Carbohydrate restriction for glycaemic control in Type 2 diabetes

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Full title

Carbohydrate restriction for glycemic control in type 2 diabetes: A systematic review & meta-analysis.

Short running title

Carbohydrate restriction & type 2 diabetes

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Abstract (250)

Aim

The aim of this systematic review and meta-analysis was to evaluate the effect of carbohydrate restriction on glycaemic control in Type 2 DM.

Methods

We searched Medline, EMBASE, & CINAHL from 1976 to April 2018. We included randomised controlled trials (RCTs) which restricted the quantity of carbohydrate compared to a control diet that aimed to maintain or increase carbohydrate, reported HbA1c as an outcome and reported the amount of carbohydrate consumed during or at the end of the study, with outcomes reported at 3 months or longer.

Results

We identified 1,402 studies. Twenty-five RCTs met inclusion criteria, incorporating 2,132 participants for the main outcome. Definitions of low carbohydrate varied in studies. The pooled effect estimate from meta-analysis was WMD -0.09% (95% CI -0.28%, 0.10%) P = 0.34, I^2 80%, P <0.001 suggesting no effect from restricting the quantity of carbohydrate on HbA1c. Sub group analysis of diets containing 50-130g of carbohydrate resulted in a pooled effect estimate of -0.49% (-0.75, -0.23) P <0.001, I^2 0%, P = 0.56 suggesting a clinically and statistically significant effect on HbA1c in favour of low CHO diets in studies of 6 months or less in duration.

Conclusions

There was no overall pooled effect on HbA1c in favour of restricting carbohydrate, however restriction of carbohydrate to 50-130g per day has beneficial effects on HbA1c in trials up to 6 months. Future RCTs should be >12months, assess pre-study carbohydrate intake, use recognised definitions of low carbohydrate diets and examine reasons for non-concordance in greater detail.

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Novelty Statement

- A large number of trials and systematic reviews in this field show conflicting results for the effect of restricting carbohydrate on glycaemic control.
- This study includes analysis of trials reporting adherence to the study diet, showing this has no material impact on the outcome, and brings the evidence up to date by including more recent trials.
- Clinicians should inform patients with Type 2 DM there are a number of effective dietary approaches for improving glycaemic control, which may include restricting carbohydrate to 50-130g per day.

Introduction

Diabetes affects an estimated 4.5 million people in the UK and 415 million globally, with Type 2 DM accounting for approximately 90% of cases.[1,2] In the United Kingdom Prospective Diabetes Study (UKPDS), each 11mmol/mol (1%) reduction in HbA1c was associated with a 21% risk reduction for any end point and 37% for macrovascular complications.[3] Nutrition therapy interventions have been shown to reduce HbA1c by up to 22mmol/mol (2.0%) and there is significant current interest in the role of dietary carbohydrates for weight control, and in the context of Type 2 DM for the control of glycaemia.[4,5] However, the ideal amount of dietary carbohydrate remains unclear. Current American & European diabetes organisations do not make strong recommendations about the quantity of carbohydrate and rather state that monitoring of total carbohydrate is a key strategy in achieving glycaemic control, with the focus for dietary change instead targeted at weight loss in the overweight.[6–8] The average proportion of energy from carbohydrate in the UK general population is 47%, and it is estimated a similar amount is consumed in people with Type 2 DM.[9]

Several reviews considering the binary options of low- or high-carbohydrate diets have produced mixed results, likely due to methodological differences and poor dietary adherence in included trials.[10–13] Recent meta-analyses of low carbohydrate diets have consistently found a small but significant reduction in HbA1c in the pooled effect at 6 months that was no longer present at 12 months, supporting the conclusions made in earlier reviews.[13–15] Another recent review found modest reductions in HbA1c present at 12 months.[16] Research by van Wyk *et al*[10] highlighted the difficulty people find in adhering to prescribed diets, showing just an 8g per day difference in the carbohydrate content of diets between study arms at the end of the studies. Recent reviews have acknowledged the issue of adherence, but none have performed sub-group analyses on trials demonstrating dietary adherence to establish the impact of this on the primary outcome. The search period of the most recent review of carbohydrate in Type 2 DM does not included the latest RCTs published.[17] There is also an increasing interest in the use and effectiveness of dietary carbohydrate restriction for managing diabetes and weight. These factors underline the need for a good quality synthesis of the evidence in this area. Therefore, the aim of this review is to provide an updated evaluation the impact of carbohydrate restriction on glycaemic control in adults with Type 2 DM including the most recently published research and with an additional focus on trials demonstrating dietary adherence.

Methods

Data Sources and Searches

This systematic review and meta-analysis was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions[18] and reported in accordance with the PRISMA statement.[19] A protocol was published and registered with PROSPERO in advance.[20] The search dates were restricted to 1976 onwards (due to the introduction of HbA1c at this time [21]) and were up to April 2018. Databases searched included Medline (1976 – April 2018), Embase (1980 – April 2018) and CINAHL (1982 – April 2018). Databases of on-going trials, The Cochrane Library and DARE, dissertations and theses and other grey literature were also searched. Search terms and the search strategy were developed by the research team and search results were independently reviewed by PDM & SKR. Summary data were sought and data extraction carried out by PDM, verified by SKR, with any conflicts over inclusion resolved by discussion.

Study Selection

Studies were eligible for inclusion if they were randomized controlled trials (RCTs) including adults diagnosed with Type 2 DM; had a minimum intervention duration of 8 weeks and outcomes reporting at a minimum of 12 weeks; and the intervention restricted the proportion or quantity of dietary carbohydrate. Studies using active control diets were included, however not if the control diet included carbohydrate restriction in comparison to the intervention diet. Studies were not grouped according to the type of control diet and all forms of control diet that did not include a carbohydrate restriction were permitted, including low fat, high carbohydrate, low glycaemic index, high protein, Mediterranean and 'healthy eating'. Included studies also needed to report actual (self-reported or measured) carbohydrate intake during or at the end of the intervention and HbA1c as an outcome measure. All countries, languages and settings were eligible.

Data Extraction and Quality Assessment

Data extraction was carried out by PDM, verified by SKR, with any conflicts over inclusion resolved by discussion. Data were extracted to a purposely designed spread sheet by PDM and checked by SKR. Data items included: study and participant characteristics (including duration, setting, ethnicity, age, sex); details of the intervention & control diets (including macronutrient composition prescribed, other dietary advice given); outcome data for HbA1c, weight, blood pressure (BP) and lipids; and details of retention rates and dietary adherence, where available. Risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions[18] at study level and inputted into Review Manager 5.3.[22]

Data Synthesis and Analysis

Means and Standard Deviations (or Standard Error) were used to conduct meta-analyses for the primary outcomes HbA1c and body weight using a random effects model and to compare interventions using weighted mean difference and 95% confidence intervals. Where data for people with diabetes was part of a larger cohort including non-diabetes participants, if separate data were not reported, authors were contacted to request the relevant values for only the participants with Type 2 DM. Additional or missing data were obtained from 4 of the 5 authors contacted [23–26] and where they were not available, the study was not included in the meta-analysis. Data for the overall meta-analyses were taken from the longest available time point for each included study. Two studies did not report data for body weight and were therefore excluded from the meta-analysis.[26,27] Comparison of the carbohydrate quantity of intervention diets was in absolute grams of carbohydrate, rather than % of total energy, to allow for direct and accurate comparison. Where studies reported only % of total energy from carbohydrate, a conversion was made using 4kcal per 1g carbohydrate, based on the mean reported energy (calorie) intake for each study, or based on an estimated calorie intake of 2,000kcal if these data were not available.[28] This level of calorie intake has been used by other researchers for conversion to grams of carbohydrate[15,29] and is similar or greater than the amounts reported in trials included in this review (**Table 1**). Included studies reported HbA1c values as DCCT-aligned (%)[30] rather than the newer IFCC-standardised concentrations[31] and these were used in this review without conversion to avoid potential errors. Heterogeneity in the sample of studies was assessed using the I^2 statistic and the significance of the associated Chi^2 value ($p<0.05$).

Sub-group Analysis

Sub-group analysis based on levels of carbohydrate intake were conducted to elicit differences in the key outcomes between groups of carbohydrate intake. Level descriptors of carbohydrate intake proposed by Feinman and Acurso[29] have been widely adopted in the field of carbohydrate research and were used to define the sub-groups in this meta-analysis. Only two studies[32,33] met the definition of 'High' carbohydrate and therefore this group was collapsed with the 'Moderate' category to form a group named 'Moderate+' in this analysis. A further sub-group analysis was undertaken to achieve a key aim of this study, by conducting a meta-analysis of a subset of included studies demonstrating dietary adherence. Adherence to the study diet was defined for this purpose as +/- 10% of the prescribed carbohydrate (g) in the restricted carbohydrate group. Heterogeneity within each subgroup was examined as well as the overall I^2, and a test for heterogeneity between subgroups was also performed.

Results

Search Results

The selection of studies is indicated in **Figure 1** according to the PRISMA[19] flow diagram. Initial database searches yielded 1,402 articles and 72 full-text articles were retrieved before eligibility could be established. There were 25 studies that met the inclusion criteria.

Study Characteristics and risk of bias

Characteristics of the 25 included trials are summarized in **Table 1**, grouped according to dietary intervention using the definitions of levels of carbohydrate prescribed and outlined in **Table 2**. The moderate and high carbohydrate categories were collapsed for the purpose of analyses as there were only two studies meeting the definition of high carbohydrate.

The publication period covered 36 years and ranged from 1981 to 2017. Study duration ranged from 12 to 208 weeks, with a mean duration of 56 weeks. The majority of studies lasted longer than 26 weeks with 7 studies longer than 52 weeks. All except one study in the Low Carbohydrate category lasted for 26 weeks or less and, although this study was 104 weeks duration, it only reported outcomes at 26 weeks.[34] Study sample sizes ranged from 12[23] to 419[35] and a total of 2,132 participants were included in this review. Of the 25 included studies, 10 of the dietary interventions met the definition of 'moderate carbohydrate' (*n*= 1,111).

Figures 2 and 3 (figure 3 available as supplementary material) show the risk of bias across all studies. The principal risk of bias stemmed from either the poor description of the randomization sequence and allocation concealment, or because there was no description of the pre-study dietary intake of participants ('Other bias'). This represented more than one third of studies included in this review.

Glycaemic Control

The baseline and post-intervention values of HbA1c, weight, total cholesterol and BP are shown in (**Tables 3 and 3a – supplementary material)**. Blood pressure and lipids were not routinely included as outcomes or reported in studies included and were not the main focus of this review.

Significant between-group differences in HbA1c were observed in just 6 of the 25 trials. [36–41] Some studies reported significant differences at 6 months which were not maintained at 12 months and beyond.[34,42] Meta-analyses conducted for HbA1c for all studies found no overall effect of modifying carbohydrate and demonstrated a high level of heterogeneity (WMD -0.09%, 95% CI -0.28%, 0.10%, P = 0.34, I^2 80%, P <0.001) (**Figure 2**). Sub-group analysis of studies meeting the definition of 'very low carbohydrate' (<50g per day) also found no overall effect with very low levels of heterogeneity observed (WMD -0.20%, 95% CI -0.42%, 0.03%, P = 0.23, I^2 25%, P = 0.09). Analysis of the sub group of 5 low carbohydrate diet studies (50-130g per day) showed a statistically and clinically significant result in favour of the intervention diet (WMD -0.48%, 95% CI -0.74%, -0.23%, P < 0.001, I^2 7%, P = 0.37). All studies in this sub-group were of 6 months or less duration, or only reported outcomes at 6 months.

Baseline HbA1c amongst the study groups ranged from 43mmol/mol (6.1%) to 87 mmol/mol (10.1%), with some studies specifically excluding participants with poorly-controlled blood glucose and others adopting the opposite strategy.

Body Weight

Changes in body weight or Body Mass Index (BMI) were included in the majority of studies, however body weight outcomes were not available for two studies which were therefore excluded from the meta-analysis.[26,27] Two studies[38,43] reported a sample with near healthy weight and BMI at baseline. Significant between-group differences in body weight were observed in just 5 of the 25 included studies, 3 of which were from the sub group of LCHDs. There was no overall effect in the meta-analyses for weight for all studies (WMD -0.13kg, 95% CI -0.33kg, 0.08kg, P = 0.22, I^2 78%, P <0.001) (**Figure 3 – supplementary material**). A high level of heterogeneity was seen in the pooled meta-analysis but not in the low carbohydrate sub group. This sub group showed a statistically significant pooled effect in favour of restricted carbohydrate (WMD -0.43kg, 95% CI -0.74kg, -0.12kg, P = 0.006, I^2 24%, P = 0.26).

Blood Pressure & Blood Lipids

Of the 25 studies, 11 did not fully report outcomes for BP and in those that did, changes were unremarkable and rarely reached statistical significance. Such differences between groups were seen only in the paper by Jonsson *et al.*[36]

Complete blood lipid outcomes were reported in 17 of the 25 studies. Statistically significant differences between groups were seen in just 7 of the studies and most commonly observed difference was a greater increase in HDL-Cholesterol in the modified carbohydrate group.

Study Diets, dietary assessment & adherence

The amount of carbohydrate participants were instructed to consume within the 'moderate+' group ranged from 138g per day to 293g per day (or 194g if the two 'high' carbohydrate studies are excluded). Half the studies included in this review did not report or record the baseline carbohydrate intake of participants. Several trials in the moderate group described the interventions as 'low carbohydrate' at a prescribed level based on 40% of total energy intake. Adherence to study diets was observed more frequently in the moderate+ group than in other groups.

13 studies demonstrated relative adherence to the prescribed carbohydrate intake in the intervention arm (+/- 10% in g carbohydrate). A further sub-group analysis of the effect on the primary outcome using only these studies showed no impact on overall carbohydrate restriction (WMD –0.06 95% CI -0.15, 0.02, $P = 0.16$, I^2 88%, $P < 0.01$) (**Figure 4 – supplementary material**). Of these 13 studies, 10 were within the 'Moderate+' group of carbohydrate restriction, 2 were 'Low Carbohydrate' and 1 from the 'Very Low Carbohydrate' group. The mean average carbohydrate intake in the intervention group of the 13 studies was 150g (range 41-209g, median 166g) and the control diets were mostly low fat, high carbohydrate in this group.

A variety of methods for dietary measurement were used by the individual studies, ranging from a 24-hour recall, food frequency questionnaires or 7-day weighed food records to smartphone apps such as MyFitnessPal. Several studies did not describe how dietary assessment was carried-out.[32,38,44]

Discussion

This systematic review and meta-analysis of carbohydrate restriction for glycaemic control in Type 2 DM has shown no significant overall effect on HbA1c or body weight. Current national nutrition guidelines for Type 2 DM reflect this and do not make a specific recommendation about the quantity of carbohydrate.[6–8]

A small and clinically-significant reduction of 5mmol/mol (0.48%) in HbA1c was seen in the sub-group of studies using 50-130g of carbohydrate per day. These studies were 6 months or less in duration, or only reported outcomes at 6 months, an important limitation to the clinical application of this finding. Earlier reviews found that reductions in HbA1c or weight at 3 or 6 months are not maintained beyond 12 months.[11,13–15] Adherence to the prescribed diets in this group was good and may be an important factor in the positive result seen in the meta-analysis, but if this success cannot be replicated in longer trials, or using even greater restrictions in carbohydrate, then this is an important finding with implications for future research and clinical practice.

Findings in the context of existing evidence

Eight other meta-analyses published in the last 5 years address a similar research question to the current review and their findings are summarized in **Table 5**. The lack of agreement amongst them is due in part to differences in the methodology, such as the inclusion criteria or the approach taken in meta-analysis. Several reviews had similar findings to the present review[13,15,45] and Snorgaard *et al*[13] also found the greatest improvements in HbA1c were associated with the greatest reductions in carbohydrate, a finding which is not replicated in the present review.

Strengths & limitations of underlying studies

Several methodological limitations are present in the studies included in this review, specifically the lack of isocaloric study arms, the varied methods of dietary assessment, differences in baseline glycaemic control of study participants, a lack of concordance with the study diet, and differences in study protocols for adjustment of diabetes medication.

Improvements in HbA1c are regularly seen in both groups in included studies and may be related to a reduction in energy intake and subsequent weight loss across the entire study population. With some exceptions,[24,34,35] most studies did not intend to keep the amount of dietary energy between study arms equal, and therefore results may have been confounded by differential changes in weight as a result of differing energy intakes between study groups. Caution should be exercised in interpreting these outcomes in the context of dietary changes, especially given the heterogeneity in the methods of dietary measurement employed, and their inherent inaccuracy.

Only 13 of the studies included in this review demonstrated overall concordance with the prescribed quantity of carbohydrate, and in several cases where there was concordance, the quantity of carbohydrate consumed was very similar to the pre-study or baseline intake.[46–49] Although in each case there was a small reduction in carbohydrate intake in the intervention group, it could be questioned whether these studies did achieve what they intended and therefore the validity of including them in this meta-analysis. The differences between the intervention and control diets often amounted to far more than a simple difference in the quantity of carbohydrate consumed. The nature of adjusting either the absolute amount or proportion of one nutrient automatically means either the proportion or absolute amount of other macronutrients will also be altered. In fact, this was sometimes the primary aim of the study.[36,49,50] The results of the present review are consistent with the findings from van Wyk *et al*[10], who concluded both low carbohydrate and high carbohydrate groups have difficulty in achieving and adhering to the prescribed level of carbohydrate intake, with a difference between groups as small as 8g per day. Most trials used an intention-to-treat approach to the analysis, however none of the studies included in the present review performed additional analysis only on participants adhering to the protocol diet.

A wide range of methods of dietary assessment were used across the studies included in this review. Despite almost all trials employing a dietitian to advise participants and administer the monitoring of dietary intake, there are inherent inaccuracies in whichever method is chosen, and comparison between methods has long been recognized as troublesome.[51,52] If randomization had left significant differences between study arms with respect to the pre-study habitual dietary intake, this would have to be acknowledged as a potential risk of bias, however many of the included studies failed to measure or report the composition of participants' diets prior to commencement of the trial. [36,38,40,44,50,53,54]

Other limitations include the wide range of baseline HbA1c values and adjustment of anti-hyperglycaemic medication. Participants with poorly-controlled blood glucose were part of the exclusion criteria in several studies, however this may not be representative of a typical clinical population. Many studies used a protocol to adjust medication according to blood glucose during the trial, whilst others excluded patients based on their diabetes medication. Investigators either advised participants to undertake a recommended amount of physical activity each day or to continue with their usual activities, but the majority did not report or adjust for physical activity level in the analysis, which could be a significant limitation.

RCTs of dietary interventions are notoriously challenging with regards to minimising bias, although numerous strategies have been recommended.[55] Blinding of treatment allocation to patients and those delivering the intervention is rarely possible, and the nature of dietary interventions involving complex lifestyle and behaviour changes means participants are likely to have a strong preference, which may in turn affect adherence and attrition. Subject bias and the Hawthorne effect are also likely in dietary intervention trials and may be evident in studies in this review, such as Jonasson *et al*[34] in which participants were informed of the diet allocation prior to assessment of baseline nutritional intake. Most studies did not sufficiently report their efforts to minimize bias and could have described how blinding of outcome assessment and the personnel involved in data handling, for instance, might contribute to minimizing bias.

Strengths of this review

This review provides an updated evaluation of research to establish the impact of carbohydrate restriction on glycaemic control in Type 2 DM and examines the potential impact of dietary adherence on the primary outcome, which previous reviews failed to fully address. Other systematic reviews and meta-analyses include database searches up to July

2017[56] and did not include a recent study[57] which has been included in this review. Two reviews also looked specifically at low carbohydrate vs. low fat rather than a range of control diets as in this review,[56,58] and the review by Sainsbury *et al*[15] included studies with participants with Type 1 DM. Therefore, the added value of this review is the sub-group analysis of the 13 studies demonstrating relative adherence to the intervention diet. This aimed to address questions regarding the role of adherence in the primary outcome, however may have been confounded by the proportion of studies in the moderate+ group which formed part of this sub-group.

The standardisation of definitions relating to the level of carbohydrate intake is an important consideration. This review categorised studies according to the proposed levels by Acurso[59] and Feinman *et al*[29], which means some individual studies were re-categorised from their stated level of restriction to match these level descriptors. For example, studies often used ≤40% of total energy to define 'low carbohydrate', however this is now accepted as 'moderate carbohydrate'. The rationale for selecting this level of restriction is rarely explicated and it is likely that this merely represents an intake that is less than the habitual intake of western populations.[60,61] However, it is much higher than levels likely to result in short-term improvements in glycaemic control, as demonstrated in this review, and led to participants consuming levels of carbohydrate not dissimilar from their pre-study consumption.

Limitations of this review

The inclusion criteria for this review was intended to encompass the breadth of evidence regarding levels of carbohydrate in Type 2 DM however the large variation in the duration of included trials, the range of dietary approaches employed and whether included studies achieved the intended dietary changes may also limit the findings. Sub-group analysis suggests that including only studies lasting 12 months or more would not have any material impact on the overall pooled effect, a finding supported by other reviews that have grouped their analyses by study duration.[15,62] The exclusion of trials that did not report the carbohydrate intake of participants is recognised as a potential source of bias, however this resulted in the exclusion of only one RCT[63] and most trials were excluded due to their duration or non-reporting of the primary outcome (HbA1c).

The meta-analysis for HbA1c includes a sub-group of trials of moderate carbohydrate in which a high level of heterogeneity is observed (I^2 82%, p<0.001). A wide range of different dietary approaches are employed in this group, which may confound the ability to draw conclusions from the pooled effect.

The present review did not undertake a meta-regression to assess the effects of other variables on the primary outcome of HbA1c, such as changes in diabetes medication, physical activity or weight. Many of the studies did not report on medication changes or physical activity, so this remains a potential unobserved confounder. Weight loss is recognised as a significant predictor of improvements in glycaemic control in Type 2 DM and the network meta-analysis by Schwingschackl *et al*[56] demonstrated a significant relationship between reduction in HbA1c and mean differences in weight. However, meta-regression is not always appropriate where there are fewer than 10 studies in a sub-group[18] as is the case for two of the sub-groups included in this meta-analysis.

Conclusion

This review provides evidence of short term improvements in glycaemic control from a restriction in carbohydrate intake to 50-130g per day, however it suggests there is little evidence to support recommending a general restriction of carbohydrate intake for all patients with Type 2 DM. Controversy in the area of dietary carbohydrate will likely persist, with recent publications such as the PURE study calling for dietary guidelines to be reconsidered.[64] However, data from studies of carbohydrate-restricted diets raises important questions over the long-term sustainability of such diets, given the poor overall concordance with the prescribed quantity of carbohydrate, even in a trial setting. As suggested by Van Wyk *et al*[10], it is likely there is significant variation in glycaemic response to carbohydrate between patients, which may explain the inconclusive nature of trials. Future research should consider the acceptability of carbohydrate-restricted diets and how to identify patients who will benefit most from being offered this approach. Researchers planning trials in this field should consider carefully the added value of further RCTs, given the number of systematic reviews already published. In order to add value, any future trials should be long-term (greater than 12 months), adopt the prevailing definitions of low carbohydrate and intend to keep both the caloric content of the diets in study arms, and any changes in body weight, equal. Current guidelines should reflect the short-term improvements in glycaemic control that diets restricted to 50-130g of carbohydrate per day can offer as the evidence-based approach in Type 2 DM.

Contributors

The study was conceived and designed by PDM, PSG and SMG. PDM and SKR undertook the literature search and data extraction. MSH contributed to the statistical analysis and all authors contributed to the interpretation and writing of the manuscript.

Transparency Declaration

PM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

PDM has received honoraria from Healthspan, Eli Lilly and NovoNordisk.

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Systematic Review Search Strategy (Ovid: Medline & Embase)

Type 2 Diabetes Mellitus

1. exp Diabetes Mellitus, Type 2/
2. (MODY or NIDDM or T2DM).tw,ot.
3. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend).tw,ot.
4. ((typ$ 2 or typ$ II) adj3 diabet$).tw,ot.
5. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ab,ti.
6. Or/1-5

Diet & Carbohydrate Interventions

7. explode Diet Therapy/ [MeSH, all subheadings]
8. (diet$ adj5 diabet$).ab,ti.
9. (diet$ adj5 carbohydrat$).ab,ti.
10. (diet$ adj5 sugar$).ab.ti
11. 7 or 8 or 9 or 10

Randomised Controlled Trials

12. randomized controlled trial.pt.
13. controlled clinical trial.pt
14. randomi?ed.ab,ti.
15. randomly.ab,ti
16. trial$.ab,ti.
17. Or/12-16

Systematic Reviews / Meta-Analysis

18. meta-analysis.pt
19. exp Meta-Analysis/
20. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
21. Or/18-20

Type 2 Diabetes and All Interventions

22. 6 and 11

Type 2 Diabetes and All Interventions and Randomised Controlled Trial

23. 22 and 17

Type 2 Diabetes and All Interventions and Systematic Reviews / Meta-Analysis

24. 22 and 21