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Carbohydrate quantity in the dietary management of type 2 diabetes – a systematic review and meta-analysis

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ABSTRACT

Aims: This systematic review and meta-analysis compares the effects of low carbohydrate diets (LCDs) on body weight, glycaemic control, lipid profile and blood pressure with those observed on higher carbohydrate diets (HCDs) in adults with type 2 diabetes.

Methods: MEDLINE, EMBASE, CENTRAL, CINAHL, Food Science Source and SweMed+ databases were systematically searched to identify randomised controlled trials (duration ≥ 3 months) investigating the effects of a LCD compared to a HCD in the management of type 2 diabetes. Data were extracted and pooled using a random effects model and expressed as mean differences and risk ratio. Subgroup analyses were undertaken to examine the effects of duration of intervention, extent of carbohydrate restriction and risk of bias. The certainty of evidence was assessed using GRADE.

Results: Of the 1589 studies identified, 23, including 2178 participants, met inclusion criteria. Reductions were slightly greater on LCDs than HCDs for HbA_{1c} (-1.0 mmol/mol, CI -1.9, -0.1 [-0.09%, CI -0.17, -0.01]) and triglycerides (-0.13 mmol/l, CI -0.24, -0.02). Changes in weight, HDL- and LDL-cholesterol, total cholesterol and blood pressure did not differ significantly between groups. Subgroup analyses suggested that the difference in HbA1c was only evident in studies with duration of ≤6 months and with high risk of bias.

Conclusions: The proportion of daily energy provided by carbohydrate intake is not an important determinant of response to dietary management, especially when considering longer term trials. A range of dietary patterns including those traditionally consumed in Mediterranean countries seems suitable for translating nutritional recommendations for people with diabetes into practical advice. Systematic review registration number: CRD42013005825.

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INTRODUCTION

Dietary advice is generally accepted as a cornerstone of the management of type 2 diabetes (T2DM) [1]. More than 80% of all patients presenting with T2DM are overweight or obese [2,3], and recommendations relating to energy intake and physical activity aimed at weight management are a core component of the treatment of T2DM worldwide [4-7]. However, advice regarding the macronutrient composition has varied over time [8]. With occasional exceptions, carbohydrate restriction was a key component of diabetic dietary prescriptions for much of the 20th Century. In the 1960's it became evident that CHD rates were exceptionally high in people with diabetes and the high fat (predominantly saturated fat) intakes associated with the reduction in carbohydrate were presumed to be a contributory factor. This observation together with the demonstration of the beneficial effects of dietary fibre on glycaemic control and blood lipids in the 1970s led to a change in the nutritional approach. Fibre-rich, low glycaemic index carbohydrates were encouraged and total carbohydrate intake was liberalized in advice to people with diabetes as well as populations at large [4,9-14].

More recent reports, have suggested the potential of appreciable reductions in carbohydrate to facilitate weight reduction and improve glycaemic control, insulin sensitivity, blood pressure, HDL-cholesterol and triglyceride levels to a greater extent than higher carbohydrate diets [15-19]. However, three recent meta-analyses of trials undertaken in people with T2DM reached different conclusions regarding the merits of carbohydrate restriction in this patient group [16,20,21]. In order to inform an update of current European Guidelines for the management and prevention of diabetes, we have undertaken a systematic review and meta-analysis which attempts to circumvent the criticisms which have been levelled at the earlier attempts to aggregate the relevant trials [22,23]. More specifically we wanted to investigate whether a low-carbohydrate diet improved weight and metabolic control more than a higher carbohydrate diet in patients with type 2 diabetes.

MATERIALS AND METHODS

This systematic review was carried out according to Cochrane recommendations [24], and reported in line with the PRISMA Statement [25] (Supplementary table 1). The protocol for this review was prospectively registered in PROSPERO (CRD42013005825).

Search strategy and study selection

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Food Science Source and SweMed+ for RCTs published between 1983 to January 2016. Our search terms were: (diet OR carbohydrate-restricted OR low carbohydrate diet OR dietary carbohydrates OR ketogenic diet OR Atkins diet OR diabetic diet) AND (type 2 diabetes OR diabetes mellitus OR type 2 OR diabetes OR non-insulin dependent diabetes mellitus), using MeSH terms when available. We also searched the reference list of identified studies and performed forward citation searches to consider further studies not identified by our online search.

We included randomised controlled trials of parallel or cross-over design with more than three months duration in adults with type 2 diabetes. We had no restrictions regarding minimum number of included subjects. Co-morbidity was accepted, but studies including individuals with impaired glucose tolerance and/or type 1 diabetes were only included whenever separate data for patients with type 2 diabetes were provided. Trials had to compare a diet below to a diet above 40% total energy (E%) from carbohydrate to be included. Complex interventions consisting of elements with the potential to interfere with the effect of the dietary intervention (e.g. parenteral administration or promotion of physical activity) were excluded.

We accepted studies written in English, Danish, Norwegian and Swedish. One review author (HKH) screened all titles and abstracts, and excluded obviously irrelevant records. For the

remaining records, full-text articles were obtained and assessed independently for inclusion by two authors (AMA and HKH). Any disagreements were resolved by consensus.

Data extraction and risk of bias

From each study we extracted the name of first author, year of publication, study design, study duration, participant details, intervention diet details, markers of compliance with diets, and the outcomes measured. The following outcomes were considered: weight, HbA_{1c}, lipids, blood pressure and compliance to dietary intervention. Data were extracted by one author (HKH), and verified by a second investigator (AMA).

We assessed risk of bias for the main items suggested by Cochrane [24]: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. For each study and outcome, two researchers (HKH and AMA) independently rated the seven domains to low, unclear or high risk of bias.

We applied the following rules to assess the overall risk of bias for each study and outcome:

- Low risk: No high risk of bias, and not more than two unclear risks of bias
- High risk: Two or more high risks of bias, one high and more than one unclear risk, or more than four unclear risks of bias
- The remaining articles were classified as unclear risk of bias

Due to the nature of delivery of dietary interventions, blinding of participants and study personnel that provided dietary advice was not possible. Hence, this item was not considered when assessing the overall risk of bias.

Data synthesis and analysis

Results were summarized qualitatively, and whenever applicable, results from available studies were combined in meta-analysis using Review Manager (RevMan) [Computer

program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. We expected clinical heterogeneity among studies, and chose the random-effects model. The weighting of individual trials was defined by inverse variance and mantel-haenszel methods for continuous and dichotomous outcomes, respectively. We calculated the mean difference (MD) for continuous outcomes, whereas dichotomous effect sizes were expressed in terms of a risk ratio (RR). For trials with multiple dietary arms, we pooled data for the higher-carbohydrate diet groups to create one control group [24]. Crossover trials were not included in meta-analysis due to short intervention period and possible carryover effect. The HbA1c unit was converted from % to mmol/mol by the use of a conversion calculator: http://www.ngsp.org/convert2.asp.

Meta-analyses were considered to be associated with heterogeneity when the I^2 value was above 50%, and/or the P value of the Cochrane Q test was less than 0.10 [24], and subgroup analysis were used to explore possible reasons for the suggested heterogeneity. In particular, we conducted post-hoc subgroup and sensitivity analyses to explore the impact of study duration (≤6 months vs. ≥12 months), varying carbohydrate content in the LCD-group (very low-carbohydrate diets, VLCD: 21-70 g carbohydrates and moderate LCD: 30-40 E% carbohydrates) [15] and risk of bias (low vs. high).

Two authors (AMA and HKH) independently graded [26] the certainty of the evidence for diets of lower carbohydrate content when compared with diets of higher carbohydrate content in the management of type 2 diabetes. We assessed publication bias for a given outcome by inspection of funnel plots.

RESULTS

Search results and characteristics of the included studies

Out of 1589 studies identified through database searches and cross reference list matching, 23 studies were included in the review [27-49] (Fig 1). Main reasons for exclusion were diet intervention not being low-carbohydrate; duration of intervention being less than three months; study sample consisting of individuals without type 2 diabetes and studies using a non-randomised and/ or non-controlled trial design (Supplementary table 2).

The total participant number in the 23 articles was 2178, 1061 participants in the low-carbohydrate group and 1194 participants in the control group. Two studies included participants with and without type 2 diabetes [31,34]. In these studies, only data on the type 2 diabetes participants were extracted. The follow up time ranged from three months [28,29,32,33,38,45,46] to over three years [30]. Studies were published between 1994 [27] and 2014 [46-49]; eight were conducted in North America [27,30,31,33,35-37,46], five in Europe [32,38,42,45,47], five in Australia [28,29,41,44,48], one in New Zealand [43], three in Israel [34,39,40] and one in Japan [49]. Randomised crossover design was used in four studies [27-29,38], and parallel randomised control trials, with one or two control groups, were implemented in 19 studies [30-37,39-49].

A summary of findings from the included studies are presented in Table 1. Twelve studies reported having included individuals who were either overweight or obese [31-35,37,39-41,43,44,48]. Physical activity was not specifically addressed in any of the studies, but several trials promoted general recommendations for physical activity.

The LCD was compared to either low-fat diets [31-34,37,42,47,49], standard diabetes care [38-40,45], high carbohydrate diets [27,29,41], low-protein diets [30,44], a standard protein diet [48], Mediterranean diets [34,39], high carbohydrate, low-fat diets [28,43], a high wheat-fibre diet [46], low-glycaemic index diets [35,36] or a high-glycaemic index diet [36]. The recommended amount of dietary carbohydrates in the low-carbohydrate interventions ranged from five [35] to 40% [27-29,33,41,43-45,48] of the total energy intake. Among the 17 studies that assessed the actual intake of

carbohydrates throughout the study period, all but one [48] found that the difference in carbohydrate intake was statistically significant between the LCD-group and comparator [28,29,32,33,36-43,45-47,49]. In six of the low-carbohydrate interventions [28,29,33,39,47,48], and ten of the comparator diets [28,29,33-35,39,40,47-49] it was intended that participants consumed energy restricted diets that ranged from approximately 5000 kJ (1200 kcal) [40] to 7500 KJ (1800 kcal) [34] per day. Fifteen studies emphasized that weight reduction was a goal of the dietary intervention. Conversely, several trials permitted study participants in the intervention to eat ad libitum while limiting carbohydrate intake.

Mean duration of diabetes among participants varied from one to over 17 years and the participants frequently used medications including insulin therapy [30,31,34,35,37,41-45,47,49], anti-hypertensive drugs [29,30,33,36,38,43,44,46] lipid lowering medications [29,30,33,36-38,42-44,46] and oral hypoglycaemic agents, such as metformin [30,31,35,37,38,42,46-49], sulfonylurea [27,30,31,37,38,42,46-49] and thiazolidinedione [38,46,48,49]. Dietary advice was provided by health professionals, such as dietitians, nutritionists, diet counsellors [29,31,33-37,39-47,49], physicians [42,47] and nurses [42] and incorporated both individual meetings and group sessions.

Risk of bias in included studies

Assessment of risk of bias is summarized in supplementary figure 1A and shown for the individual studies in supplementary figure 1B. Method of random sequence generation was reported and found adequate in 15 studies. Eight trials provided sufficient information about the proceedings of allocation concealment and they were rated as low risk. As expected, few studies blinded study participants and personnel to the dietary interventions (with the exception of one trial [40]), and were thus rated as unclear risk of bias. Five studies reported blinding of outcome assessors. Furthermore, one study [29] had high risk of attrition bias due to incomplete reporting of outcome data, as only compliers were incorporated in analysis and non-adhering participants were excluded. Selective reporting was found in four trials. Overall,

when using the predefined criteria, the study level assessment showed that ten trials had high risk of bias [27-32,35,45,47,49], three had low risk of bias [41,43,48] and the remaining ten studies were considered as unclear risk of bias [33,34,36-40,42,44,46], (Supplementary figure 1). The Funnel plots for the different outcomes did not indicate any publication bias (Supplementary figure 2).

Body weight

Of the 20 studies that incorporated changes in body weight as an outcome, 17 provided sufficient information to be included in the meta-analysis, comprising 739 participants randomised to the LCD and 848 randomised to the HCD. Overall, LCD was not associated with greater weight loss than HCD in either short or long term studies (Figure 2A), but subgroup analysis suggested more positive results in short term studies (≤ 6 months) than in studies with longer follow up (Supplementary table 3a). Sensitivity analysis showed less difference between LCD and HCD in studies with low risk of bias than in studies with high risk of bias (supplementary table 3C). In the three cross-over studies of 3 months duration [28,29,38] which did not fulfill criteria for inclusion in the meta-analysis, one [38] showed greater weight loss associated with LCDs. The certainty of evidence was moderate, with little heterogeneity (I^2 = 29%), (Supplementary table 4).

Glycaemic control

LCD was associated with a greater overall reduction in HbA_{1c} (MD -1.0 mmol/mol, 95% CI -1.9, -0.1 [-0.09 %, 95% CI -0.17, -0.01]) in the 16 studies included in this analysis. This result is largely driven by the results of the short term studies (Figure 2B, Supplementary table 3a), and by trials associated with high risk of bias (Supplementary table 3C). Of the three further short term studies not included in the meta-analysis [28,29,38] one [38] showed greater improvements on LCDs. The evidence was considered as having moderate certainty for this outcome (Supplementary table 4).

Serum lipids and blood pressure

Sixteen RCTs are included in the pooled analyses of the effects on HDL-cholesterol and Triglycerides, 15 studies in the analysis of LDL-cholesterol and 14 in the analysis of total cholesterol. The meta-analyses showed no significant difference between groups in effect on HDL-cholesterol (MD 0.04 mmol/l, 95% CI -0.01, 0.10; low evidence), LDL-cholesterol (MD -0.01 mmol/l, 95% CI -0.13, 0.11; low evidence), and total cholesterol (MD 0.04 mmol/l, 95% CI -0.12, 0.20; low evidence), but a slightly greater reduction in triglycerides with LCD (MD -0.13, 95% CI -0.24, -0.02 mmol/l; low evidence), (Figure 3D, Supplementary table 4). There was evidence for considerable between-study heterogeneity for triglycerides (I^2 = 57%, $p < 0.003$), HDL-cholesterol (I^2 = 72%, $p < 0.0001$), LDL-cholesterol (I^2 = 64%, $p = 0.0004$) and total cholesterol (I^2 = 71%, $p < 0.0001$).

The reasons for the observed heterogeneity were explored in subgroup and sensitivity analysis. No consistent subgroup effects were observed across the three outcomes, even though HDL-cholesterol was slightly higher on LCD than HCD in long term studies (p=0.10, Figure 3B, Supplementary table 3A) and LDL-cholesterol was higher in VLCD-trials compared with moderate LCD (p=0.05, Supplementary table 3B and Supplementary figure 3). Trials with low risk of bias showed less difference between LCD and HCD for changes in HDL-cholesterol and triglyceride than trials associated with high risk of bias, whereas the results were more consistent for LDL- and total cholesterol.

Sixteen trials examined the effect of a LCD on blood pressure. As shown in Figure 4A and B, the pooled effect from the meta-analysis indicated no significant difference in effect of the LCD on systolic (SBP) and diastolic blood pressure (DBP) when compared to control (SBP: MD -0.93 mmHg, 95% CI -2.24, 0.37, DBP: MD -0.21 mmHg, 95% CI -1.20, 0.79). Two of the three studies that were not included in the meta-analyses showed a greater reduction in

DBP in the LCD group [36,38]. The certainty of evidence was considered low for both outcomes due to risk of bias and imprecision (Supplementary table 4). No evidence of between study heterogeneity was identified in the meta-analyses ($I^2 = 0\%$).

Compliance and attrition rate

By using 24-hour recalls or food records, nine out of 18 studies found that dietary intake of carbohydrates in the LCD were 5 E% within what was recommended. In seven out of nine trials that observed low compliance, participants were on VLCD with 5 to 22 E% from carbohydrates [31,32,34,35,37,40,42]. Four of these studies were based on an Atkins diet [34,35,37,40]. In the meta-analysis of attrition rates between LCD and HCD, no detectable difference in attrition was observed: RR 1.08 (95% CI 0.92, 1.27; $I^2 = 0\%$), (Figure 4C). The results were similar in trials associated with high and low risk of bias. The certainty of evidence for attrition was downgraded to low due to risk of bias and imprecision (Supplementary table 4).

Carbohydrate and fat quality in the diets

Seven of the included studies gave no information regarding dietary intake or only information on macronutrient distribution. Sixteen studies assessed dietary intake and 15 of these reported information regarding the nature of carbohydrate eaten (fibre, Glycemic Index or load, sucrose, key foods provided in feeding trials). In 9/15 trials the intake of fibre was higher in the HCD, while six trials reported no differences in fibre intake. GI /GL were higher in the HCD in the two studies that reported this, while the intake of sucrose was lower in the LCD in one of the three trials that reported sucrose intake. In seven of the trials unsaturated fatty acids substituted carbohydrates in the LCDs. This resulted in a significantly higher intake of unsaturated fatty acids in the LCD compared with the HCD in six of the trials that reported fatty acid composition while intake of saturated fat increased only in two of these studies

DISCUSSION

This systematic review and meta-analysis shows that the minimally lower levels of HbA_{1c} apparent when comparing diets with very low (21 – 70g) or low (30 to 40 E%) carbohydrate content with those providing a higher carbohydrate content (greater than 40 E%) are driven by trials with a duration of six months or less and by trials associated with high risk of bias. The only consistent difference between the studies with higher and lower carbohydrate intakes was a small difference (0.13mmol/l) in triglyceride levels, but this was also most evident in trials with high risk of bias. No differences in weight, blood pressure or total, LDL and HDL cholesterol were apparent in either the relatively short or longer term trials.

Our systematic review and meta-analysis identified all relevant trials published between 1983 and January 2016 and therefore included an appreciably greater number of studies than earlier meta-analyses, thus enabling more convincing conclusions than previously possible. Other strengths included strict compliance with the established criteria for the conduct of such a review and meta-analysis, including registration and specification of methodology prior to the literature search, the involvement of two researchers to independently extract and assess the trials, and the use of GRADE methodology to evaluate the certainty of the evidence. The inevitable limitation of any such review stems from the quality of the included trials and the extent to which participants achieved adherence to prescribed diets, which in studies of free living individuals inevitably diminishes over time. The observation that trials with high risk of bias are associated with more favourable results for the LCD in many analysis highlights a potential pitfall in the interpretation of individual studies, meta-analysis and subgroup analysis. We attempted to assess compliance with prescribed diets and determine the extent to which nature of carbohydrate might have influenced outcome. While there appeared to be a relatively high level of compliance with the LCD, it was evident that the ability to follow a

diet with *very* low-carbohydrate content was generally poor. Furthermore, changes in medications over time may have blurred effects of differences in diet composition. The limited information given in the included studies suggests that particularly the very low-carbohydrate diet groups had a greater reduction in the use of diabetes medication (mainly insulin) that may have masked a more positive impact on glycaemic control than what we have shown. On the other hand, only four studies showed a significant difference in change in diabetes medication between the diets and some of the studies repeated their analyses adjusting for difference in medication and found that it did not alter the conclusions.

Ajala et al [16] reported a review and meta-analysis which examined the effects of low-carbohydrate, low-GI, high-fibre, high-protein, Mediterranean, vegetarian and vegan diets compared with control diets in trials continued for six months or more. They reported a range of benefits including an improvement in glycaemic control associated with all these dietary patterns and concluded that they were appropriate for people with diabetes. However given that neither the low carbohydrate nor the comparator diets were clearly defined, it is not possible to disentangle the effect of carbohydrate quantity from other dietary attributes on the various outcome measures. Our meta-analysis also included trials with a range of carbohydrate intakes, but differences between low and higher intakes were clearly specified and we used a random effects analysis, rather than a fixed effect analysis (as performed by Ajala and colleagues [16]) to take into account the heterogeneity of studies. Naude et al [20], on the other hand, concluded that there were no differences in either body weight or glycaemic control when altering carbohydrate quantity, but their meta-analysis included only five trials which involved isoenergetic comparisons, thus limiting any chance of finding differences in weight change or glycaemic control as a consequence of altering macronutrient distribution.

In a more recently published systematic review and meta-analysis, Snorgaard et al [21], like us concluded that the modestly beneficial effect on glycaemia conferred by low carbohydrate

diets was only apparent in the short term. However, our analysis differed from their approach in that we considered the outcomes of the relatively short and longer term trials separately, whereas five of the eight studies providing 3-6 month data in the Snorgaard et al review were also the source of the 12 month data. They also reported that the effect on glycaemic control was related to the extent of carbohydrate restriction. This association was totally dependent upon the findings of two trials [50,51] of 3 months duration that were not included in our analyses because they included subjects with prediabetes [50] or implemented an additional physical activity intervention [51]. When examining the forest plots for VLCD diets and moderate LCD diets separately there appeared to be a better effect of VLCD on HbA_{1c} also in our meta-analysis, but post hoc subgroup analysis did not confirm this. On the contrary, the subgroup analysis showed that VLCD had a less favourable effect on LDL-cholesterol compared with HCD while this difference was not shown in studies using moderate LCD. The period of Snorgaard et al's [21] search (2004 – 2014) was appreciably shorter than the period covered by the present study and the upper cut-off used to define low carbohydrate diets was 45 E% whereas we chose the somewhat lower cut-off, 40 E% .

Short term benefits of low and very low carbohydrate diets in terms of weight loss and improvements in blood pressure and blood lipid profile have also been shown in normoglycaemic individuals [18,19]. It has not been possible to disentangle whether the short term improvement in glycaemic control and a range of cardiovascular risk factors is a consequence of the weight loss or a direct result of carbohydrate restriction and/or the consequential redistribution of the proportion of energy provided by other macronutrients. It is also uncertain whether the failure to demonstrate meaningful long term benefits results from failure to comply with advice to reduce carbohydrate or a consequence of adaptation to an altered dietary pattern. Nevertheless it is clearly the longer term outcome data which are of relevance to the practical application of these findings.

Several issues need to be taken into account when translating these findings into nutritional advice for people with type 2 diabetes. Weight reduction was a goal in the majority of the studies and the improvements seen on lower carbohydrate diets were mainly observed when weight loss was achieved. Thus it is unclear whether the patient would benefit from carbohydrate reduction if weight loss is not achieved. Advice regarding the proportion of total energy provided by carbohydrate also needs to take into account the source and nature of carbohydrate and the effects of the other macronutrients. A substantial number of studies mainly carried out in the 1980s and 1990s demonstrated benefit in terms of glycaemic control and cardiovascular risk factors in association with relatively high carbohydrate diets rich in dietary fibre derived from legumes, vegetables and fruit [4]. Of particular relevance to the interpretation of the results of the present analysis, is that triglyceride levels were not increased even when carbohydrate intakes were high (around 60 E%) in these earlier studies provided that much of the carbohydrate was derived from sources rich in dietary fibre and slowly digested starches. Altered intakes of fat and protein resulting from changing the proportion of energy from carbohydrate may also influence glycaemic control and indicators of cardiovascular risk. Many of the LCD interventions included in our meta-analysis promoted increased intake of unsaturated fat but not saturated fat. Thus the findings have no direct bearing on several widely promoted low carbohydrate high fat diets in which saturated fat is not restricted or may even be encouraged. Detailed dietary data was not provided in many of the studies included in the meta-analysis so it is not possible at present to disentangle the effects of carbohydrate quantity from carbohydrate quality and other macronutrients. Finally, of the 13 studies that reported on the incidence of adverse effects only one [30] reported worse outcome on indicators of nephropathy with the HCD. The rest of the trials reported no serious or important adverse events and no difference between groups in reported mild adverse effects such as mild hypoglycaemia.

Further long term dietary intervention studies taking into account both amount and source of carbohydrate would be helpful in refining nutritional recommendations for people with diabetes. However, in practice nutrition recommendations require translation into dietary patterns in order for them to be implemented. On the basis of currently available systematic reviews and meta-analyses there is an appreciable body of evidence to suggest that a traditional Mediterranean type diet is particularly appropriate for people with T2DM [16, 52-54]. Mediterranean diets vary in the proportion of energy provided by macronutrients but are typically rich in pulses, fruits, vegetables, and nuts with olive oil being a major contributor to fat intake. Other dietary approaches including a healthy Nordic diet and vegetarian diets may also be beneficial for people with diabetes [16, 52, 54-59]. None of these dietary patterns is particularly low or high in carbohydrate. The range of possibilities enhances the concept of personal preference playing a key role in the prescription of dietary advice as well as permitting appreciable restriction of rapidly digested starches and sugars for those with insulin resistance. While energy balance remains a cornerstone of all dietary advice for people with diabetes, the proportion of macronutrients seems to be less important.

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Figure legends

Figure 1 PRISMA Study eligibility flow chart

Figure 2 Meta-analysis of changes in body weight (kg) [A] and HbA1c (%) [B] divided according to study duration

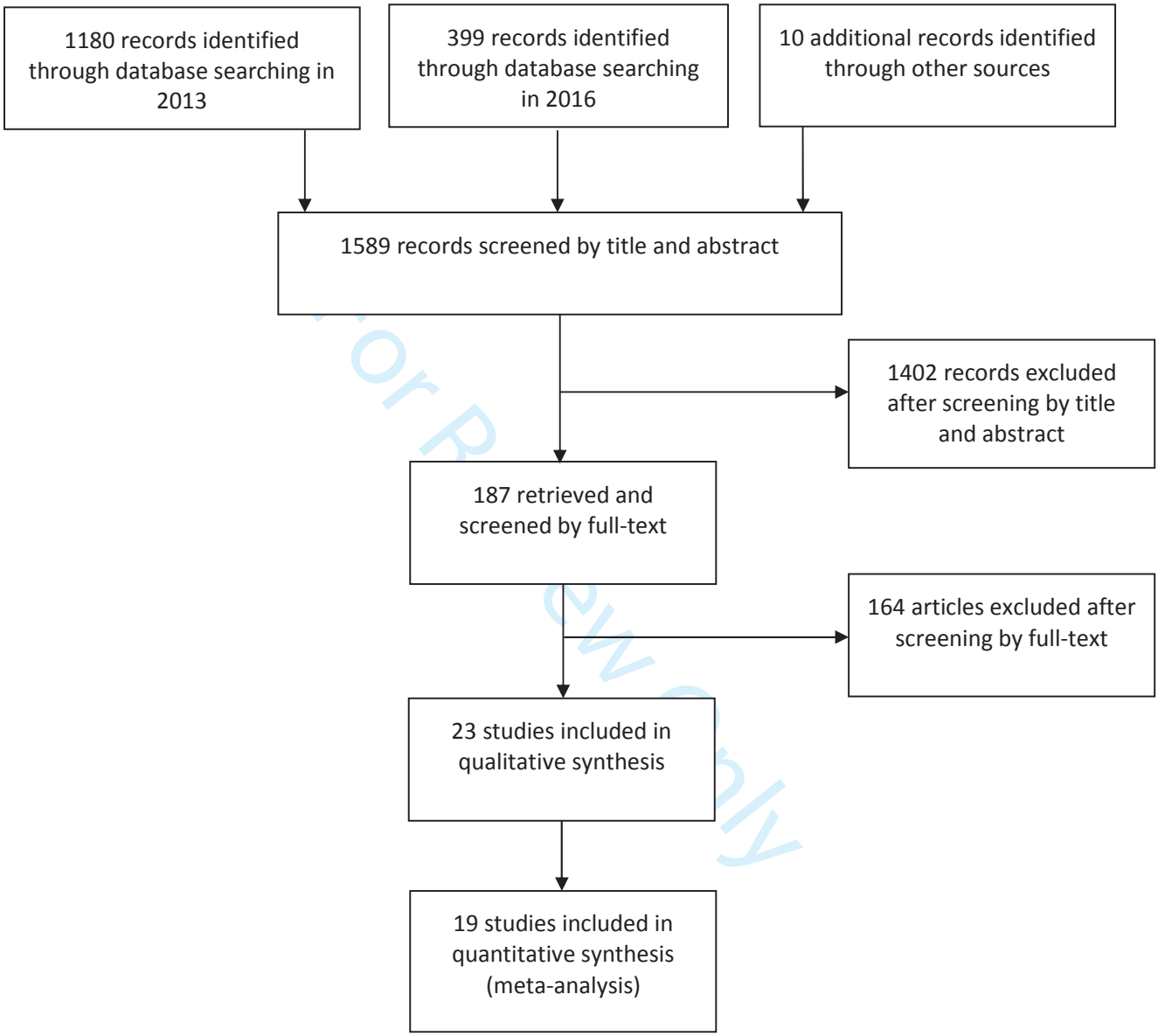
Figure 3 Meta-analysis of changes in LDL-cholesterol[A], HDL-cholesterol [B], Total cholesterol [C] and Triacylglyserols [D], all measured in mmol/l, divided according to study duration

Figure 4 Meta-analysis of Systolic [A] and Diastolic blood pressure (mmHg) [B] and Attrition rate(Risk ratio) [C] divided according to study duration

Supplementary Appendix:

- Supplementary table 1: PRISMA Checklist for preferred reporting items in systematic reviews and Meta-Analyses
- Supplementary table 2: List of excluded studies
- Supplementary table 3
  - A) Subgroup-analysis based on study duration ≤6 months (short term) vs ≥12 moths (long term)
  - B) Subgroup-analysis based on the amount of carbohydrates in the LCD group, LCD (21-70 g CHO) vs LCD (30-40% TE CHO)
  - C) Sensitivity-analysis based on high versus low risk of bias
- Supplementary table 4: Summary of findings across studies

- Supplementary figure 1: Risk of bias graphs.
  - A) Summary of the internal validity of the included studies
  - B) Summary for the individual RCTs
- Supplementary figure 2: Funnel plots for the individual outcomes
- Supplementary figure 3: Forest plots divided according to carbohydrate restriction in the LCD group



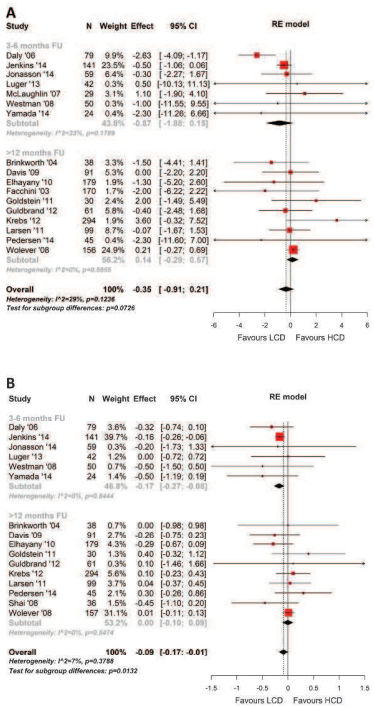


Figure 2 Meta-analysis of changes in body weight (kg) [A] and HbA1c (%) [B] divided according to study duration

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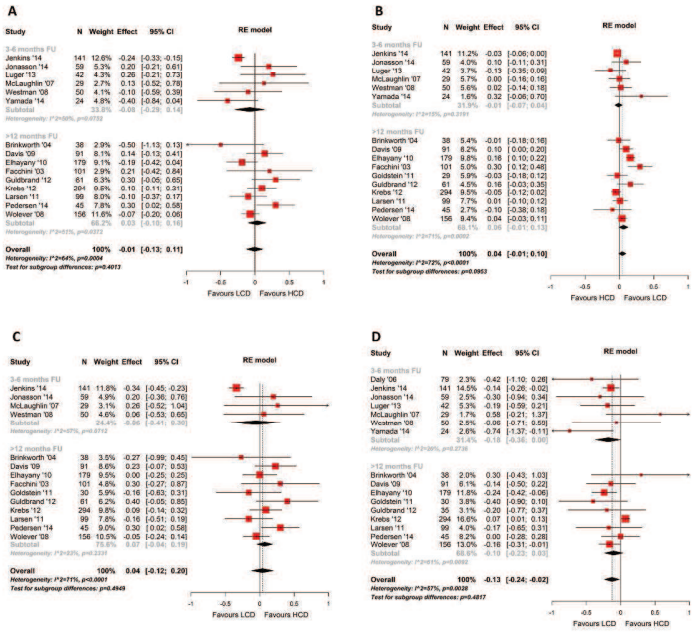

Figure 3 Meta-analysis of changes in LDL-cholesterol[A], HDL-cholesterol [B], Total cholesterol [C] and Triacylglyserols [D], all measured in mmol/l, divided according to study duration

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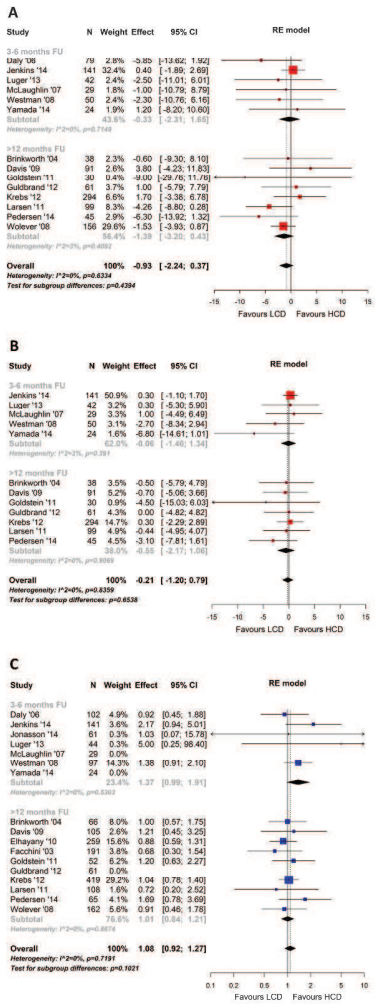

Figure 4 Meta-analysis of Systolic [A] and Diastolic blood pressure (mmHg) [B] and Attrition rate (Risk ratio) [C] divided according to study duration

275x397mm (300 x 300 DPI)

Table 1 Characteristics and summary of findings of studies selected for inclusion in the review. Outcomes show significant findings within the low-carbohydrate group, and between dietary groups

Study details	Study design	Participants randomized	LCD	Comparator	Outcome	Duration	Weight	HbA1c	Serum lipids	Blood pressure	Compliance to LCD – Presented as mean±SD
MODERATE LOW-CARBOHYDRATE DIETS											
Brinkworth et al., [44] Australia (2004)	Randomised controlled trial	66 obese type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 E% protein	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition[a]	16 months	Weight reduced (p<0.01). No difference between groups	NS	HDL increased (p<0.001). No difference between groups	DBP reduced (p<0.05). Greater reduction in SBP and DBP with the LCD (p=0.04 and <0.008)[b]	NA
Elhayany et al., [39] Israel (2010)[c]	Randomised controlled trial	259 overweight type 2 diabetes patients	35 E% CH 45 E% fat 15-20 E% protein	50-55 E% CH 30 E% fat 20 E% protein	Weight, HbA1c LDL, HDL TG, TC Compliance by food records and attrition	12 months	Weight reduced (p<0.001). No difference between groups	HbA1c reduced (p<0.001). Greater reduction with the LCD (p=0.021) [d, e]	LDL, HDL, TG and TC improved (p<0.001). Greater improvements in LDL[d], HDL[d e] and TG[d] with the LCD (p=0.036, <0.001 and <0.001)	NA	42 E% CH
Facchini et al., [30] USA (2003)	Randomised control trial	191 type 2 diabetes patients with renal failure	35 E% CH 30 E% fat 25-30 E% protein 5-10 E% ethanol	65 E% CH 25 E% fat 10 E% protein	Weight HbA1c LDL, HDL, TC	Mean follow-up 3.0±1.8 years	NS	NS	HDL increased [f] No difference between groups	NA	NA
Garg et al., [27] USA (1994)	Randomised crossover trial	21 type 2 diabetes patients	40 E% CH 45 E% fat 15 E% protein	55 E% CH 30 E% fat 15 E% protein	LDL, HDL TG, TC	14 weeks	NA	NA	TG reduced (p=0.03). No difference between groups	NA	NA
Jenkins et al., [46] Canada (2014)	Randomised controlled trial	141 type 2 diabetes patients	39 E% CH [g] 37 E% fat [g] 20 E% protein[g]	49 E% CH [g] 27 E% fat [g] 20 E% protein [g]	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition	3 months	Weight reduced (p<0.05). No difference between groups	HbA1c reduced (p<0.05). No difference between groups	LDL, HDL, TG and TC reduced (p<0.05). Greater reduction in LDL, HDL, TC and TG with the LCD (p<0.01, =0.04, <0.01 and =0.18)	SBP and DBP reduced (p<0.05). No difference between groups	Not applicable [g]
Jönsson et al., [38] Sweden (2009)	Randomised crossover trial	13 non-insulin treated type 2 diabetes patients	32 E% CH 39 E% fat 24 E% protein	42 E% CH 34 E% fat 20 E% protein	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records	3 months	Weight reduced (p=0.005 and 0.01). Greater reduction in weight with the LCD (p=0.01 and 0.04)	HbA1c reduced (p<0.001). Greater reduction with the LCD (p=0.02)	TG reduced (p=0.003). Greater improvements in HDL and TG with the LCD (p=0.03 and 0.003)	SBP reduced (p=0.048). Greater reduction in DBP with the LCD (p=0.03)	32±7 E% CH 39±5 E% fat 24±3 E% protein
Krebs et al., [43]	Randomised	419 overweight	40 E% CH	55 E% CH	Weight	24 months	Weight reduced	NS[f]	NS[f]	NS	46±7 E% CH

New Zealand (2012)	controlled trial	type 2 diabetes patients	30 E% fat 30 E% protein	30 E% fat 15 E% protein	HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition		(p<0.001). No difference between groups				33±6 E% fat 21±4 E% protein
Larsen et al., [41] Australia (2011)	Randomised controlled trial	108 overweight and obese type 2 diabetes patients	40 E% CH 30 E% Fat 30 E% Protein	55 E% CH 30 E% Fat 15 E% Protein	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	12 months	Weight reduced (p<0.001). No difference between groups	HbA1c reduced (p<0.001). No difference between groups	HDL and TG improved[f]. No difference between groups	NS[f]	42 E% CH 31 E% fat 27 E% protein
Luger et al., [45] Austria (2013)	Randomised controlled trial	44 insulin treated type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	55 E% CH 30 E% fat 15 %% protein	Weight HbA1c LDL, HDL, TG Blood pressure Compliance by food records and attrition	3 months	Weight reduced (p<0.001). No difference between groups	HbA1c reduced (p=0.05). No difference between groups	TG reduced (p=0.01). No difference between groups	DBP reduced (p=0.005). No difference between groups	38±7 E% CH 35±6 E% fat 26±5 E% protein
McLaughlin et al., [33] USA (2007)	Randomised controlled trial	29 overweight, diet-treated type 2 diabetes patients	40 E% CH 45 E% fat 15 E% protein	60 E% CH 25 E% fat 15 E% protein	Weight LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	3 months	Weight reduced (p<0.001). No difference between groups	NA	TG reduced (p=0.008). No difference between groups	NS	43 E% CH 38 E% fat 19 E% protein
Pedersen et al., [48] Australia (2014)	Randomised controlled trial	76 overweight type 2 diabetes patients	40 E% CH 30 E% fat 30 E% protein	50 E% CH 30 E% fat 20 E% protein	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition	12 months	Weight reduced (p<0.001). No difference between groups	HbA1c reduced (p=0.01). No difference between groups	HDL and TG improved (p<0.01 and <0.001). Greater increase in LDL with the LCD (p=0.05)	Greater reduction in DBP with the LCD (p=0.01)	197±16 g CH (40 E%) 78±7 g fat (35 E%) 131±10 g protein (26 E%)
Walker et al., [28] Australia (1995)	Randomised crossover trial	24 type 2 diabetes patients	40 E% CH 40 E% fat	59 E% CH 21 E% fat	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records	3 months	Weight reduced (p<0.005). No difference between groups	NS	NS	NS	40±1 E% CH 36±1 E% fat 22±1 E% protein
Walker et al., [29] Australia (1999)	Randomised crossover trial	34 post-menopausal women with type 2 diabetes	40 E% CH 40 E% fat	60 E% CH 20 E% fat	Weight HbA1c HDL, TG, TC Compliance by food records	3 months	Weight reduced (p<0.01). No difference between groups	NS[h]	NS[h]	NA	43±5 E% CH 33±5 E% fat 21±2 E% protein
Wolever et al., [36] Canada (2008)	Randomised controlled trial	162 diet-treated type 2 diabetes patients	39 E% CH[g] 40 E% fat[g] 19 E% protein[g]	47 E% CH[g] 31 E% fat[g] 20 E% protein[g] 52 E% CH[g] 27 E% fat[g] 21 E% protein[g]	Weight HbA1c LDL, HDL TG, TC Blood pressure Compliance by attrition	12 months	Weight reduced (p=0.003). No difference between groups	HbA1c increased (p<0.0001). No difference between groups	LDL reduced (p=0.0079). No difference between groups	DBP reduced (p=0.0080). Greater reduction in DBP with the LCD (p=0.020)	Not applicable[g]
Yamada et al., [49] Japan (2014)	Randomised controlled trial	24 type 2 diabetes patients	<130-70 g/day CH (33 E%)	50-60 E% CH <25 E% fat	Weight, HbA1c	6 months	NS	HbA1c reduced (p=0.03). Greater	TG reduced (p=0.02). No	NS	30±13 E% CH 45±9 E% fat

				<20 E% protein	LDL, HDL, TG Blood pressure Compliance by food records and attrition			reduction with the LCD (p=0.03)	difference between groups		25±7 E% protein
VERY LOW-CARBOHYDRATE DIETS											
Daly et al., [32] UK (2006)	Randomised controlled trial	102 obese patients with poorly controlled type 2 diabetes	< 70 g/d CH (22 E%) No information provided on intake of fat and protein	45 E% CH[g] 33 E% fat[g] 21 E% protein[g]	Weight HbA1c TG SBP Compliance by food records and attrition	3 months	Greater reduction in weight with the LCD (p=0.001)	No difference between groups	No difference between groups	No difference between groups	34 E% CH 40 E% fat 26 E% protein
Davis et al., [37] USA (2009)	Randomised controlled trial	105 overweight type 2 diabetes patients	20-25 g/d CH (5-6 E%) for two weeks, then a 5 g increase each week	50 E% CH[g] 25 E% fat 19 E% protein[g]	Weight HbA1c1 LDL, HDL, TG, TC Blood pressure Compliance by food records and attrition	12 months	NS[f]	NS[f]	Greater increase in HDL with the LCD (p=0.002).	NS[f]	33±13 E% CH 44±11 E% fat 23±7 E% protein
Goldstein et al., [40] Israel (2011)	Randomised controlled trial	56 obese type 2 diabetes patients	<25 g/d CH (<6 E%) for 6 weeks, then <40 g/d (<10 E%) No restrictions on intake of fat and protein	80 E% divided between CH and fats 10-20 E% protein	Weight HbA1c HDL, TG, TC Blood pressure Compliance by food records and attrition	12 months	Weight reduced (p<0.001). No difference between groups	Reduction in HbA1c[f] No difference between groups	NS	NS	85±35 g CH (20 E%) 111±45 g fat (58 E%) 102±37 g protein (24 E%)
Guldbrand et al., [42] Sweden (2012)	Randomised controlled trial	61 type 2 diabetes patients	20 E% CH 50 E% fat 30 E% protein	55-60 E% CH 30 E% fat 10-15 E% protein	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	24 months	Weight reduced (p=0.020 and 0.011). No difference between groups	NS	LDL and HDL improved (p=0.020 and <0.001). No difference between groups	SBP and DBP reduced (p=0.012 and 0.004). No difference between groups	31±6 E% CH 44±5 E% fat 24±4 E% protein
Jonasson et al., [47] Sweden (2014)	Randomised controlled trial	61 type 2 diabetes patients	20 E% CH 50 E% fat 30 E% protein	55-60 CH 30 E% fat 10-15 E% protein	Weight[f], HbA1c LDL, HDL TG, TC Compliance by food records and attrition	6 months	Weight reduced[f].. No difference between groups	HbA1c reduced (p<0.01). No difference between groups	HDL increased (p<0.05). No difference between groups	NA	25±8 E% CH 49±8 E% fat 23±4 E% protein
Samaha et al., [31] USA (2003)	Randomised controlled trial	52 severely obese type 2 diabetes patients	<30 g/d CH (8 E%) No restrictions on intake of fat	51 E% CH[g] 30 E% fat 16 E% protein[g]	HbA1c Compliance by food records[i]	6 months	NA	NS[f]	NA	NA	37±18 E% CH 41±16 E% fat 22±9 E% protein
Shai et al., [34] Israel (2008)	Randomised controlled trial	46 moderately obese type 2 diabetes patients	20 g/d CH (6 E%) for two months, then max 120 g/d (34 E%) No restrictions on intake of fat and protein	51 E% CH[g] 30 E% fat 19 E% protein[g] 50 E% CH[g] 35 E% fat 19 E% protein[g]	HbA1c Compliance by food records[i]	24 moths	NA	Hba1c reduced (p<0.05). No difference between groups	NA	NA	40±7 E% CH 39±5 E% fat 22±4 E% protein

Westman et al., [35] USA (2008)	Randomised controlled trial	84 obese type 2 diabetes patients	< 20 g/d CH (5 E%) No information provided on intake of fat and protein	55 E% CH[g] 36 E% fat 20 E% protein[g]	Weight, HbA1c LDL, HDL TG, TC Blood pressure Compliance by food records and attrition	6 months	Weight reduced ($p<0.05$). Greater reduction in weight and BMI with the LCD ($p=0.008$ and 0.05)	HbA1c reduced ($p=0.009$). Greater reduction with the LCD ($p=0.03$)	HDL and TG improved ($p<0.05$). Greater increase in HDL with the LCD ($p<0.001$)	SBP and DBP reduced ($p<0.05$). No difference between groups	13 E% CH 59 E% fat 28 E% protein

LCD, low-carbohydrate diet; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triacylglycerol; TC, total cholesterol; E%, percent of energy from macronutrient; CH, carbohydrate; NS, not significant; N/A, not assessed

[a] Compliance measured at three months

[b] P value represent between groups change from week 12 to 64

[c] Two control groups with the same macronutrient composition (American Diabetic Association (ADA) vs. Traditional Mediterranean Diet (TMD)

[d] LCD significantly improved compared to ADA

[e] LCD significantly improved compared to TM

[f] p-value on effect within diet group not provided

[g] Macronutrient value shows the actual intake during study/end of study

[h] P value on effect between groups not provided, but the authors state that no difference was seen between the two diets; no information available on within-group effect

[i] Data on macronutrient intake during study was extracted from the whole study population