. Summary and interpretation of the study results

A total of 304 participants with T2DM across 3 REMIT trials (REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi) with completed FFQ data at baseline and 12 weeks, and outcome data for diabetes remission at 24 weeks after randomization were included in the analyses.

7.1.1. Relative intake of carbohydrates as a predictor of diabetes remission

In the first set of logistic regression models (Models A1-A4), we evaluated the associations between daily dietary GL, daily dietary GI, and daily carbohydrate intake at 12 weeks with the likelihood of diabetes remission at 24 weeks after randomization. This was done by comparing the higher quartiles of data with the lowest quartile (reference) for each dietary predictor variable. After adjusting for age, sex, ethnicity, duration of diabetes, baseline FPG, use of diabetes medications at baseline, and treatment group, we found that daily dietary GL at 12 weeks was not associated with diabetes remission. However, for each quartile comparison, we have noticed a consistent direction of effects towards lower odds of diabetes remission with a higher daily GL at 12 weeks. After adjusting for the same covariates, we also found that daily

dietary GI at 12 weeks was not associated with diabetes remission. A potential reason why dietary GL and dietary GI may not predict diabetes remission is that although these measures provide a unique method of quantifying the glycemic response from different food items, there can be large variability in the glycemic response both within and between individuals even when consuming the same food item[90,91]. These variations could be attributed to overall health and lifestyle factors, such as disease status, physical activity, stress, etc[90]. Differences in agricultural conditions or methods of food preparation can also introduce variability as well[90]. In this case, these measures may not accurately reflect the true impact that food items have on glycemic levels.

Daily carbohydrate intake (g) at 12 weeks was also not associated with diabetes remission, but we found that higher daily carbohydrate intake (% of daily energy intake) at 12 weeks decreases the likelihood of diabetes remission at 24 weeks after randomization. The odds ratio of diabetes remission was 0.289 (95% CI 0.124-0.673, p = 0.004) when comparing participants in the highest quartile (Q4) of daily carbohydrate intake to participants in the lowest quartile (Q1). The medians and interquartile ranges of the highest and lowest quartiles of daily carbohydrate intake were 53% (IQR, 51-55) and 37% (IQR, 35-39) of daily energy intake from carbohydrates. Thus, in comparison to participants in the lowest quartile of daily carbohydrate intake, participants in the highest quartile had a 71.1% decrease in the odds of achieving diabetes remission at 24 weeks after randomization. A possible explanation of why measures of the relative intake of carbohydrates may be important for diabetes remission is that different people have varying nutritional needs and may respond differently to macronutrients[3]. Individual variations in metabolism may become even more pronounced in populations with metabolic diseases such as T2DM[3,92]. Thus, absolute measures of carbohydrate intake (quantity or quality)

may not accurately describe its underlying effects on health and disease. Comparisons of the relative intake or changing the balance of dietary macronutrients may have stronger implications on metabolic health and predicting related outcomes such as diabetes remission.

In exploratory models that assess the role of daily caloric intake as a potential confounder (Models E1-E4), we found that the effect estimates of the significant relationship between carbohydrate intake (% of daily energy intake) at 12 weeks with diabetes remission did not change after adjusting for daily caloric intake at 12 weeks. As a result, the daily caloric intake was not considered a confounder of the relationship between carbohydrate intake and diabetes remission. The implications of these findings suggest that the significant effects of carbohydrate intake on diabetes remission can be attributed to the unique properties of consuming carbohydrates that go above and beyond overall changes in total energy intake.

In the second set of logistic regression models (Models C1-C4), we assessed the relationships between the change in dietary GL, dietary GI, and carbohydrate intake from baseline to 12 weeks with the likelihood of diabetes remission at 24 weeks after randomization. Instead of comparing categorical quartiles, the change in dietary predictor variables was expressed in absolute values as continuous data. After adjusting for the same covariates in the first set of models, we found that the relationships between the change in dietary GL, dietary GI, and carbohydrate intake from baseline to 12 weeks with diabetes remission at 24 weeks after randomization were not statistically significant.

However, we also compared these results in sensitivity analyses with and without adjustment for the baseline value of the dietary predictor variable. The results of these models were robust to adjustments for the baseline, with the exception of one model (See Table 3). When evaluating the relationship between the change in carbohydrate intake (% of daily energy

intake) from baseline to 12 weeks with diabetes remission, the results became statistically significant after adjusting for carbohydrate intake at baseline. The odds ratios with and without adjustment for the baseline value were 0.750 (95% CI 0.587-0.956, p = 0.020) and 0.868 (95% CI 0.707-1.061, p = 0.168), respectively. The discrepancy in the results of this model after adjusting for carbohydrate intake at baseline suggests that differences in carbohydrate intake at baseline might be an important component to consider when evaluating the relationship between the change in daily carbohydrate intake with diabetes remission. In particular, the effects on diabetes remission from an increase in daily carbohydrate intake (% of daily energy intake) appear to change depending on the initial value of daily carbohydrate intake. For example, the change in odds of diabetes remission by increasing daily carbohydrate intake from 20 to 25% differs when compared to the same magnitude of increase in daily carbohydrate intake but from 50 to 55%. When the baseline value is not controlled for, there is no apparent relationship between changes in daily carbohydrate intake (% of daily energy intake) and diabetes remission. However, after accounting for baseline differences, we observe a 25% reduction in the odds of diabetes remission for every 5% increase in daily carbohydrate intake (% of daily energy intake).

In mediation analyses, we assessed the potential role of weight loss as a mediator in the relationship between change in carbohydrate intake and diabetes remission, after adjusting for the baseline. In the second step of Baron and Kenny's approach to mediation analyses, we did not find a statistically significant relationship between the change in carbohydrate intake and weight loss (p = 0.055)[87]. As a result, we could not calculate a mediation effect using weight loss on the relationship between changes in daily carbohydrate intake and diabetes remission. There are several reasons to explain why a mediation effect was not observed in our study. The mediation analyses may be limited by the small sample size and measurement errors in the

estimation of dietary intake[93]. Small sample sizes may not provide sufficient statistical power to detect the effects of mediation, even if they exist. Measurement errors in the dietary predictor variables may also lead to data that are not representative of the true relationships and attenuate the effect estimates of the mediation analyses[93]. Although we conclude that weight loss does not mediate this relationship in our study, further work should continue to explore weight loss as a potential mediator of the relationships between carbohydrate-related dietary variables and diabetes remission.

In summary, measures of the absolute quantity or quality of carbohydrates consumed in the diet were not statistically significant predictors of diabetes remission. Daily dietary GL, GI, and carbohydrate intake (g) at 12 weeks or as a change from baseline to 12 weeks were not associated with diabetes remission at 24 weeks after randomization. Instead, a measure of the relative intake of carbohydrates in the diet (% of daily energy intake) was a statistically significant dietary predictor of diabetes remission. The change in daily carbohydrate intake (% of daily energy intake) was also a statistically significant predictor of diabetes remission, after adjusting for the baseline value of daily carbohydrate intake (% of daily energy intake).

7.2. Comparisons with the existing literature

To the best of our knowledge, this was the only epidemiological study that explored the associations between dietary GL or dietary GI with diabetes remission. One systematic review and meta-analysis synthesized evidence from prospective cohort studies on the associations between dietary GL (15 studies) and GI (10 studies) with the risk of T2DM, but not with diabetes remission[61]. The pooled risk ratio of incident T2DM was 1.26 (95% CI 1.15-1.37) per 80 units increase in GL and 1.27 (95% CI 1.15-1.40) per 10 units increase in GI. Increased dietary GL and GI were both associated with an increased risk of incident T2DM[61]. A separate systematic

review and meta-analysis of 29 randomized controlled trials (n = 1617) found that low GL/GI dietary patterns can lead to small improvements in glycemic control and other cardiovascular risk factors in participants with T2DM[65]. Low GL/GI dietary patterns reduced HbA_{1c} with a mean difference of -0.31% (95% CI -0.42 to -0.19%) when compared to higher GL/GI control diets. Although previous evidence shows that lower dietary GL and GI can reduce the risk of T2DM and improve glycemic control, our study did not identify any statistically significant associations between dietary GL or GI with diabetes remission.

With regards to carbohydrate intake, we identified one systematic review and meta-analysis of 8 randomized controlled trials (n = 264) that assessed the effects of low-carbohydrate diets on diabetes remission[8]. Low-carbohydrate diets were defined as diets consisting of < 26% of daily energy intake from carbohydrates or < 130 g/day. Diabetes remission at 6 months was observed in 57% of patients adhering to the low carbohydrate diets versus only 31% in patients on a control diet (risk difference = 0.32, 95% CI 0.17-0.47). However, in these 8 studies, diabetes remission was defined as HbA_{1c} < 6.5% independent of medication use, which differs from the criteria used in our analyses[8]. In the 5 studies (n = 199) that measured diabetes remission with the same criteria as our study, low carbohydrate diets were not associated with diabetes remission (risk difference = 0.05, 95% CI -0.05-0.14)[8]. In contrast to the results of this systematic review and meta-analysis, our study found that the odds of diabetes remission were lower in participants of the highest quartile of daily carbohydrate intake measured by the FFQ (OR = 0.289, 95% CI 0.124-0.673) when compared to the lowest quartile. A change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks was also a statistically significant predictor of diabetes remission after adjusting for the baseline value of daily carbohydrate intake (% of daily energy intake). Increasing daily carbohydrate intake (% of daily

energy intake) by 5% was associated with decreased odds of diabetes remission (OR = 0.750, 95% CI 0.587-0.956). Although our study observed a significant result between daily carbohydrate intake and diabetes remission, it is important to note there were differences in the methodology for defining carbohydrate intake. While our study compared quartiles of carbohydrate intake, the systematic review compared low-carbohydrate versus control diets using cutoffs for percent of daily energy intake (< 26%) and total intake (< 130 g/day)[8]. Our study also explored the effects of changes in daily carbohydrate intake across two different time points on diabetes remission, which has not been explored in previous literature.

7.3. Implications and significance of study findings

Diabetes remission has recently been established as a practical target in the treatment of T2DM. Non-surgical interventions that include lifestyle modifications are capable of inducing diabetes remission and improving other health outcomes[4,30-36]. Identifying potential dietary predictors of diabetes remission can aid in developing more effective lifestyle interventions that target this outcome and improve our overall understanding of diabetes remission. The findings of this study suggest that daily carbohydrate intake (% of daily energy intake) at 12 weeks and as a change from baseline to 12 weeks (after adjusting for its baseline value) might be important dietary predictors of diabetes remission.

However, the generalizability of the study findings may be limited. The study population consisted primarily of European-Caucasians who completed the European-Caucasian version of the FFQ. Although we observed that certain relationships in our study were statistically significant, these conclusions may not apply to other ethnic populations with their own cultural dietary preferences. Further research will be needed to confirm these results in larger and more ethnically diverse populations, but this study can aid in the development of current and new

lifestyle interventions targeting the induction of diabetes remission. Adjusting the dietary components of these interventions to focus on relative carbohydrate intake may increase the success of achieving diabetes remission in different populations with T2DM.

7.4. Strengths of the study

7.4.1. Data availability of covariates and measurement of the outcome

With the exception of the dietary predictor variables derived from the FFQ, data for the covariates included in the models were collected and available for a high percentage of participants. Covariates including age, sex, ethnicity, diabetes duration, use of diabetes medications at baseline, and treatment group were available for all 416 participants randomized in the REMIT trials. Baseline FPG was available for 411 out of 416 participants. The outcome of diabetes remission measured at 24 weeks after randomization was available for all 416 participants. Only two participants were excluded from the main sets of analyses because of missing data related to important covariates included in the models (specifically, fasting plasma glucose).

In addition, the measurement of the outcome of diabetes remission was done according to prespecified criteria. In the REMIT trials[35,36], the criteria for diabetes remission were HbA_{1c} levels < 6.5% with the discontinuation of glucose-lowering medications for at least 12 weeks. The HbA_{1c} is an objective measure that can reliably reflect average glycemic levels over a longer period of time.

7.4.2. Extensive considerations for potential sources of confounding, effect modification, and mediation

In our study methods, we proposed several types of analyses a priori to explain potential sources of confounding, effect modification, and mediation associated with our relationships of interest. The models we highlighted in our analyses reflect our careful consideration of these issues and the measures we took to investigate them.

The first potential source of confounding we considered was the treatment groups that participants were assigned to during the REMIT trials. Since we were interested in the relationships between dietary variables and diabetes remission in the participants of the REMIT trials, it was essential to consider how the participant's assigned treatment group may affect the relationships of interest. We adjusted for the treatment group in the main sets of the regression models but also proposed exploratory models to adjust for the non-dietary components of the interventions. This was to consider the possibility that adjusting for the treatment group altogether may bury some of the important effects on diabetes remission that could be attributable to the dietary components of the intervention, which we would like to capture with the dietary predictor variables of interest. We adjusted for fasting capillary glucose at 12 weeks and total physical activity measured by the IPAQ at 12 weeks to account for the effects of the non-dietary components of the intervention (medical therapy and physical activity) on diabetes remission.

In addition to controlling for potential confounding by the assigned treatment group, we also tested for potential effect modification by the treatment group. This included adding an interaction term to the models to assess whether the effects of the dietary predictor variables on diabetes remission may vary depending on the level of a third variable. In contrast to confounders where they need to be accounted for to prevent the distortion of results, the presence of effect modification provides important information that requires reporting separate stratum-

specific effect estimates. We decided to conduct and present the results of the stratified analyses even though this interaction effect was not detected, because of limitations in the sample size and statistical power. The results of these analyses were exploratory in nature.

In another set of exploratory models, we also included an adjustment for daily caloric intake at 12 weeks to test if daily caloric intake may be a potential confounder and distort the relationships between the dietary predictor variables and the outcome. These models help us identify if the observed effects of the carbohydrate-related predictor variables on diabetes remission are specific to the macronutrient itself or simply due to changes in overall energy intake. By adjusting for daily caloric intake, we can assess the effects of our dietary predictor variables on diabetes remission when holding daily caloric intake constant.

In our mediation analyses, these models were proposed to explore the potential role of weight loss as a mediator of any significant relationships between dietary variables that were expressed as a change from baseline to 12 weeks with diabetes remission. Weight loss has closely been linked to diabetes remission, so these mediation analyses were planned to help us understand if any observed effects on diabetes remission operate through an underlying mechanism of weight loss. Accordingly, we followed Baron and Kenny's approach to test if weight loss mediates the significant relationship between change in carbohydrate intake (% of daily energy intake) and diabetes remission[87].

7.5. Limitations of the study

7.5.1. Missingness of the FFQ data

One of the limitations of the study is the large number of original REMIT trial participants that were excluded from the analyses due to missing FFQ data. The correspondingly

smaller sample size of the analyses introduces concerns about the statistical power and reasons for the missingness of available data.

There was a total of 416 participants selected and randomized across the 3 REMIT trials (REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi). However, only 344 participants had available FFQ data at the relevant time points (baseline and/or 12 weeks) for the analyses. The exclusion of 72 participants with missing FFQ data may be a source of missing data bias. We were unable to identify the exact reasons for the missingness of such data, but they were suspected to be missing due to participants' refusal to complete FFQs. Thus, the missingness of FFQ data was likely because of a drop in compliance with completing the FFQ, which may not have been strictly enforced throughout the trials. Filling out a long questionnaire can also be a tedious and time-consuming process, which may have discouraged some participants from doing so.

7.5.2. Measurement errors of the FFQ

The dietary predictor variables in the study were derived and estimated from participant responses to the FFQ. Although the FFQ is a commonly used dietary assessment tool for measuring dietary intake in epidemiological studies, there are several limitations and sources of bias associated with its use.

The versions of the FFQ used in the REMIT trials have been validated, but it was reported in these validation studies that the FFQ generally underestimated macronutrient and overestimated micronutrient intake when compared to food records[94]. This is supported by the findings of other FFQ evaluation studies where it was also mentioned that FFQs tend to underestimate the true intakes of both energy and macronutrients[95,96]. The inaccuracies of these

estimates may be related to errors made by the respondents or from the design of the questionnaire itself[94-96].

Individuals who misreport their dietary intake, either by over- or underreporting, is quite common and often unavoidable. Self-reported dietary assessments like the FFQ require respondents to perform complex cognitive memory and averaging tasks. The respondents were asked to remember the frequencies and portion sizes of food and beverage items they consumed in the last 3 months from a comprehensive list. This may introduce recall bias that occurs when individuals do not accurately remember the details of certain events and experiences, such as what they consume and how much they consume of an item. It may also be possible that individuals are prone to certain types of response bias such as social desirability. Respondents may have been inclined to complete the FFQ in a manner that will be viewed favorably by research staff and adheres to the dietary recommendations they received. It may consist of over-reporting desirable behaviors and under-reporting undesirable behaviors such as consuming more healthy items and less unhealthy items in the FFQ.

In our analyses, we were mindful of these limitations and decided to make relative comparisons of dietary intake by comparing quartiles in models that assessed the dietary predictor variables at 12 weeks. Although the categorization of continuous variables loses meaningful information about specific data observations, it was considered necessary to avoid the use of absolute energy and macronutrient estimates from the FFQ, which are likely to be inaccurate. In addition, we also set data restrictions based on energy and carbohydrate intake to remove individuals who may have misreported their dietary intake that would otherwise be unrealistic. This includes individuals who reported a caloric or carbohydrate intake that was either extremely high or extremely low that would be considered implausible.

7.5.3. Lack of ethnic diversity in the study population and homogeneity in food choices in the FFQ

The study population was comprised of participants in the REMIT trials that were recruited in several sites across Canada. Of the participants included in the analyses, over 90% of participants were European-Caucasian. As a result, a large majority of the participants completed the European-Caucasian versions of the FFQ. We decided against including the small number of participants (less than 5%) who completed the South Asian and Chinese versions of the FFQ because estimating dietary intake using several different versions of the FFQ adds statistical noise to the dataset. In doing so, we gain more precision in the estimates of dietary intake, but the conclusions we draw from the data become limited.

Consequently, the lack of ethnic diversity in the study population and the homogeneity of food items included in a single version of the FFQ reduces the generalizability of our findings. We are able to make uniform conclusions about certain associations in a specific study population, but the lack of diversity limits the applicability of the observed effects, which may or may not exist in other populations.

7.5.4. Potential concerns with multiple testing

Since there were a multitude of statistical tests conducted in our analyses to answer our research questions, it is important to consider the impact of multiple testing. The significance level of the study was set at a 5% limit for the alpha error. However, the probability of type 1 errors increases according to the number of comparisons made[97,98]. In these situations, it may be appropriate to implement a Bonferroni correction and adjust the limits for the alpha error[97-98]. For our analyses, we considered this option but ultimately decided against using this correction

because we were testing only one hypothesis from our primary research question. The remaining research questions and statistical tests were simply hypothesis-generating in nature. The interpretation of the results from hypothesis-testing versus hypothesis generating research questions correspondingly reflects this consideration.

7.6. Future directions

Although dietary GL and GI were not associated with diabetes remission, carbohydrate intake expressed as a percentage of daily energy intake was a statistically significant predictor of diabetes remission in secondary analyses. This suggests that the relative intake of carbohydrates in the diet may be an important factor to consider when trying to induce diabetes remission in patients with T2DM. Alternatively, it may also reflect the potential benefits that energy from non-carbohydrate sources have on this outcome. Since we observed a lower odds of diabetes remission in the highest quartile of daily carbohydrate intake (% of daily energy intake), we could also attribute these effects on diabetes remission to a lower collective intake of protein and fat. It may be worthwhile to further explore the potential impact of protein and/or fat consumption on diabetes remission.

To confirm the findings of this study, it will be important to explore these relationships in larger and more diverse cohorts of patients with T2DM. One of the limitations of the study was the lack of diversity both in the study population and in the versions of the FFQs used to measure diet. Future studies evaluating the same relationships with larger and more diverse populations would be beneficial to understand how these associations may change in different populations. They should also consider incorporating the use of different versions of the FFQ to capture cultural differences in the diet and unique food items that different groups may consume.

In nutritional epidemiology, the FFQ is one of the more common and useful tools to capture dietary intake. In our study, there were large amounts of missing data for the FFQ. Many participants did not attempt the FFQ likely because completing long questionnaires was a tedious and time-consuming task. To improve the collection of FFQ data and minimize sources of missing data, future studies should implement more rigorous methods of collecting FFQ data and provide more incentives for successfully completing the FFQ. The use of a combination of multiple dietary assessment tools such as FFQs and 24-hour recalls may also improve accuracy and provide a more comprehensive assessment of dietary intake.

8. Conclusions

The current approaches to treating type 2 diabetes focus on lifelong treatment combining pharmacological and lifestyle therapies to manage and prevent complications associated with the disease. Thus, developing new strategies that can reverse the progression of the disease and induce diabetes remission is beneficial for patients, communities, and healthcare systems around the world. The goal of this study was to identify potential dietary predictors of diabetes remission by evaluating the relationships between measures of the quantity and/or quality of carbohydrates consumed in the diet with diabetes remission. We hypothesized that consuming higher daily quantities and lower quality carbohydrates (high daily dietary glycemic load, high daily dietary glycemic index, and high daily carbohydrate intake) will decrease the likelihood of diabetes remission. The results of our analyses found that daily dietary GL, daily dietary GI, and daily carbohydrate intake (g) at 12 weeks or as a change from baseline to 12 weeks, were not associated with diabetes remission. However, higher levels of daily carbohydrate intake (% of daily energy intake) at 12 weeks predicted a lower likelihood of diabetes remission at 24 weeks after randomization. Increasing daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks also predicted a lower likelihood of diabetes remission after adjusting for the baseline value of daily carbohydrate intake (% of daily energy intake). Further work will be necessary to confirm the findings of our study in larger and more diverse cohorts of patients with type 2 diabetes.

Tables

Table 1. List of multivariable logistic regression models proposed to evaluate the relationships of interest.

Regression Models	Adjusted Covariates in the Model
Predictor variables at 12 weeks ➢ Model A1 – Daily dietary GL ➢ Model A2 – Daily dietary GI ➢ Model A3 – Daily carbohydrate intake (g) ➢ Model A4 – Daily carbohydrate intake (% of daily energy intake)	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, treatment group
Predictor variables at 12 weeks (intervention group only & control group only) ➢ Model B1 – Daily dietary GL ➢ Model B2 – Daily dietary GI ➢ Model B3 – Daily carbohydrate intake (g) ➢ Model B4 – Daily carbohydrate intake (% of daily energy intake)	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline
Change in predictor variables from baseline to 12 weeks ➢ Model C1 – Daily dietary GL ➢ Model C2 – Daily dietary GI ➢ Model C3 – Daily carbohydrate intake (g) ➢ Model C4 – Daily carbohydrate intake (% of daily energy intake)	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, treatment group
Change in predictor variables from baseline to 12 weeks (intervention group only & control group only) ➢ Model D1 – Daily dietary GL ➢ Model D2 – Daily dietary GI ➢ Model D3 – Daily carbohydrate intake (g) ➢ Model D4 – Daily carbohydrate intake (% of daily energy intake)	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline

GL, glycemic load; GI, glycemic index; g, grams; FPG, fasting plasma glucose.

Table 2. List of multivariable logistic regression models proposed to evaluate the exploratory questions.

Regression Model	Adjusted Covariates in the Model
Mediation analyses for percent weight loss ➢ Any significant models with change in predictor variables from baseline to 12 weeks	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, treatment group
Predictor variables at 12 weeks adjusted for daily caloric intake at 12 weeks ➢ Model E1 – Daily dietary GL ➢ Model E2 – Daily dietary GI ➢ Model E3 – Daily carbohydrate intake (g) ➢ Model E4 – Daily carbohydrate intake (% of daily energy intake)	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, treatment group, total caloric intake at 12 weeks
Predictor variables at 12 weeks adjusted for non-dietary components of study interventions ➢ Model F1 – Daily dietary GL ➢ Model F2 – Daily dietary GI ➢ Model F3 – Daily carbohydrate intake (g) ➢ Model F4 – Daily carbohydrate intake (% of daily energy intake)	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, fasting capillary glucose on drugs at 12 weeks, total physical activity at 12 weeks
Predictor variables at 12 weeks ➢ Model G1 – Daily dietary fiber intake ➢ Model G2 – Daily consumption of starchy foods ➢ Model G3 – Daily consumption of SSBs ➢ Model G4 – Daily consumption of sweets	Age, sex, ethnicity, baseline FPG, duration of diabetes, use of diabetes medications at baseline, treatment group

GL, glycemic load; GI, glycemic index; g, grams; FPG, fasting plasma glucose; SSB, sugar-sweetened beverages.

Table 3. Baseline characteristics of the study population included in the analyses.

Variable	Overall	Remission Group	Non-Remission Group	P-value
N (%)	304 (73.1)	81 (26.6)	223 (73.4)	
Assigned to intervention group (%)	168 (55.3)	52 (64.2)	116 (52.0)	
Age, years	56.8 ± 9.6	57.5 ± 8.8	56.6 ± 9.8	0.44
Males (%)	178 (58.6)	44 (54.3)	134 (60.0)	0.37
European-Caucasian (%)	274 (90.1)	76 (93.8)	198 (88.8)	0.19
BMI, kg/m^2	32.7 ± 5.9	32.7 ± 5.5	32.6 ± 6.1	0.94
Duration of diabetes, months	29.5 ± 22.0	21.7 ± 19.5	32.3 ± 22.2	0.0002
Using glucose-lowering medications (%)	275 (90.5)	74 (91.4)	201 (90.1)	0.75
FPG at baseline, mmol/L	7.6 ± 1.8	6.7 ± 1.0	8.0 ± 1.9	<0.0001
HbA_{1c} at baseline, %	6.7 ± 0.7	6.2 ± 0.5	6.9 ± 0.6	<0.0001
Daily caloric intake, kcal	1813.5 ± 632.4	1833.8 ± 643.0	1806.1 ± 629.7	0.74
Daily dietary GL, GL units	84.5 ± 36.3	81.0 ± 33.0	83.0 ± 33.5	0.63
Daily dietary GI, GI units	45.5 ± 5.8	45.1 ± 6.2	45.5 ± 5.7	0.64
Daily carbohydrate intake				
➢ Total grams, g	202.6 ± 72.1	200.5 ± 70.5	203.4 ± 72.8	0.76
➢ Percent of daily energy intake, %	45.1 ± 7.3	43.5 ± 7.6	45.6 ± 6.8	0.02

Study population includes trial participants with type 2 diabetes treated with either an intensive metabolic intervention or standard diabetes care for 12 weeks. Frequencies (%) or means ± SDs are provided. Comparisons of the baseline characteristics and dietary variables at baseline between the remission and non-remission groups were done using a two-sample t-test or a chi-square test.

SD, standard deviation; BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; GL, glycemic load; GI, glycemic index; g, grams.

Table 4. Comparing effect estimates and p-values with and without the removal of high-leverage points.

ORs (95% CI), P-value		
Dietary variable	No removal of high-leverage points from model	Removal of high-leverage points from model
Daily dietary GL at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	(n = 304) 0.498 (0.221-1.122), p = 0.093 0.701 (0.303-1.626), p = 0.408 0.552 (0.239-1.276), p = 0.165	(n = 300) 0.508 (0.226-1.144), p = 0.102 0.709 (0.306-1.649), p = 0.423 0.573 (0.243-1.358), p = 0.204
Change in daily dietary GL from baseline to 12 weeks (per 10 GL units increase)	(n = 304) 0.961 (0.868-1.062), p = 0.408	(n = 292) 0.961 (0.851-1.083), p = 0.476
Daily dietary GI at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	(n = 304) 1.040 (0.459-2.353), p = 0.925 1.191 (0.517-2.742), p = 0.681 1.087 (0.479-2.463), p = 0.842	(n = 293) 1.177 (0.499-2.778), p = 0.710 1.369 (0.570-3.289), p = 0.482 1.248 (0.526-2.961), p = 0.615
Change in daily dietary GI from baseline to 12 weeks (per 5 GI units increase)	(n = 304) 0.895 (0.681-1.176), p = 0.426	(n = 292) 0.970 (0.677-1.389), p = 0.860
Daily carbohydrate intake (g) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	(n = 304) 0.843 (0.380-1.873), p = 0.676 0.566 (0.247-1.294), p = 0.177 0.790 (0.353-1.771), p = 0.568	(n = 298) 0.852 (0.384-1.889), p = 0.693 0.571 (0.250-1.304), p = 0.184 0.773 (0.336-1.779), p = 0.545
Change in daily carbohydrate intake (g) from baseline to 12 weeks (per 100 g increase)	(n = 304) 0.819 (0.495-1.221), p = 0.338	(n = 298) 0.819 (0.448-1.349), p = 0.376
Daily carbohydrate intake (% of daily energy intake) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	(n = 304) 0.469 (0.206-1.066), p = 0.071 0.599 (0.271-1.328), p = 0.207 0.289 (0.124-0.673), p = 0.004	(n = 297) 0.525 (0.227-1.214), p = 0.132 0.664 (0.295-1.492), p = 0.321 0.341 (0.145-0.806), p = 0.014
Change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks (per 5% increase)	(n = 304) 0.868 (0.707-1.061), p = 0.168	(n = 289) 0.837 (0.641-1.099), p = 0.199

OR, odds ratio; CI, confidence interval; GL, glycemic load; GI, glycemic index; g, grams.

Table 5. Comparing effect estimates and p-values with and without adjusting for the baseline value of the dietary predictor variable.

ORs (95% CI), P-value		
Dietary variable	Not adjusting for baseline value of dietary predictor	Adjusting for baseline value of dietary predictor
Daily dietary GL at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.498 (0.221-1.122), p = 0.093 0.701 (0.303-1.626), p = 0.408 0.552 (0.239-1.276), p = 0.165	 0.476 (0.205-1.106), p = 0.085 0.643 (0.251-1.649), p = 0.358 0.491 (0.177-1.358), p = 0.171
Change in daily dietary GL from baseline to 12 weeks (per 10 GL units increase)	0.961 (0.868-1.062), p = 0.408	0.923 (0.817-1.051), p = 0.220
Daily dietary GI at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 1.040 (0.459-2.353), p = 0.925 1.191 (0.517-2.742), p = 0.681 1.087 (0.479-2.463), p = 0.842	 1.020 (0.438-2.378), p = 0.963 1.154 (0.463-2.875), p = 0.759 1.042 (0.403-2.695), p = 0.932
Change in daily dietary GI from baseline to 12 weeks (per 5 GI units increase)	0.895 (0.681-1.176), p = 0.426	0.895 (0.666-1.199), p = 0.461
Daily carbohydrate intake (g) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.843 (0.380-1.873), p = 0.676 0.566 (0.247-1.294), p = 0.177 0.790 (0.353-1.771), p = 0.568	 0.840 (0.374-1.886), p = 0.673 0.559 (0.227-1.380), p = 0.207 0.777 (0.293-2.060), p = 0.612
Change in daily carbohydrate intake (g) from baseline to 12 weeks (per 100 g increase)	0.819 (0.495-1.221), p = 0.338	0.670 (0.366-1.221), p = 0.163
Daily carbohydrate intake (% of daily energy intake) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.469 (0.206-1.066), p = 0.071 0.599 (0.271-1.328), p = 0.207 0.289 (0.124-0.673), p = 0.004	 0.470 (0.204-1.085), p = 0.077 0.605 (0.254-1.441), p = 0.256 0.293 (0.113-0.755), p = 0.011
Change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks (per 5% increase)	0.868 (0.707-1.061), p = 0.168	0.750 (0.587-0.956), p = 0.020

OR, odds ratio; CI, confidence interval; GL, glycemic load; GI, glycemic index; g, grams.

Table 6. Models E1-E4: Associations between dietary variables at 12 weeks with diabetes remission at 24 weeks after randomization after adjusting for total daily caloric intake at 12 weeks.

ORs (95% CI), P-value	
Dietary variable	Adjusting for daily caloric intake at 12 weeks + other covariates (n = 304)
Daily dietary GL at 12 weeks	
➢ Q2 vs Q1	0.429 (0.181-1.020), p = 0.056
➢ Q3 vs Q1	0.531 (0.195-1.445), p = 0.215
➢ Q4 vs Q1	0.336 (0.093-1.220), p = 0.098
Daily dietary GI at 12 weeks	
➢ Q2 vs Q1	1.056 (0.461-2.418), p = 0.898
➢ Q3 vs Q1	1.205 (0.520-2.793), p = 0.663
➢ Q4 vs Q1	1.092 (0.481-2.479), p = 0.833
Daily carbohydrate intake (g) at 12 weeks	
➢ Q2 vs Q1	0.738 (0.312-1.746), p = 0.490
➢ Q3 vs Q1	0.427 (0.146-1.246), p = 0.120
➢ Q4 vs Q1	0.486 (0.116-2.031), p = 0.323
Daily carbohydrate intake (% of daily energy intake) at 12 weeks	
➢ Q2 vs Q1	0.468 (0.206-1.065), p = 0.071
➢ Q3 vs Q1	0.602 (0.271-1.333), p = 0.211
➢ Q4 vs Q1	0.288 (0.124-0.671), p = 0.004

OR, odds ratio; CI, confidence interval; GL, glycemic load; GI, glycemic index; g, grams.

Table 7. Models F1-F4: Associations between dietary variables at 12 weeks with diabetes remission at 24 weeks after randomization after adjusting for the non-dietary components of the interventions.

ORs (95% CI), P-value	
Dietary variable	Adjusting for the non-dietary components of the intervention + other covariates (n = 268)
Daily dietary GL at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.452 (0.177-1.153), p = 0.097 0.848 (0.328-2.193), p = 0.734 0.613 (0.239-1.570), p = 0.308
Daily dietary GI at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 1.339 (0.539-3.330), p = 0.530 1.059 (0.411-2.725), p = 0.906 1.222 (0.480-3.111), p = 0.674
Daily carbohydrate intake (g) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.730 (0.292-1.825), p = 0.501 0.592 (0.233-1.501), p = 0.269 0.826 (0.339-2.014), p = 0.674
Daily carbohydrate intake (% of daily energy intake) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.437 (0.173-1.104), p = 0.080 0.482 (0.195-1.191), p = 0.114 0.267 (0.102-0.700), p = 0.007

The non-dietary components of the intervention include fasting capillary glucose on diabetes medications at 12 weeks and total physical activity measured by IPAQ at 12 weeks.

IPAQ, international physical activity questionnaire; OR, odds ratio; CI, confidence interval; GL, glycemic load; GI, glycemic index; g, grams.

Table 8. Mediation by weight loss on relationship between change in daily carbohydrate intake (% of daily energy intake) and diabetes remission.

Effect	Regression Coefficient	95% CI	P-value
Total effect (b1) = OR for diabetes remission per 5% increase in daily carbohydrate intake (% of daily energy intake)	0.750	0.587-0.956	0.020
*Effect of X on M (b2) = percent weight loss per 5% increase in daily carbohydrate intake (% of daily energy intake)	-0.281	-0.568-0.006	0.055
Direct effect (b4)	/	/	/
Mediation effect (b1-b4)	/	/	/

Mediation analyses were conducted to explore the mediation effect by percent weight loss from baseline to 12 weeks on the statistically significant relationship between the change in daily carbohydrate intake (% of daily energy intake) from baseline to 12 weeks and diabetes remission at 24 weeks after randomization after adjusting for the baseline value of daily carbohydrate intake (% of daily energy intake) in the regression model.

*Since there was no statistically significant relationship between the change in carbohydrate intake (% of daily energy intake) from baseline to 12 weeks and percent weight loss from baseline to 12 weeks, mediation effect could not be calculated.

OR, odds ratio; CI, confidence interval.

Table 9. Models G1-G4: Associations between daily dietary fiber intake, daily consumption of starchy foods, SSBs, and sweets at 12 weeks with diabetes remission at 24 weeks after randomization.

ORs (95% CI, P-value)	
Dietary variable	(n = 304)
Daily dietary fiber intake (g) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.791 (0.350-1.789), p = 0.574 1.433 (0.652-3.146), p = 0.371 0.655 (0.285-1.504), p = 0.318
Daily consumption of starchy foods (number of medium-sized servings per day) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 0.737 (0.326-1.665), p = 0.463 0.982 (0.428-2.250), p = 0.965 0.951 (0.406-2.224), p = 0.907
Daily consumption of SSBs (number of medium-sized servings per day) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 1.203 (0.560-2.583), p = 0.635 0.551 (0.233-1.300), p = 0.174 0.492 (0.212-1.142), p = 0.099
Daily consumption of sweets (number of medium-sized servings per day) at 12 weeks ➢ Q2 vs Q1 ➢ Q3 vs Q1 ➢ Q4 vs Q1	 1.597 (0.720-3.545), p = 0.250 0.766 (0.327-1.797), p = 0.541 0.783 (0.343-1.789), p = 0.562

Comparisons of quartiles were done using the lowest quartile as the reference.

OR, odds ratio; CI, confidence interval; g, grams; SSB, sugar-sweetened beverages.

Figures

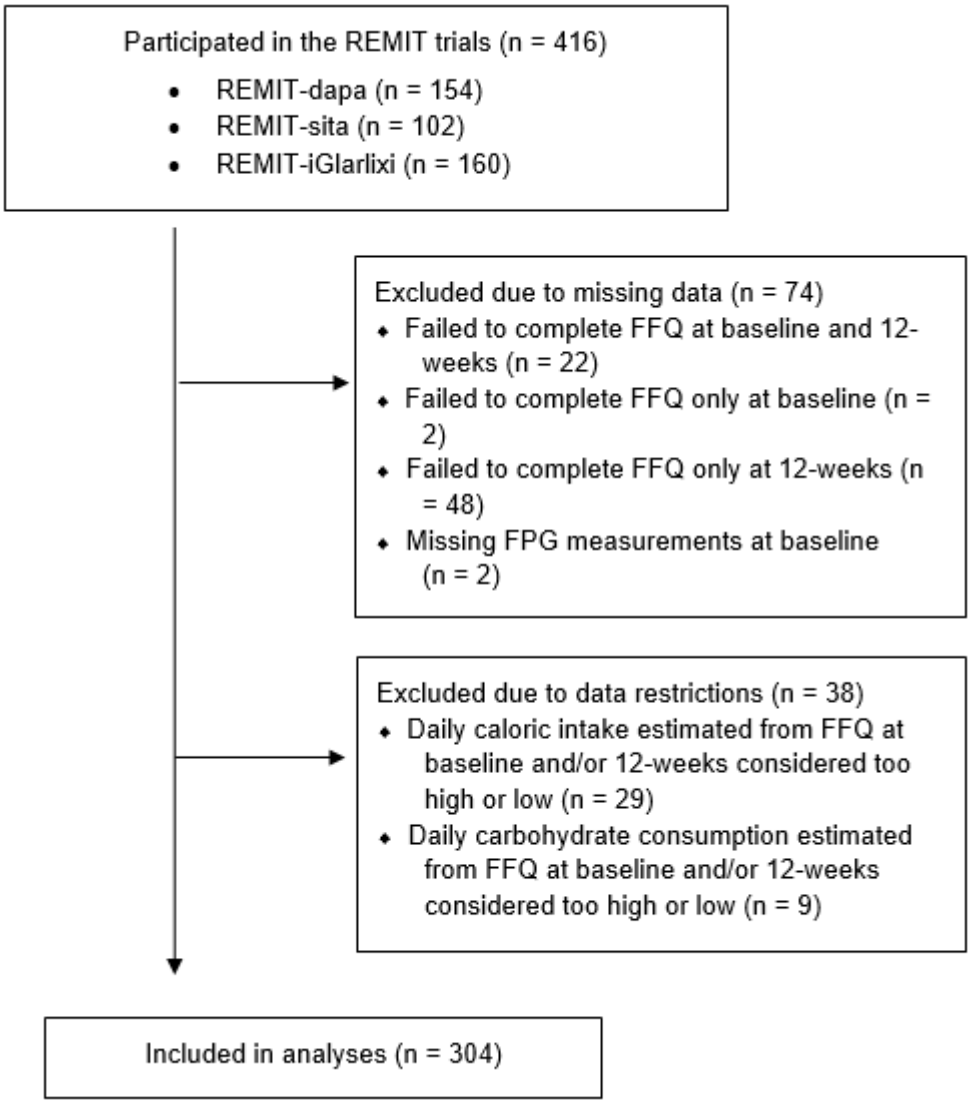
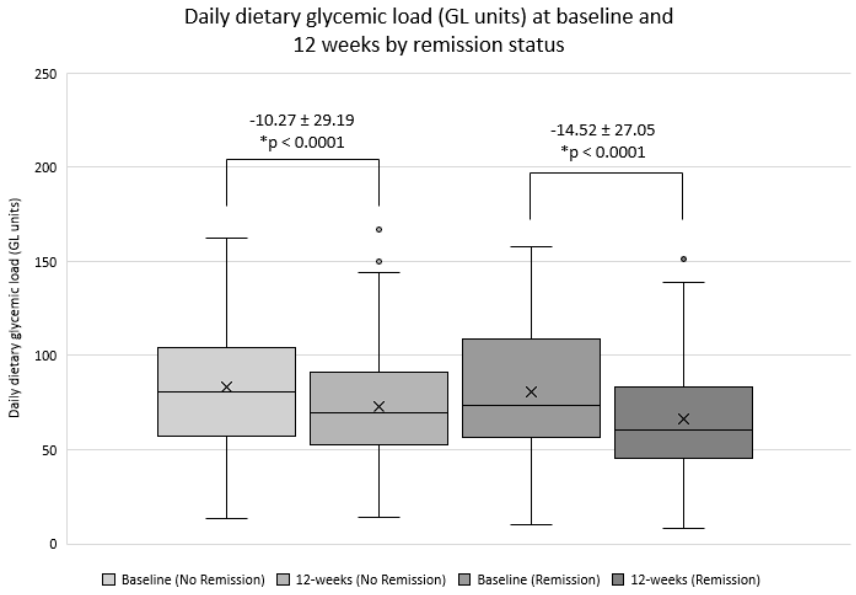


Figure 1. Selection of the study population to be included in the analyses from participants of the REMIT (Remission Evaluation of Metabolic Interventions in Type 2 Diabetes) trials.

FFQ, food frequency questionnaire; FPG, fasting plasma glucose.

(A)



(B)

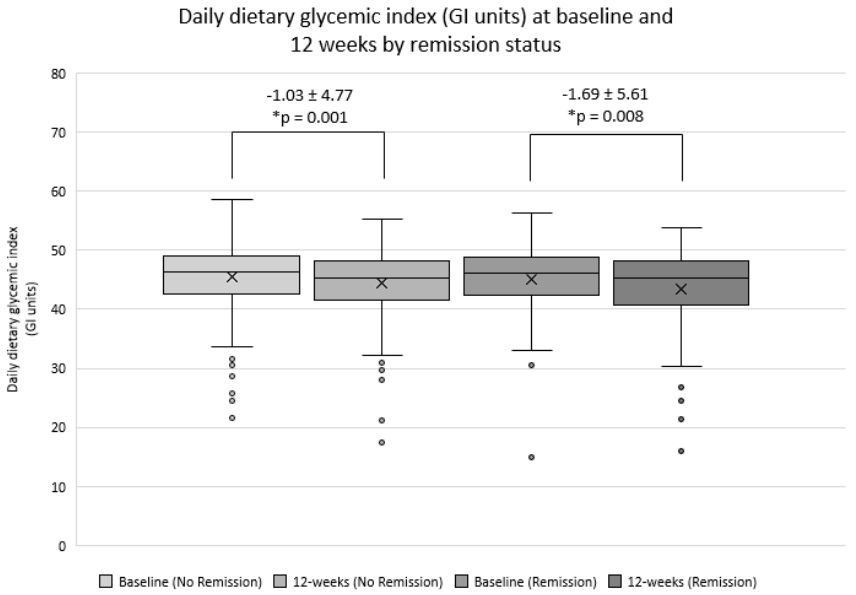
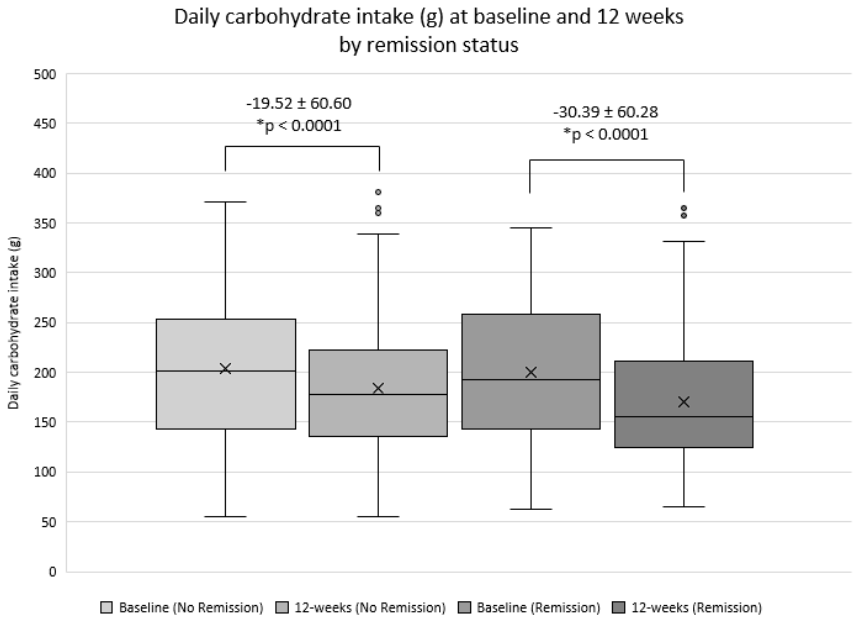


Figure 2. Distributions of the baseline and 12-week measures of daily dietary GL or daily dietary GI shown separately in the remission and non-remission groups.

(A) Daily dietary GL (GL units). **(B)** Daily dietary GI (GI units). The distributions of daily dietary GL at baseline and 12 weeks were compared using a paired two-sample t-test (compared separately in remission and non-remission groups). The distributions of daily dietary GL in remission and non-remission groups were compared using a two-sample t-test (compared separately for baseline and 12 week measures). All 4 comparisons were repeated for daily dietary GI. Brackets describe the mean differences ± SDs between groups. Significant tests are indicated with an asterisk (*).

GL, glycemic load; GI, glycemic index; SD, standard deviation.

(A)



(B)

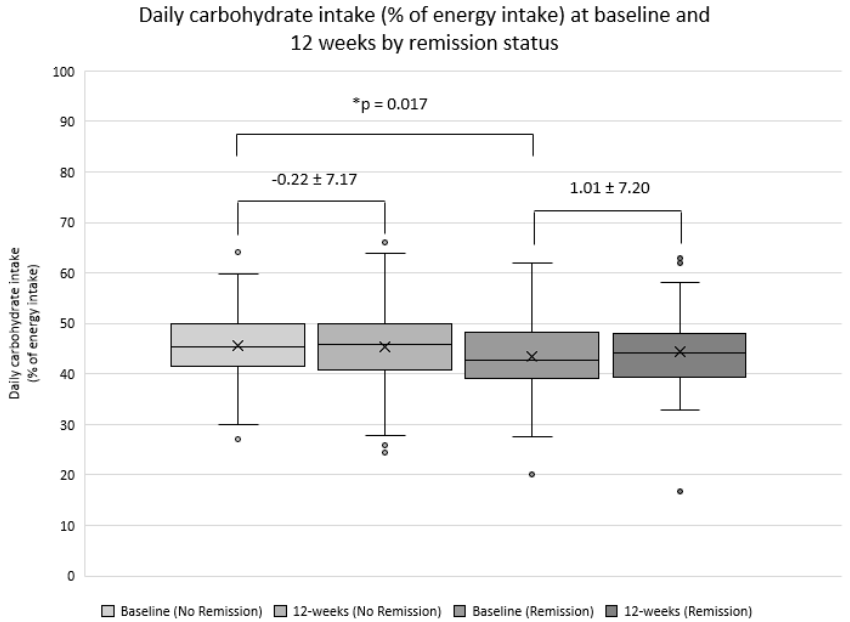
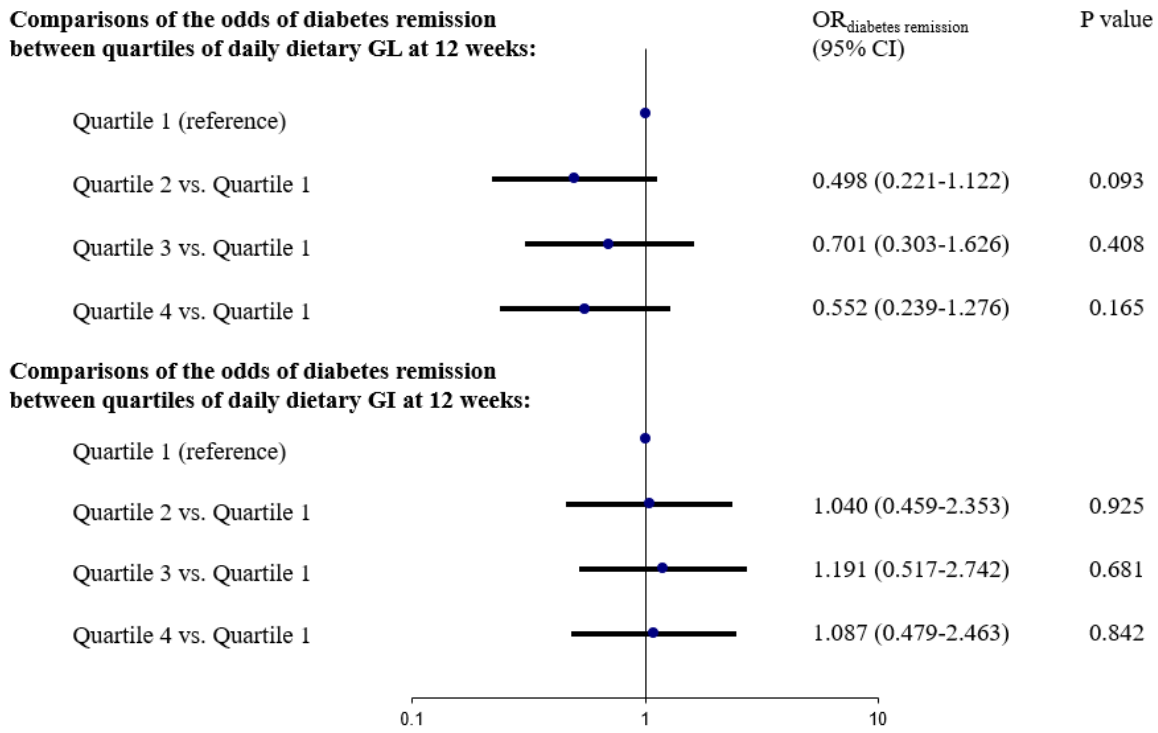


Figure 3. Distributions of the baseline and 12-week measures of daily carbohydrate intake shown separately in the remission and non-remission groups.

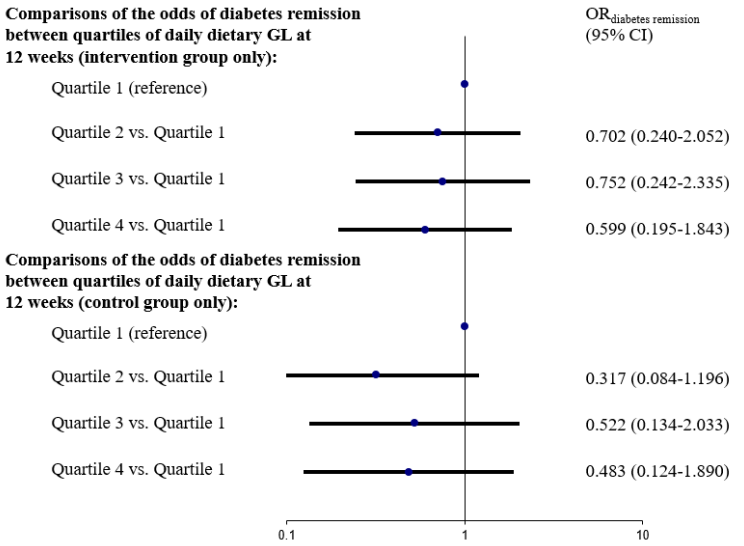
(A) Daily carbohydrate intake (g). **(B)** Daily carbohydrate intake (% of daily energy intake). The distributions of daily carbohydrate intake (g) at baseline and 12 weeks were compared using a paired two-sample t-test (compared separately in remission and non-remission groups). The distributions of daily carbohydrate intake (g) in remission and non-remission groups were compared using a two-sample t-test (compared separately for baseline and 12 week measures). All 4 comparisons were repeated for daily carbohydrate intake (% of daily energy intake). Brackets describe the mean differences ± SDs between groups. Significant tests are indicated with an asterisk (*).

g, grams; SD, standard deviation.

(A) Models A1 and A2.



(B) Model B1.



(C) Model B2.

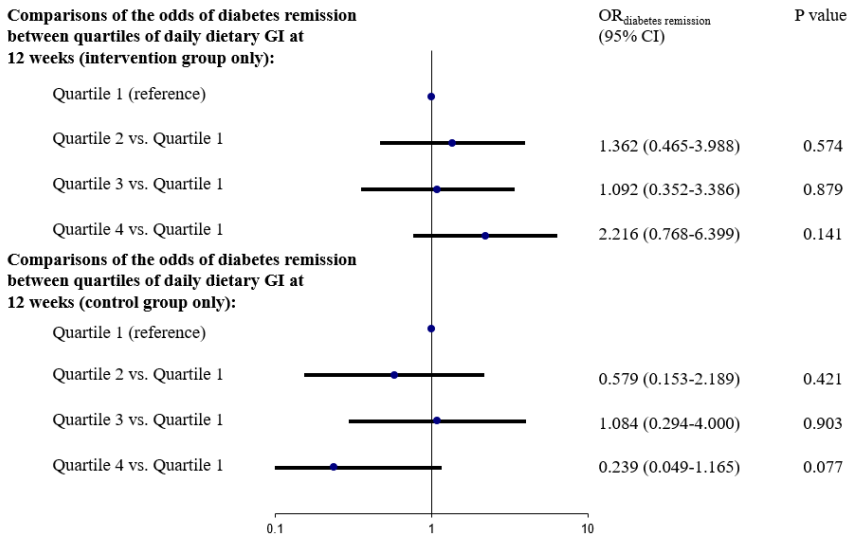
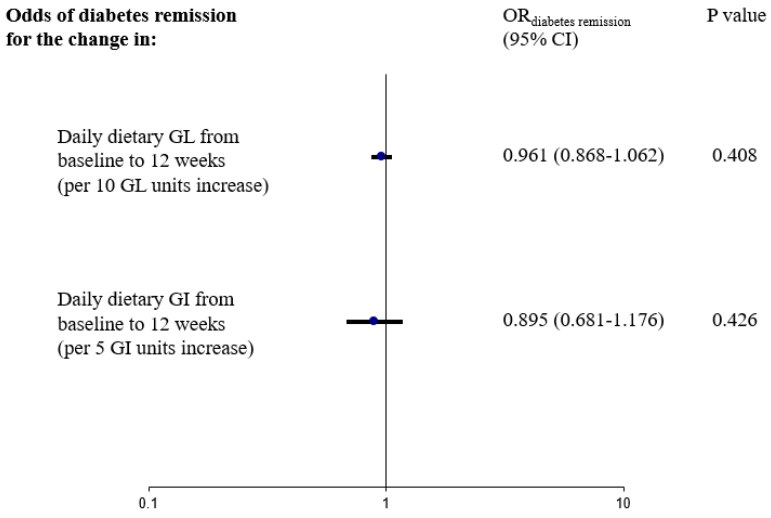


Figure 4. Comparisons between quartiles of daily dietary GL or daily dietary GI at 12 weeks with respect to associations with diabetes remission at 24 weeks after randomization.

(A) Daily dietary GL (GL units) and daily dietary GI (GI units) at 12 weeks in all participants. **(B)** Daily dietary GL (GL units) at 12 weeks separately in intervention and control groups. **(C)** Daily dietary GI (GI units) at 12 weeks separately in intervention and control groups. ORs (95% CI) of diabetes remission between quartiles are shown, adjusted for other covariates.

GL, glycemic load; GI, glycemic index; OR, odds ratio; CI, confidence interval.

(A) Models C1 and C2



(B) Models D1 and D2.

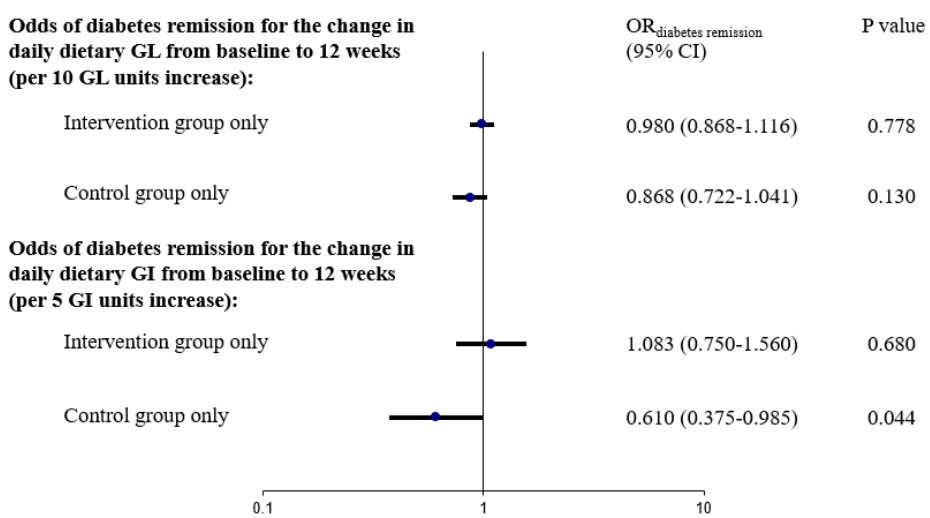
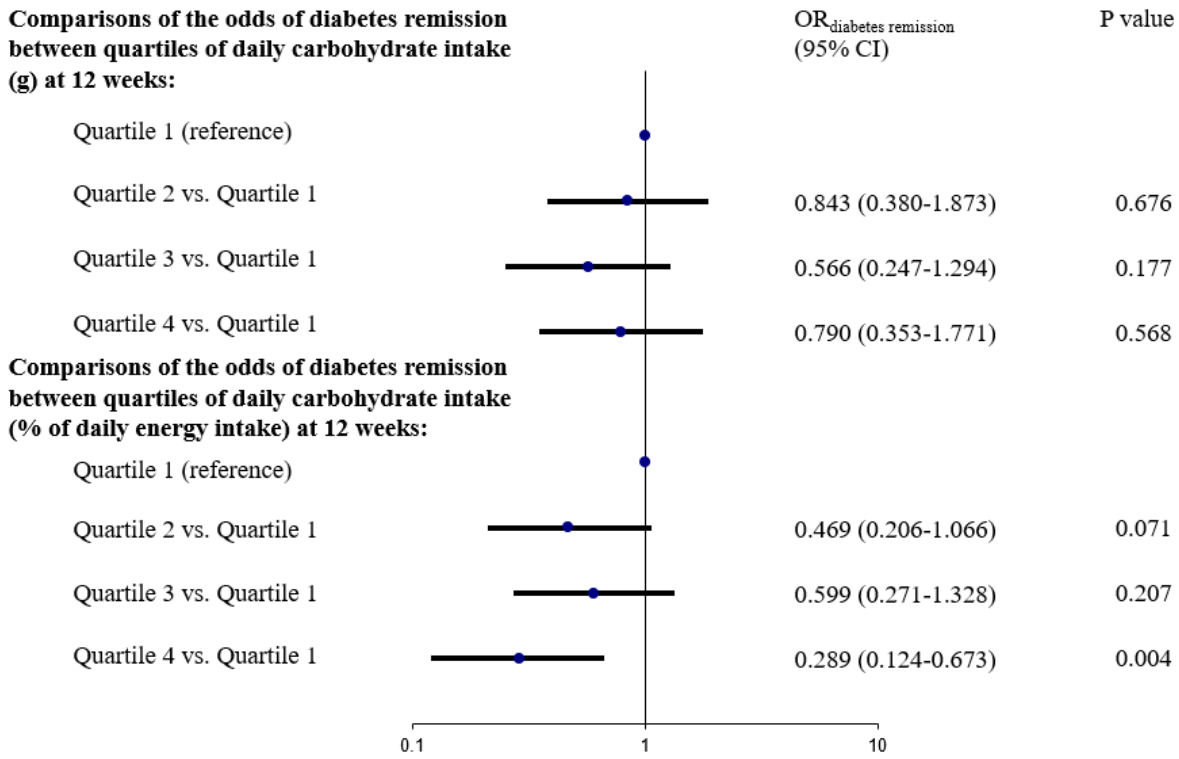


Figure 5. Relationships between the change in daily dietary GL or daily dietary GI from baseline to 12 weeks with diabetes remission at 24 weeks after randomization.

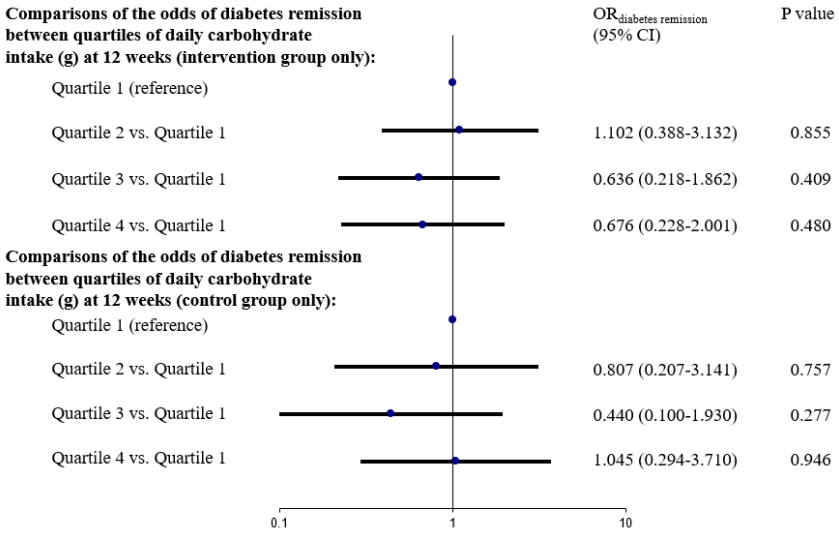
(A) Change in daily dietary GL (GL units) and change in daily dietary GI (GI units) from baseline to 12 weeks in all participants. **(B)** Change in daily dietary GL (GL units) and daily dietary GI (GI units) from baseline to 12 weeks separately in intervention or control groups. ORs (95% CI) of diabetes remission per 10 GL units or 5 GI units increase are shown, adjusted for other covariates.

GL, glycemic load; GI, glycemic index; OR, odds ratio; CI, confidence interval.

(A) Models A3 and A4.



(B) Model B3.



(C) Model B4.

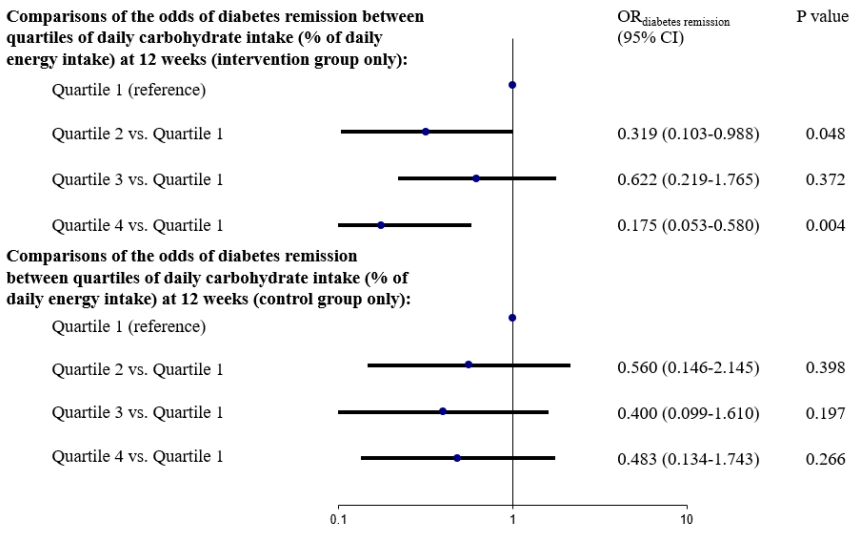


Figure 6. Comparisons between quartiles of daily carbohydrate intake at 12 weeks with respect to associations with diabetes remission at 24 weeks after randomization.

(A) Daily carbohydrate intake (g or % of daily energy intake) at 12 weeks in all participants. **(B)** Daily carbohydrate intake (g) at 12 weeks separately in intervention or control groups. **(C)** Daily carbohydrate intake (% of daily energy intake) at 12 weeks separately in intervention and control groups. ORs (95% CI) of diabetes remission between quartiles are shown, adjusted for other covariates.

g, grams; OR, odds ratio; CI, confidence interval.

(A) Models C3 and C4 ± adjusted for baseline value of carbohydrate intake (g or % of daily energy intake)**.**

(B) Models D3 and D4.

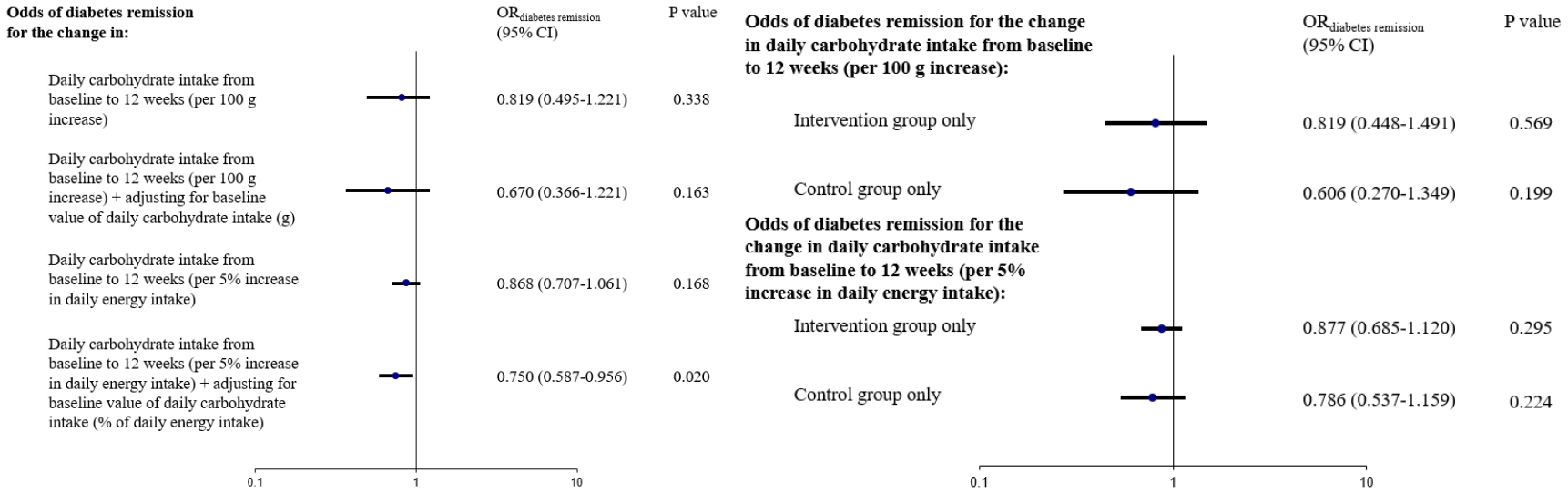


Figure 7. Relationships between the change in daily carbohydrate intake from baseline to 12 weeks with diabetes remission at 24 weeks after randomization.

(A) Change in daily carbohydrate intake (g or % of daily energy intake) from baseline to 12 weeks in all participants, with or without adjustment for the baseline value of daily carbohydrate intake (g or % of daily energy intake). **(B)** Change in daily carbohydrate intake (g or % of daily energy intake) from baseline to 12 weeks separately in intervention and control groups. ORs (95% CI) of diabetes remission per 100 g or 5% increase in daily energy intake are shown, adjusted for other covariates ± baseline value of carbohydrate intake (g or % of daily energy intake).

g, grams; OR, odds ratio; CI, confidence interval.

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Appendix

Supplementary Table 1. Inclusion and exclusion criteria of trial participants in the REMIT-dapa, REMIT-sita, and REMIT-iGlarlixi trials.

Trial	Inclusion criteria	Exclusion criteria
REMIT-dapa	1. Men and women between the ages of 30-80 2. Diagnosed with type 2 diabetes mellitus within the last 8 years 3. Anti-diabetic drug regimen unchanged in last 8 weeks before randomization 4. HbA_{1c} between 6.5-9.5% on no hypoglycemic agents or $HbA_{1c} \leq 8.0\%$ on ≤ 2 glucose-lowering agents 5. BMI ≥ 23 kg/m^2 6. Ability to and willingness to perform self-monitoring of capillary blood glucose 7. Ability and willingness to self-inject insulin 8. Provision of informed consent	1. Current use of insulin therapy 2. History of hypoglycemia unawareness or severe hypoglycemia requiring assistance 3. History of end-stage renal disease or renal dysfunction as evidenced by eGFR < 60 mL/min/1.73 m^2 4. History of lactic acidosis or diabetic ketoacidosis 5. Active liver disease or ALT levels $\geq$ 2.5x upper limit of normal 6. History of bladder cancer or undiagnosed hematuria 7. History of breast cancer 8. History of polycythemia 9. Evidence of volume depletion or hypotension (systolic blood pressure < 90 mmHg) 10. Systolic blood pressure > 180 mmHg or diastolic blood pressure > 105 mmHg 11. Diagnosed cardiovascular disease including history of acute coronary syndrome, hospitalization for unstable angina, myocardial infarction, revascularization with coronary artery bypass grafting or percutaneous coronary artery disease, peripheral vascular disease, valvular heart disease, cardiomyopathy, aortic dissection, tachyarrhythmias, bradyarrthymias, prior stroke, or transient ischemic attack, prior hospitalization for heart failure, or ECG findings concerning for ischemic heart disease 12. Dependence on oxygen 13. History of any disease requiring systemic glucocorticoid treatment 14. History or planned bariatric surgery in next 1.5 years 15. History of major illness with life expectancy < 3 years 16. History of injury or condition that limits ability to achieve moderate levels of physical activity 17. History of excessive alcohol intake

		18. Currently pregnant or not using reliable methods of birth control 19. Hypersensitivity to Forxiga, metformin, or insulin glargine
REMIT-sita	1. Men and women between the ages of 30-80 2. Diagnosed with type 2 diabetes mellitus within the last 5 years 3. Anti-diabetic drug regimen unchanged in last 8 weeks before randomization 4. $HbA_{1c} \leq 9.5\%$ on no hypoglycemic agents or $HbA_{1c} \leq 8.0\%$ on 1 glucose-lowering agent or on half-maximal doses of 2 agents 5. BMI ≥ 23 kg/m^2 6. Negative pregnancy test and agreement to use birth control for duration of trial in females with childbearing potential 7. Ability to and willingness to perform self-monitoring of capillary blood glucose 8. Ability and willingness to self-inject insulin 9. Provision of informed consent	1. Current use of insulin therapy 2. History of hypoglycemia unawareness or severe hypoglycemia requiring assistance 3. Renal dysfunction as evidenced by serum creatinine ≥ 124 μmol/L 4. History of lactic acidosis or diabetic ketoacidosis 5. Active liver disease or ALT levels ≥ 2.5x upper limit of normal 6. History of pancreatitis 7. Systolic blood pressure > 180 mmHg or diastolic blood pressure > 105 mmHg 8. Diagnosed cardiovascular disease including history of coronary artery disease or angina, peripheral vascular disease, stenotic valvular heart disease, cardiomyopathy, aortic dissection, tachyarrhythmias, bradyarrthymias, prior stroke, or transient ischemic attack, heart failure, or left bundle branch block or second or third degree atrioventricular block 9. History of any disease requiring systemic glucocorticoid treatment 10. History of major illness with life expectancy < 3 years 11. History of injury or condition that limits ability to achieve moderate levels of physical activity 12. History of excessive alcohol intake 13. Hypersensitivity to any DPP-4 inhibitor, metformin, or insulin glargine
REMIT-iGlarlixi	1. Men and women between the ages of 30-80 2. Diagnosed with type 2 diabetes mellitus within the last 5 years 3. Anti-diabetic drug regimen unchanged in	1. Current use of insulin therapy 2. History of hypoglycemia unawareness or severe hypoglycemia requiring assistance 3. History of end-stage renal disease or renal dysfunction as evidenced by eGFR < 45 mL/min/1.73 m^2 4. History of lactic acidosis or diabetic ketoacidosis

	last 10 weeks before randomization 4. HbA_{1c} between 6.5-9.5% on no hypoglycemic agents or $HbA_{1c} \leq 8.5\%$ on 1 glucose-lowering agent or $HbA_{1c} \leq 8.0\%$ on 2 glucose-lowering agents 5. BMI ≥ 23 kg/m^2 6. Ability to and willingness to perform self-monitoring of capillary blood glucose 7. Ability and willingness to self-inject insulin 8. Provision of informed consent	5. Active liver disease or ALT levels $\geq$ 2.5x upper limit of normal 6. History of pancreatitis or medullary thyroid cancer, or calcitonin level $\geq$ 20 pg/mL 7. Diagnosed cardiovascular disease including acute coronary syndrome, hospitalization for unstable angina, myocardial infarction, revascularization with coronary artery bypass grafting or percutaneous coronary artery disease, peripheral vascular disease, valvular heart disease, cardiomyopathy, aortic dissection, tachyarrhythmias, bradyarrthymias, prior stroke, or transient ischemic attack, prior hospitalization for heart failure, or ECG findings concerning for ischemic heart disease 8. History of any disease requiring systemic glucocorticoid treatment 9. History or planned bariatric surgery in next 1.5 years 10. History of major illness with life expectancy < 3 years 11. History of injury or condition that limits ability to achieve moderate levels of physical activity 12. History of excessive alcohol intake 13. Currently pregnant or not using reliable methods of birth control 14. Hypersensitivity to lixisenatide, metformin, or insulin glargine