Low Carbohydrate versus Isoenergetic Balanced Diets for Reducing Weight and Cardiovascular Risk: A Systematic Review and Meta-Analysis

Celeste E. Naude1*, Anel Schoonees1, Marjanne Senekal2, Taryn Young1,3, Paul Garner4, Jimmy Volmink1,3

1 Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, 2 Division of Human Nutrition, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa, 3 South African Cochrane Centre, South African Medical Research Council, Cape Town, South Africa, 4 Effective Health Care Research Consortium, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Abstract

Background: Some popular weight loss diets restricting carbohydrates (CHO) claim to be more effective, and have additional health benefits in preventing cardiovascular disease compared to balanced weight loss diets.

Methods and Findings: We compared the effects of low CHO and isoenergetic balanced weight loss diets in overweight and obese adults assessed in randomised controlled trials (minimum follow-up of 12 weeks), and summarised the effects on weight, as well as cardiovascular and diabetes risk. Dietary criteria were derived from existing macronutrient recommendations. We searched Medline, EMBASE and CENTRAL (19 March 2014). Analysis was stratified by outcomes at 3–6 months and 1–2 years, and participants with diabetes were analysed separately. We evaluated dietary adherence and used GRADE to assess the quality of evidence. We calculated mean differences (MD) and performed random-effects meta-analysis. Nineteen trials were included (n = 3209); 3 had adequate allocation concealment. In non-diabetic participants, our analysis showed little or no difference in mean weight loss in the two groups at 3–6 months (MD 0.74 kg, 95% CI −1.49 to 0.01 kg; I² = 53%; n = 1745, 14 trials; moderate quality evidence) and 1–2 years (MD 0.48 kg, 95% CI −1.44 kg to 0.49 kg; I² = 12%; n = 1025; 7 trials, moderate quality evidence). Furthermore, little or no difference was detected at 3–6 months and 1–2 years for blood pressure, LDL, HDL and total cholesterol, triglycerides and fasting blood glucose (>914 participants). In diabetic participants, findings showed a similar pattern.

Conclusions: Trials show weight loss in the short-term irrespective of whether the diet is low CHO or balanced. There is probably little or no difference in weight loss and changes in cardiovascular risk factors up to two years of follow-up when overweight and obese adults, with or without type 2 diabetes, are randomised to low CHO diets and isoenergetic balanced weight loss diets.

Background

Overweight, obesity and the related burdens of cardiovascular disease (CVD), type 2 diabetes, other non-communicable diseases (NCD) and premature mortality are escalating globally [1–3]. Nearly 80% of annual NCD deaths occur in low and middle income populations [4] and the NCD burden is projected to rise disproportionately in these populations over the next ten years [5]. Some weight loss diets widely promoted through the media, such as the Atkins diet [6,7], recommend a regimen greatly restricting carbohydrates (CHO), with increased protein and unrestricted total and saturated fat intake. Advocates claim these diets are more effective for losing weight compared to balanced weight loss diets and also improve cardiovascular health, and prevent or cure diabetes [8]. To achieve the very low CHO intake, these diets prescribe restriction of most vegetables and fruit,
wholegrains, legumes and other carbohydrate-containing foods. It is plausible that these low CHO diets could be harmful, especially over the longer term [9–11]. We therefore sought to determine whether low CHO diets have any beneficial or harmful effects on weight and cardiovascular risk factors when compared to balanced diets.

What do existing systematic reviews say?

We first examined evidence from existing systematic reviews. We sought any review that synthesised evidence on dietary macronutrient manipulation and cardiovascular outcomes or risk factors (last search: 3 March 2014). We found 50 reviews but these had a number of methodological constraints precluding the possibility that they could meaningfully address the question we set out to answer (see Supporting Information S1 for detailed summary). The main constraints were: they did not adequately define the macronutrient composition of treatment and control diets; the total energy intake in treatment and control diets was not considered or was different between groups; arms included additional interventions that could confound the findings, such as exercise; inclusion of non-randomised studies and studies with dissimilar follow-up periods (Table 1). In light of these shortcomings, which make interpretation of the previous reviews problematic, we carried out our own systematic review.

Macronutrient recommendations and low carbohydrate diets

Nutrition specialists have defined “recommended, balanced diets” in terms of macronutrient composition, micronutrients and dietary quality to ensure adequate nutrition, energy balance for health and weight maintenance, and prevention of NCDs in healthy populations [12–15]. Recommended macronutrient ranges have been developed in the USA and Canada, Australia and New Zealand and Europe [12–15] and are very similar across the various countries and regions. For CHO, the recommended range varies between 45 and 65% of total energy, for protein between 10 and 35% and for fat between 20 and 35%. Since not only quantity (% contribution to total energy intake), but also quality (type and nature) of macronutrients are important, guidance on the quality aspects of CHO and fats are also included in most recommendations [12–15]. Balanced weight loss diets restrict total energy and adhere to the principles of a balance between energy derived from CHO, protein and fat, as well as the recommended quality of each macronutrient.

To further improve our understanding of these diets, we examined and summarised the main themes in the advocacy literature on low CHO diets and their supposed benefits. We identified two main variants of low CHO diets. In Table 2, we summarise examples of these, along with a balanced weight loss diet, comparing key characteristics. Essentially, low CHO diets emphasise a change in recommended macronutrient balance with CHO restriction implemented by elimination or reduction of specific foods and food groups and replacement of these with high fat and protein foods. All restrict CHO intake, but the definitions used for ‘low’ and the specific implementation, advice and health claims provided with these diets vary. Very low CHO diets advocate extreme restriction of CHO and are consequently high in both protein and fat (which we have labelled high fat variant). A second variant is also high in protein, but the amount of fat is within recommended ranges and therefore restriction of CHO is less extreme (labelled high protein variant). This information helped to inform the protocol, specifically the sub-group analysis, for our systematic review of relevant randomised controlled trials.

**Objective**

To compare the effects of low CHO and isoenergetic balanced weight loss diets in overweight and obese adults.

**Inclusion Criteria**

**Types of studies**

We included randomised controlled trials (RCTs) in humans published in English. Trials could be of a parallel or crossover design, however, crossover trials were only included if first period data could be extracted. We excluded trials with less than 10 participants randomised in each group.

**Table 1.** Main limitations identified in existing systematic reviews that served as constraints to interpretation of the evidence and what we did to address them in our review.

| What answering the research question requires | Why was it identified as a limitation in existing reviews? | What we did to address identified limitations in our review |
|-----------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|
| Explicit definition of treatment and control diets with complete macronutrient profile | If unclear, any effects seen on weight loss and CVD risk factors cannot be attributed to a well-defined intervention diet compared to a well-defined control diet | Used explicit cut-off ranges for macronutrients for treatment and control diets; the complete macronutrient profile of intervention diets had to be available (proportions of total energy intake) |
| Recommended energy intake in treatment and control groups needs to be similar | If different, any effects seen on weight loss and CVD risk factors would be confounded by total energy intake | Only included isoenergetic diet comparisons |
| Co-interventions, such as drugs given as part of the intervention, or recommendations for exercise, need to be similar in the comparison groups | If different, any effects on CVD risk factors could be confounded by co-interventions | Only included interventions with a diet component alone, or combined interventions that were similar to prevent confounding by co-interventions |
| Appropriate study design for the question | Methodological heterogeneity: some reviews included both controlled and uncontrolled trials | Only included randomised controlled trials |
| Meaningful and comparable follow-up in trials needs to be considered | Outcomes of trials with different follow-ups were pooled; generalised conclusions about weight loss may be skewed by early changes; or follow-up may be insufficient to detect CVD risk factor changes | Only included studies with 12 weeks or more follow-up, and outcomes were grouped by defined lengths of follow-up |

CVD: cardiovascular disease.

Note: see Supporting Information S1 for the critical summary of existing systematic reviews.

doi:10.1371/journal.pone.0100652.t001
Types of participants
People who are overweight or obese, have diabetes, glucose intolerance or insulin resistance, cardiovascular conditions or risk factors such as hypertension and dyslipidaemia, as defined by trial authors. We excluded pregnant and lactating women and individuals younger than 18 years.

Types of interventions
We required the studies to provide the macronutrient goals of the diet in terms of their contribution to total energy intake, or that these goals could be calculated as proportions of total energy intake, for both the treatment and comparison arms. Treatment diets were low CHO weight loss diet plans, including a) low CHO, high fat, high protein diet (high fat variant) or b) low CHO, recommended fat, high protein diet (high protein variant) (Table 3). Control diets were balanced weight loss diet plans (Table 3) with the same or similar prescribed energy content as the treatment diet.

We excluded studies where: the treatment and control diets were not adequately defined or where the control diet was defined as ‘no dietary intervention’; diets were combined with any other interventions (e.g. exercise, pharmacological, surgical) so that the effect of diet alone could not be assessed; dietary interventions had an exclusive focus on energy restriction, i.e. no macronutrient manipulation was instituted; a substantial disparity in energy intake (>500 kilojoules) between the prescribed treatment and control diets was present; an ad libitum energy prescription was used; interventions focused on specific foods, food groups or food components (e.g. dairy, oats, plant sterols), meal replacement or supplement products were used; the duration of the intervention was less than 12 weeks or test meal responses (post-prandial) were assessed.

Types of outcome measures

**Weight.** Total weight change (kg); body mass index (BMI) (kg/m²).

**Markers of cardiovascular disease risk.** Diastolic blood pressure (DBP) and systolic blood pressure (SBP) (mmHg); serum cholesterol; low density lipoprotein (LDL), high density lipoprotein (HDL) and total (mmol/L); serum triglycerides (TG) (mmol/L).

---

**Table 2.** Low carbohydrate (CHO) diets compared with a recommended, balanced weight loss diet.

|                        | Low CHO diet, high fat variant* | Low CHO diet, high protein variantb | Balanced weight loss diet |
|------------------------|--------------------------------|------------------------------------|---------------------------|
| **Examples**           | Atkins diet [6,7]              | Zone diet [67,68]                  | British Dietetic Association weight loss plan [69] |
| **Energy**             |                                |                                    |                           |
| Is energy explicitly restricted? | No                            | No†                               | Yes                       |
| **Macronutrients**     |                                |                                    |                           |
| CHO                    | Extreme restriction            | Moderate restriction               | 45–65% of total energy    |
| Fat                    | Unrestricted fat               | 25–35% of total energy            | 25–35% of total energy    |
| Protein                | Unrestricted protein           | Promotes lean protein              | 10–20% of total energy    |
| **Quality**            |                                |                                    |                           |
| CHO                    | Extreme restriction of all CHO food sources | Extreme restriction of grains and starches; fruit and vegetables recommended | High fibre, unprocessed; promotion of fruit, vegetables and legumes |
| Protein                | Unrestricted, especially animal protein | Increased lean animal protein, protein bars and shakes | Emphasis on plant protein and lean animal protein |
| Fat                    | Promotion of increased ‘natural’ fats, including saturated (animal) fats | Promotion of monounsaturated fats, mention of omega-3 fats | Promotion of polyunsaturated and monounsaturated fats, replacement of saturated fats with unsaturated fats, avoidance of trans fats; adequate omega-3 fats |
| **Micronutrients**     |                                |                                    |                           |
| Is micronutrient intake addressed? | Not specificallyd               | Not specifically*                  | Not specificallyf          |
| **Selected claimed health benefits** |                                |                                    |                           |
| Main                   | Weight loss                    | Weight loss                        | Weight loss (if energy is restricted) |
| Other                  | “Improvement in risk factors for heart disease, hypertension and diabetes, inflammation” | “Reverses cellular inflammation”; “Cellular inflammation is what makes us gain weight, accelerate the development of chronic disease, and decrease our physical performance” | Reduces risk of obesity-related illness; Reduces risk of non-communicable diseases; Promotes nutritional adequacy |

*Energy reduction is implicit as a consequence of extreme restriction of carbohydrates, the reported satiating effect of protein, and appetite suppressing effect of ketones.
†Energy reduction is implicit as a consequence of extreme restriction of grains and starches and reported satiating effect of protein.
‡Portion guides sometimes provided.
§Potential risks of inadequacies by extreme restriction of carbohydrates, including most vegetables and fruit.
∥Potential risks of inadequacies by restricting grains and starches.
Promoted indirectly through recommending a variety of foods from all food groups and quality food choices (including plenty of vegetables and fruit).

doi:10.1371/journal.pone.0100652.t002
### Table 3. Cut-off ranges* used to classify the macronutrient goals of treatment and control diets.

| Macronutrients                  | Classifications |
|--------------------------------|-----------------|
| Carbohydrate (% of total energy)| Low: <45        |
|                                | Balanced: 45 to 65 |
|                                | High: >65       |
| Fat (% of total energy)        | Low: <25        |
|                                | Balanced: 25 to 35 |
|                                | High: >35       |
| Protein (% of total energy)    | Low: <10        |
|                                | Balanced: 10 to 20 |
|                                | High: >20       |

*Established by drawing on macronutrient recommendations from five global institutions and governments [12–15,70].

doi:10.1371/journal.pone.0100652.t003

### Table 4. Search strategies for EMBASE.

**Search: 22 October 2012**

| No. | Query                                                                 | Results |
|-----|----------------------------------------------------------------------|---------|
| #5  | #3 AND #4                                                            | 1312    |
| #4  | ‘randomised controlled trial’/exp OR ‘randomised controlled trial’ OR ‘randomised controlled trials’ OR ‘randomized controlled trial’/exp OR ‘randomized controlled trial’ OR ‘randomized controlled trials’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1-1-1966]/sd NOT [22-10-2012]/sd AND [1966–2012]/py | 49285   |
| #3  | #1 AND #2                                                           | 2862    |
| #2  | ‘carbohydrate restricted diet’/exp OR ‘carbohydrate restricted diets’ OR ‘high fat diet’/exp OR ‘high fat diets’ OR ‘fat restricted diet’/exp OR ‘fat restricted diets’ OR ‘ketogenic diet’/exp OR ‘ketogenic diets’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1-1-1966]/sd NOT [22-10-2012]/sd AND [1966–2012]/py | 11176   |
| #1  | ‘randomised controlled trial’/exp OR ‘randomized controlled trials’ OR ‘randomized controlled trial’/exp OR ‘randomized controlled trial’ OR ‘randomized controlled trials’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1-1-1966]/sd NOT [22-10-2012]/sd AND [1966–2012]/py | 879594  |

**Updated search: 5 June 2013**

| No. | Query                                                                 | Results |
|-----|----------------------------------------------------------------------|---------|
| #5  | #3 AND #4                                                            | 80      |
| #4  | ‘randomised controlled trials’/exp OR ‘randomized controlled trials’ OR ‘randomized controlled trial’/exp OR ‘randomized controlled trials’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [23-10-2012]/sd NOT [6-6-2013]/sd | 20424   |
| #3  | #1 AND #2                                                           | 236     |
| #2  | ‘carbohydrate restricted diet’/exp OR ‘carbohydrate restricted diets’ OR ‘high fat diet’/exp OR ‘high fat diets’ OR ‘fat restricted diet’/exp OR ‘fat restricted diets’ OR ‘ketogenic diet’/exp OR ‘ketogenic diets’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [23-10-2012]/sd NOT [6-6-2013]/sd | 1005    |
| #1  | ‘randomised controlled trial’/exp OR ‘randomized controlled trials’ OR ‘randomized controlled trial’/exp OR ‘randomized controlled trial’ OR ‘randomized controlled trials’/exp OR ‘randomized controlled trials’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [23-10-2012]/sd NOT [6-6-2013]/sd | 73855   |

**Updated search: 19 March 2014**

| No. | Query                                                                 | Results |
|-----|----------------------------------------------------------------------|---------|
| #5  | #3 AND #4                                                            | 145     |
| #4  | ‘randomised controlled trials’/exp OR ‘randomized controlled trials’ OR ‘randomized controlled trial’/exp OR ‘randomized controlled trial’ OR ‘randomized controlled trials’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [7-6-2013]/sd NOT [18-3-2014]/sd | 29989   |
| #3  | #1 AND #2                                                           | 384     |
| #2  | ‘carbohydrate restricted diet’/exp OR ‘carbohydrate restricted diets’ OR ‘high fat diet’/exp OR ‘high fat diets’ OR ‘fat restricted diet’/exp OR ‘fat restricted diets’ OR ‘ketogenic diet’/exp OR ‘ketogenic diets’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [7-6-2013]/sd NOT [18-3-2014]/sd | 1731    |
| #1  | ‘randomised controlled trial’/exp OR ‘randomized controlled trial’ OR ‘randomized controlled trial’ OR ‘randomized controlled trial’ OR ‘randomized controlled trials’ OR ‘randomized controlled trials’ AND [humans]/lim AND [english]/lim AND [embase]/lim AND [7-6-2013]/sd NOT [18-3-2014]/sd | 108635  |

doi:10.1371/journal.pone.0100652.t004
Markers of diabetes mellitus risk or glycaemic control. Glycosylated haemoglobin (HbA1c) (%); fasting blood glucose (FBG) (mmol/L).

Mortality, myocardial infarction and stroke were not explicitly excluded as outcomes, but we did not expect to find randomised controlled trials with these outcomes where dietary manipulations were under study.

Search Methods for Identification of Studies

Electronic searches were done in MEDLINE via PubMed, Excerpta Medica Database (EMBASE) and The Cochrane Central Register of Clinical Trials (CENTRAL), with the last search on 19 March 2014. The full electronic search strategy for EMBASE is detailed in Table 4. In addition, the references of the previously mentioned 50 existing systematic reviews were searched.

Data Collection and Analysis

Selection of studies

Two authors (CN and AS) screened titles and abstracts of all search results and identified potentially eligible studies using the pre-specified eligibility criteria. Full text articles for these studies were obtained and assessed by the two authors simultaneously. Studies not fulfilling eligibility criteria were excluded with reasons. All discrepancies were resolved by consensus.

Data extraction and management

Two authors (CN and AS) extracted data using an electronic data extraction spreadsheet in Microsoft Excel. The main sections of the spreadsheet included information on the design, country, participants, treatment, control, diet quality, energy and nutrient composition, adherence, outcomes and results, funding, conflict of interest, and risk of bias. The extracted data were collated in tables.
Table 5. Characteristics of included randomised controlled trials.

| First author (follow-up in weeks) | Year of publication | Country | Parallel design | No randomised | No Completed in Rx group | Dropout in Rx group | No Completed in Control group | Dropout in Control group | Gender | Age Range (yrs) | Types of Participants | Total Intervention Period in weeks |
|----------------------------------|---------------------|---------|----------------|---------------|-------------------------|-------------------|-----------------------------|------------------------|--------|----------------|----------------------|-------------------------------------|
| **Overweight and obese adults**  |                     |         |                |               |                         |                   |                             |                        |        |                |                      |                                     |
| Aude (12) [24]                  | 2004                | USA     | Yes            | 60            | 29                      | 1                 | 25                          | 5                      | Both   | 27–71          | Overweight or Obese        | 12                                   |
| De Luis (12) [27]               | 2009                | Spain   | Yes            | 118           | 52                      | 0                 | 66                          | 0                      | Both   | NR             | Overweight or Obese         | 12                                   |
| De Luis (12) [26]               | 2012                | Spain   | Yes            | 305           | 147                     | 0                 | 158                         | 0                      | Both   | NR             | Obese                 | 12                                   |
| Farnsworth (16) [28]            | 2003                | UK      | Yes            | 66            | 28                      | NR                | 29                          | NR                     | Both   | 20–65          | Overweight or Obese         | 16                                   |
| Frisch (52) [29]                | 2009                | Germany | Yes            | 200           | 85                      | 15                | 80                          | 20                     | Both   | 18–70          | Overweight or Obese         | 52                                   |
| Keogh (52) [31]                 | 2008                | Australia | Yes           | 36            | 7                       | NR                | 6                           | NR                     | Both   | 20–65          | Overweight or Obese         | 52                                   |
| Klemsdal (52) [32]              | 2010                | Norway  | Yes            | 202           | 78                      | 22                | 86                          | 16                     | Both   | 30–65          | Overweight or Obese and CVD risk | 52                                   |
| Krauss (12) [33]                | 2006                | USA     | Yes            | 224           | 40                      | 12                | 49                          | 8                      | Males  | NR             | Overweight or Obese with Dyslipidaemia | 12                                   |
| Lasker (16) [36]                | 2008                | USA     | Yes            | 65            | 25                      | 7                | 25                          | 8                      | Both   | 40–56          | Overweight or Obese         | 16                                   |
| Layman (52) [37]                | 2009                | USA     | Yes            | 130           | 41                      | 23               | 30                          | 36                     | Both   | 40–57          | Overweight or Obese         | 52                                   |
| Lim (64) [38]                   | 2010                | Australia | Yes           | 113           | 17                      | 13                | 15                          | 15                     | Both   | 20–65          | Overweight or Obese with CVD risk | 64                                   |
| Luscombe (16) [39]              | 2003                | Australia | Yes           | 36            | 17                      | 0                | 19                          | 0                      | Both   | 20–65          | Overweight or Obese          | 16                                   |
| Sacks (104) [16]                | 2009                | USA     | Yes            | 811           | 168                     | 33               | 169                         | 35                     | Both   | 30–70          | Overweight or Obese          | 104                                  |
| Wycherley (52) [41]             | 2012                | Australia | Yes           | 123           | 33                      | 26               | 35                          | 29                     | Males  | 20–65          | Overweight or Obese          | 52                                   |
| **Overweight and obese adults with Type 2 diabetes mellitus** |                     |         |                |               |                         |                   |                             |                        |        |                |                      |                                     |
| Guldbrand (104) [30]            | 2012                | Sweden  | Yes            | 61            | 30                      | 0                | 31                          | 0                      | Both   | NR             | Overweight or Obese with T2DM | 104                                  |
| Brinkworth (64) [23]            | 2004                | Australia | Yes           | 66            | 19                      | 14               | 19                          | 14                     | Both   | 58–65          | Overweight or Obese with T2DM | 64                                   |
and figures. The author of one included RCT [16] was contacted and provided means and standard deviations that could not be read accurately from a figure in the publication.

**Length of follow-up**

Outcomes were grouped into those measured between baseline and three to six months of follow-up, and between baseline and one to two years of follow-up. For trials measuring outcomes at several time points within either of these two categories, we took the values for the longest follow-up within that category (for example, where results were available at three and six months, the results at six months were used).

**Risk of bias assessment**

Two authors (CN and AS) assessed the risk of bias in the included studies by using the Cochrane Collaboration risk of bias tool [17], where domains include random sequence generation, allocation concealment, performance and detection bias, attrition bias, reporting bias and ‘other’ bias. Criteria for low risk, high risk and unclear risk of bias per the Cochrane Handbook for Systematic Reviews of Interventions [17] were used.

**Adherence**

For energy, the prescribed and reported total energy intakes (kilojoules) for each reported follow-up category in the trial were tabulated per group, as were group comparisons of mean reported energy intake reported by trial authors. For macronutrients, adherence was calculated as the difference between the reported mean and prescribed distribution of energy intake (% of total energy) from CHO, fat and protein for each follow-up category. For trials reporting dietary intake at several time points within either of the two follow-up categories, we took the values for the longest follow-up within that category. Specifically, adherence was calculated using a Mahalanobis distance equation, which can be used to measure the similarity between a set of actual conditions relative to a set of ideal conditions [18]. The equation generated an adherence score that represents the degree of deviation from the prescribed goals for macronutrients in the treatment and control groups. A lower score reflects better adherence and a higher score reflects poorer adherence.

The equation for the macronutrient adherence score, where $TE$ is total energy:

$$
\sqrt{\frac{(\text{mean reported }% \text{ carbohydrate of } TE - \text{prescribed goal }% \text{ carbohydrate of } TE)^2}{\text{prescribed goal }% \text{ carbohydrate of } TE}} + \frac{(\text{mean reported }% \text{ fat of } TE - \text{prescribed goal }% \text{ fat of } TE)^2}{\text{prescribed goal }% \text{ fat of } TE} + \frac{(\text{mean reported }% \text{ protein of } TE - \text{prescribed goal }% \text{ protein of } TE)^2}{\text{prescribed goal }% \text{ protein of } TE}
$$

**Measures of treatment effect**

Review Manager (RevMan) 5.2 was used to manage the extracted data and to conduct meta-analyses [19] for each outcome, where relevant, to determine a pooled effect of low CHO diets compared to balanced diets. Mean differences (MD) were calculated for continuous data and reported alongside 95% confidence intervals (CIs). Where change per group was not available, end values were used and we combined change from baseline results with end values [17]. Footnotes on the figures of forest plots indicate when end values were used.

**Unit of analysis issues**

No crossover trials met the inclusion criteria. In the case of multiple intervention groups, we selected one pair of interventions...
Table 6. Prescribed dietary goals per length of follow-up for included randomised controlled trials.

| First author (follow-up in weeks) | Year of publication | No. of weeks of weight loss | Prescribed energy for Rx group (kJ) | Prescribed energy for Control group (kJ) | Prescribed CHO for Rx group (% of TE) | Prescribed CHO for Control group (% of TE) | Prescribed fat for Rx group (% of TE) | Prescribed fat for Control group (% of TE) | Prescribed protein for Rx group (% of TE) | Prescribed protein for Control group (% of TE) |
|-----------------------------------|---------------------|-----------------------------|------------------------------------|------------------------------------------|--------------------------------------|------------------------------------------|----------------------------------------|------------------------------------------|----------------------------------------|------------------------------------------|
| **Overweight and obese adults: High fat variant of low CHO diet** |                     |                             |                                    |                                          |                                      |                                          |                                        |                                        |                                        |                                        |
| Aude (12) 2004                    | 12                  | 5460–6720                   | 5460–6720                          | 28                                       | 39                                   | 33                                       | 55                                     | 30                                       | 15                                     |                                        |
| De Luis (12) 2009                 | 12                  | 6300                        | 6330                               | 38                                       | 36                                   | 26                                       | 52                                     | 27                                       | 20                                     |                                        |
| De Luis (12) 2012                 | 12                  | 6329                        | 6300                               | 38                                       | 36                                   | 26                                       | 53                                     | 27                                       | 20                                     |                                        |
| Frisch (24 and 52) 2009           | 24                  | 2100 deficit                | 2100 deficit                       | <40                                      | >35                                  | 25                                       | >55                                    | <30                                      | 15                                     |                                        |
| Klemstadal (24 and 52) 2010       | 24                  | 2100 deficit                | 2100 deficit                       | 30–35                                    | 35–40                                | 25–30                                    | 55–60                                  | <30                                      | 15                                     |                                        |
| Krauss (12) 2006                  | 5                   | 4200 deficit                | 4200 deficit                       | 26                                       | 45                                   | 29                                       | 54                                     | 30                                       | 16                                     |                                        |
| Lim (24 and 64) 2010              | 24                  | 6500                        | 6500                               | 4                                        | 60                                   | 35                                       | 50                                     | 30                                       | 30                                     |                                        |
| Sacks (24 and 104) 2009           | 24                  | 3150 deficit                | 3151 deficit                       | 35                                       | 40                                   | 25                                       | 65                                     | 20                                       | 15                                     |                                        |
| **Overweight and obese adults: High protein variant of low CHO diet** |                     |                             |                                    |                                          |                                      |                                          |                                        |                                        |                                        |                                        |
| Farnsworth (16) 2003              | 12                  | 6000–6300                   | 6000–6300                          | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Keogh (12 and 52) 2008            | 12                  | 6000                        | 6000                               | 33                                       | 27                                   | 40                                       | 60                                     | 20                                       | 20                                     |                                        |
| Lasker (16) 2008                  | 16                  | 7100                        | 7100                               | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Layman (16 and 52) 2009           | 16                  | 7100–7940                   | 7100–7940                         | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Luscombe (16) 2003                | 12                  | 6500–8200                   | 6500–8201                          | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Wycheley (12 and 52) 2012         | 52                  | 7000                        | 7000                               | 40                                       | 25                                   | 35                                       | 58                                     | 25                                       | 17                                     |                                        |
| **Overweight and obese adults with type 2 diabetes mellitus: High fat variant of low CHO diets** |                     |                             |                                    |                                          |                                      |                                          |                                        |                                        |                                        |                                        |
| Gouldband (12–24) 2012            | 12–24               | M.6696_M.6696;              | 20                                  | 50                                       | 30                                   | 55–60                                    | 30                                     | 10–15                                    |                                        |                                        |
| Gouldband (104) 2012              | 104                 | M.6696;M.6696;              | 20                                  | 50                                       | 30                                   | 55–60                                    | 30                                     | 10–15                                    |                                        |                                        |
| **Overweight and obese adults with type 2 diabetes mellitus: High protein variant of low CHO diets** |                     |                             |                                    |                                          |                                      |                                          |                                        |                                        |                                        |                                        |
| Brinkworth (12) 2004              | 8                   | NR                          | NR                                 | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Brinkworth (64) 2004              | NR                  | NR                          | NR                                 | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Krebs (24 and 104) 2012           | 12                  | 2000 deficit                | 2000 deficit                       | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Larsen (12) 2011                  | 12                  | 6400/–30%E                  | 6400/–30%E                         | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Larsen (52) 2011                  | N/A                 | E balance                   | E balance                          | 40                                       | 30                                   | 30                                       | 55                                     | 30                                       | 15                                     |                                        |
| Parker (12) 2002                  | 8                   | 6720-E balance              | 6721-E balance                     | 40                                       | 30                                   | 30                                       | 60                                     | 25                                       | 15                                     |                                        |

CHO = carbohydrate; E = energy; F = females; g = gram; kJ = kilojoule; M = males; MJ = megajoule; N/A = not applicable; No = number; NR = not reported; Rx = treatment; TE = total energy.

doi:10.1371/journal.pone.0100652.t006
i.e. treatment and control that was most relevant to this systematic review question [17].

Assessment of heterogeneity
Statistical heterogeneity was assessed with the Chi^2 test (significance level \( p < 0.1 \)) and quantified with the I^2 test [20] where I^2 values of 50% or more indicate a substantial level of heterogeneity and values of 75% or more indicate considerable heterogeneity [17].

Assessment of reporting bias
We assessed reporting bias with funnel plots when we had 10 or more studies per outcome, which was the case for five outcomes in non-diabetic overweight and obese adults in the early follow-up category.

Data synthesis and investigation of heterogeneity
The outcomes were reported as the difference in the mean change between the treatment and control groups. Because the presence of diabetes is likely to influence the effects of the diet, we stratified by trials of overweight and obese participants without and with type 2 diabetes. Heterogeneity between the included studies was anticipated due to variations in dietary plans and goals, length of follow-up and dietary methodology, and the random-effects model was therefore used for all meta-analyses. We stratified the analysis by whether the treatment group was the high fat variant or the high protein variant of low CHO diets, and pooled the estimate if there was no obvious heterogeneity.

GRADE analysis
We assessed the quality of evidence using GradePro (GradeProfiler) 3.2.2 software [21,22]. We used standard terms to translate the quality of the evidence, as assessed by GRADE, into words to express the quality of evidence and magnitude of effect. For example, for large effects and moderate quality evidence, we use the word “probably”, whereas for low quality we use the word “may” [23].

Results

Description of studies

Results of the search and included studies. We screened 3450 records and retrieved and screened 179 full-text articles, after which we included 19 RCTs (Figure 1). We included 19 RCTs with 3209 participants [16,24–41]. All trials used a parallel group design, were published after 2001 and were conducted in high-income countries (United States of America (5), Australia (7), New Zealand (1), Germany (1), Norway (1), United Kingdom (1), Sweden (1) and Spain (2)). Sample size varied between 25 and 402 participants. Follow-up ranged from 12 weeks to two years.

There were 14 trials in people without diabetes [16,24,26–29,31–33,36–39,41] and five trials in people with type 2 diabetes mellitus [25,30,34,35,40]. Nine trials tested the high fat variant of the low CHO diet and 10 trials tested the high protein variant. Figure 1 displays the number of trials and variants of the low CHO diet used as treatments in each population. In people without diabetes, eight trials examined the high fat variant [16,24,26,27,29,32,33,38] and 6 the high protein variant [28,31,36,37,39,41]. A single trial [30] evaluated the high fat variant and four [25,34,35,40] evaluated the high protein variant in adults with type 2 diabetes mellitus. No included trials reported mortality, myocardial infarction or stroke as outcomes.

Two trials were only in men [33,41] and the rest were mixed. All trials included only participants who were overweight or obese (BMI of 26 kg/m^2 or greater). In all trials that reported baseline BMIs, the mean baseline BMI in both groups was greater than 30 kg/m^2. The WHO classifies an individual as overweight when their BMI is greater than or equal to 25 kg/m^2 and as obese when BMI is greater than or equal to 30 kg/m^2 [42]. Table 5 provides

---

Table 7. Excluded studies and reasons for exclusion.

| Reasons for exclusion                                                                 | Number of studies excluded |
|--------------------------------------------------------------------------------------|----------------------------|
| Not a randomised controlled trial                                                   | 4 [71–74]                 |
| Duration of the intervention >12 weeks                                              | 40 [75–114]               |
| All three macronutrients not prescribed (or cannot be calculated as proportions of the total energy intake) | 20 [115–134]             |
| Non-English language                                                                 | 1 [135]                   |
| Test meal response measured                                                          | 1 [136]                   |
| Meal replacement                                                                     | 2 [137,138]               |
| Combined interventions were involved                                                | 3 [139–141]               |
| Treatment and control both low carbohydrate – not an eligible comparison             | 3 [142–144]               |
| Comparison not meaningful (carbohydrate content of treatment and controls differ <5% of TE) | 2 [145,146]             |
| No eligible balanced carbohydrate control                                            | 1 [147]                   |
| Crossover trial where first period data cannot be extracted:                          | 1 [148]                   |
| Substantial disparity in energy intake between prescribed intervention diets         | 13 [49,51,149–159]        |
| Treatment diet is not low in carbohydrates                                           | 26 [160–185]              |
| Control diet is not within balanced macronutrient range                               | 4 [186–189]               |
| Duplicate and/or complimentary                                                       | 24 [190–213]              |
| Energy intake ad libitum                                                             | 8 [214–221]               |
| Ineligible low carbohydrate diet variant                                             | 6 [222–227]               |
| Less than 10 participants randomised per group                                       | 1 [228]                   |

RCT = randomised controlled trial; CHO = carbohydrate.

doi:10.1371/journal.pone.0100652.t007
Table 8. Risk of bias in overweight and obese adult population.

| First author | Year published | Risk of bias | Random sequence generation | Allocation concealment | Performance bias | Performance bias Comment | Detection bias | Detection bias Comment | Attrition bias | Attrition bias Comment (Rx/Control group) | Reporting bias | Reporting bias Comment | Other bias | Other bias Comment |
|--------------|----------------|--------------|-----------------------------|------------------------|-----------------|--------------------------|---------------|------------------------|--------------|------------------------------------------|--------------|------------------------|----------|---------------------|
| Aude         | 2004           | Low risk     | Block design               | Unclear risk           | NR               | Unclear risk             | Equal contact time but not blinded | Low risk     | Assessors blinded         | High risk    | 3%/17% attrition (differential), no reasons | Low risk     | Protocol not available, but prespecified and all NB outcomes addressed | High risk | Food choice advice & fibre supplements only given to Rx group |
| De Luis      | 2009           | Low risk     | Random number list         | Unclear risk           | “closed envelope” | Unclear risk             | Equal contact time but not blinded | Unclear risk | Not blinded              | Low risk     | No attrition               | Low risk     | Protocol not available, but prespecified and all NB outcomes addressed | High risk | Funding & COI NR, imbalanced baseline SBP, HDL, TG |
| De Luis      | 2012           | Unclear risk | NR                          | Unclear risk           | NR               | Unclear risk             | Equal contact time but not blinded | Unclear risk | Not blinded              | Low risk     | No attrition               | High risk    | No prespecified outcomes, protocol not available | High risk | Funding & COI NR, imbalanced baseline SBP, HDL |
| Farnsworth   | 2003           | Unclear risk | NR                          | Unclear risk           | NR               | Unclear risk             | Equal contact time but not blinded | Unclear risk | Not blinded              | Low risk     | 14% total attrition, attrition & reasons not provided per group | High risk    | No prespecified outcomes, protocol not available | Unclear risk | Funding: possible influences |
| Frisch       | 2009           | Low risk     | Computer generated random no. lists | Unclear risk           | NR               | Unclear risk             | Equal contact time but not blinded | Unclear risk | Not blinded              | Low risk     | ITT analysis               | Low risk     | Prespecified and all NB outcomes addressed, protocol available | Low risk | - |

Notes:
- NR: Not reported
- DBP: Diastolic Blood Pressure
- HDL: High Density Lipoprotein
- TG: Triglycerides
| First author | Year published | Random sequence generation Judgement | Random sequence generation Comment | Allocation concealment Judgement | Allocation concealment Comment | Performance bias Judgement | Performance bias Comment | Detection bias Judgement | Detection bias Comment | Attrition bias Comment (Rx/Control group) | Reporting bias Judgement | Reporting bias Comment | Other bias Comment | Other bias Comment |
|--------------|----------------|-------------------------------------|----------------------------------|-------------------------------|--------------------------------|---------------------------|-------------------------|---------------------|---------------------|-----------------------------------------------|-------------------------|----------------------------|----------------------|----------------------|
| Keogh [31]   | 2008           | Unclear risk                        | NR                               | Unclear risk                  | NR                              | Unclear risk              | Equal contact time but not blinded | Unclear risk        | Not blinded         | 36% total attrition, attrition & reasons not provided per group | Low risk                | Prespecified and NB outcomes addressed, protocol available | High risk             | COI NR               |
| Klemsdal [32] | 2010           | Unclear risk                        | NR                               | Unclear risk                  | NR                              | Unclear risk              | Equal contact time but not blinded | Unclear risk        | Not blinded         | ITT analysis                              | Low risk                | Prespecified and NB outcomes addressed, protocol available | Low risk               | COI NR               |
| Krauss [33]  | 2006           | Low risk                            | Blocks of 4, 8, 12, 16, 20, 24   | Unclear risk                  | Sequentially no. envelopes, not opaque | Unclear risk              | Equal contact time but not blinded | Unclear risk        | Not blinded         | 23/14% attrition (differential), reasons not per group | High risk               | Only 1 outcome prespecified, protocol not available | Unclear risk           | COI NR               |
| Lasker [36]  | 2008           | Low risk                            | Block randomisation              | Unclear risk                  | NR                              | Unclear risk              | Equal contact time but not blinded | Unclear risk        | Not blinded         | 22/24% attrition, no reasons                  | Low risk                | Protocol not available, but prespecified and all NB outcomes addressed | High risk              | Funding: possible influences |
| Layman [37]  | 2009           | Unclear risk                        | NR                               | Unclear risk                  | NR                              | Unclear risk              | Equal contact time but not blinded | Unclear risk        | Not blinded         | 36/59% attrition (differential), reasons differ per group | Low risk                | Protocol not available, but prespecified and all NB outcomes addressed | Unclear risk           | Funding and COI reported: possible influences |
| Lim [38]     | 2010           | Unclear risk                        | NR                               | Unclear risk                  | NR                              | Unclear risk              | Equal contact time but not blinded | Unclear risk        | Not blinded         | 43/50% attrition, reasons differ per group (differential) | Low risk                | Protocol not available, but prespecified and all NB outcomes addressed | Low risk               | -                   |
| First author | Year published | Random sequence generation Judgement | Random sequence generation Comment | Allocation concealment Comment | Allocation concealment Judgement | Performance bias Comment | Performance bias Judgement | Detection bias Comment | Detection bias Judgement | Attrition bias Comment (Rx/Control group) | Attri| Reporting bias Comment | Reporting bias Judgement | Other bias Comment | Other bias Judgement | Other bias Comment |
|--------------|----------------|--------------------------------------|-----------------------------------|-------------------------------|---------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|----------------------------------------|--------------|------------------------|--------------------------|-------------------|-------------------|--------------------------|
| Luscombe [39] | 2003           | Unclear risk                         | NR                                | Unclear risk                  | NR                              | Unclear risk             | Equal contact time but not blinded | Unclear risk             | Not blinded             | No attrition                           | High risk     | No prespecified outcomes, protocol not available |                      |                  |                  |                  |
| Sacks [16]   | 2009           | Unclear risk                         | NR                                | Low risk                      | Centrally                       | Low risk                 | Participants blinded          | Low risk                 | Assessors blinded | ITT                                    | Low risk      | Prespecified and all NB outcomes addressed, protocol available |                      |                  |                  |                  |
| Wycherley [41]| 2012           | Low risk                             | Computer generated random no. lists | Unclear risk                  | NR                              | Unclear risk             | Equal contact time but not blinded | Unclear risk             | Not blinded             | 44/45% attrition                        | Unclear risk  | Protocol retrospectively registered, outcomes only specified in abstract, NB outcomes addressed |                      |                  |                  |                  |

**Overweight and obese adults with Type 2 diabetes mellitus**

| Brinkworth [25] | 2004           | Low risk                             | Random no. generator            | Unclear risk                  | NR                              | Unclear risk             | Equal contact time but not blinded | Unclear risk             | Not blinded             | 42/42% attrition, reasons differ per group | Low risk      | Protocol not available, but prespecified and all NB outcomes addressed |                      |                  |                  |                  |
| Guildbrand [30] | 2012           | Low risk                             | Drawing blinded ballots         | Unclear risk                  | NR                              | Unclear risk             | Equal contact time but not blinded | Unclear risk             | Not blinded             | Low risk                             | No attrition | Protocol available: prespecified outcomes vague |                      |                  |                  |                  |
### Table 8. Cont.

| First author | Year published | Random sequence generation Judgement | Random sequence generation Comment | Allocation concealment Judgement | Allocation concealment Comment | Performance bias Judgement | Performance bias Comment | Detection bias Judgement | Detection bias Comment | Attrition bias Comment (Rx/Control group) | Other bias Judgement | Other bias Comment |
|----------------|-----------------|-------------------------------------|-----------------------------------|---------------------------------|-------------------------------|----------------------------|--------------------------|------------------------|------------------------|---------------------------------|-------------------|---------------------|
| Krebs [34] | 2012 | Low risk | Computer generated random no. | Low risk | Independent biostatistician | Unclear risk | Equal contact time but not blinded | Unclear risk | Not blinded | High risk | 30/29%, reasons differ per group (differential) | Low risk | Prespecified and NB outcomes addressed, protocol available |
| Larsen [35] | 2011 | Low risk | Random block sizes | Low risk | Centrally | Unclear risk | Equal contact time but not blinded | Low risk | Assessors blinded | High risk | 16/12% attrition, reasons differ per group (differential); LOCF analysis only on some missing participants | Low risk | Prespecified and NB outcomes addressed, protocol available |
| Parker [40] | 2002 | Unclear risk | NR | Unclear risk | NR | Unclear risk | Equal contact time but not blinded | Unclear risk | Not blinded | Unclear risk | 19/18% attrition, no reasons | High risk | No prespecified outcomes, protocol not available |

*Bnumber of attrition per group given for longest follow-up within the categories;

BMI = body mass index; BP = blood pressures; COI = conflict of interest; DBP = diastolic blood pressure; HDL = high density lipoprotein cholesterol; ITT = intention-to-treat; LOCF: Last observation carried forward; NB = important; No = number; NR = Not reported; Rx = treatment; TG = triglycerides.
characteristics of included trials per population group and Table 6, the prescribed dietary goals for the treatment and control diets per included trial and population group. We excluded 160 full-text articles with reason given in Table 7; the most common reason was follow-up less than 12 weeks.

Risk of bias in included studies. Risk of bias is reported in Table 8 and displayed in Figure 2.

Generation of sequence and allocation concealment: Ten trials reported the method of randomisation; three trials reported adequate concealment and in the rest it was unclear.

Blinding: Blinding of participants in diet trials is not easy as they usually have to follow specific dietary plans in order to attain the prescribed goals of the intervention diets. Three trials blinded the outcome assessors of which one also reported blinding the participants.

Incomplete outcome data: After 3–6 months, reported loss to follow-up ranged from no loss to 42%, peaking at 47% after 15 months in one of the trials. Ten trials had overall attrition greater than 20%, differential attrition between groups, or both. Six trials had differential loss and/or different or unspecified reasons for loss to follow-up. Seven trials had low risk of attrition bias, with four reporting no attrition and three performing intention-to-treat analysis.

Selective reporting: Six trials did not have protocols available or outcomes were not pre-specified in the methods section of the trial reports and one trial had an unclear risk of reporting bias. The remaining 12 trials were judged to have low risk of reporting bias.

Publication bias: Assessment of the funnel plot asymmetry for the five outcomes in overweight and obese adults in the early follow-up category showed that for weight loss, small studies with a negative mean difference are missing. Similarly, smaller studies appear to be missing for the other four outcomes, namely serum LDL, HDL and total cholesterol, and serum triglycerides (data not shown).

Other potential sources of bias: Nine trials were judged to have a high risk of other types of bias. Six trials were funded independently, five were funded by industry, five by a combination of independent and industry funding and the remaining three trials did not report their funding source. Four trials had low risk of other bias.

Adherence to prescribed dietary goals. Table 9 shows the energy prescriptions for the weight loss diets were expressed as absolute goals or ranges, or as absolute or percentage deficits, with some trials using sex-specific goals. In the 12 trials that reported group comparisons in energy intake, only one found a difference, with a lower reported intake in the balanced diet group [34] (Table 9). None of these 12 trials demonstrated a difference in weight loss between the low CHO and balanced diet groups at any follow-up category.

Thirteen and eight trials reported mean CHO, fat and protein intakes at 3–6 months and 1–2 years, respectively (Table 9). Calculated adherence scores were variable across the two diet groups and follow-up categories. Four trials showed similar adherence (difference in scores between groups <1) to prescribed macronutrient goals in the two diet groups after 3–6 month follow-up [16,29–31]. Five trials showed better adherence in the low CHO diet groups [35–37,40,41] and four trials showed better adherence in the balanced diet group [28,34,38,39]. At 1–2 years follow-up, there were greater discrepancies in the adherence scores between the two diet groups. The low CHO diet group showed better adherence to macronutrient prescriptions in three trials [16,35,41] and the balanced diet group showed better adherence in five trials [29,30,34,37,38] (Table 9).

Effects of interventions
The effect estimates between the two dietary variants (high fat and high protein) did not show a qualitative difference and the heterogeneity between the groups was small or not detectable, so we pooled data across the two low CHO diet variants in the analysis.

Trials in participants without type 2 diabetes
Total weight loss. At 3–6 months, the average weight loss in trials in the low CHO group ranged from 2.65 to 10.2 kg and in the isonenergetic balanced diet group from 2.65 to 9.4 kg. At 1–2 years, the range of weight loss was 2.9 to 12.3 kg with low CHO diets and 3.5 to 10.9 kg with isonenergetic balanced diets.

The meta-analysis of the mean difference in weight loss between the low CHO diet and the balanced diet showed a difference at 3–6 months (–0.74 kg, 95%CI –1.49 to 0.01; 14 trials) (Table 10; Figure 3) and at 1–2 years (–0.48 kg, 95%CI –1.44 to 0.49; 7 trials) (Table 11; Figure 4). In the study [16] that concealed allocation, there was no mean difference in weight loss at 3–6 months (0.20 kg, 95%CI –0.88 to 1.28; n = 402) and at 1–2 years (0.60 kg, 95%CI –0.76 to 1.96).
Table 9. Group comparisons of mean reported energy intakes and calculated adherence scores per diet group for all lengths of follow-up.

| Study ID   | Length of follow-up (weeks) | Energy prescription in both groups in kJ | Mean reported energy intake (SD) in kJ | Group comparison of mean reported energy intake reported by trial authors | Adherence scores\(a\) for macronutrients |
|------------|-----------------------------|-----------------------------------------|---------------------------------------|------------------------------------------------------------------------|------------------------------------------|
| Aude 2004  | 12                          | 6720 (m): 5460 (f)                     | –                                    | NA                                                                     | –                                        |
| Brinkworth 2004 | all equivalent         | –                                      | –                                    | NA                                                                     | –                                        |
| De Luis 2009 | 12                         | 6330                                    | 6592 (NR)                           | 6775 (NR)                                                             | –                                        |
| De Luis 2012 | 12                         | 6300–6329                               | 6598 (NR)                           | 6779 (NR)                                                             | –                                        |
| Farnsworth 2003 | 12                         | 6000–6300                              | 6300 (529)                           | 6500 (539)                                                            | “did not differ”                        |
|             | 16                          | balance                                | 8000 (1058)                          | 8200 (1077)                                                           | 5.93                                     | 4.00                                     |
| Frisch 2009 | 24                          | 2100 deficit                            | 7316 (2621)                          | 7489 (2507)                                                           | p = 0.636                                | 5.96                                     | 6.13                                     |
|             | 52                          |                                        | 7837 (2982)                          | 7787 (2621)                                                           | p = 0.903                                | 7.08                                     | 5.19                                     |
| Guldbrand 2012 | 12–24                      | 7531 (m): 6954 (f)                     | 5791 (1531)                          | 6498 (1878)                                                           | p = 0.065 for change                     | 7.87                                     | 8.54                                     |
|             | 52                          |                                        | 6017 (2075)                          | 6619 (2075)                                                           | over all time points                     |                                         |                                          |
|             | 104                         |                                        | 5234 (1799)                          | 6104 (1891)                                                           | between groups                           | 13.89                                   | 9.49                                     |
| Keogh 2008  | 12                          | 6000                                    | 6242 (4576)                          | 6262 (3876)                                                           | “did not differ”                        | 6.81                                     | 7.15                                     |
|             | 52                          |                                        | –                                    | –                                                                     | NA                                       | –                                        |                                          |
| Klemsdal 2010 | All                        | 2100 deficit                            | –                                    | –                                                                     | NA                                       | –                                        |                                          |
| Krauss 2006 | 12                          | 4200 deficit                            | –                                    | –                                                                     | NA                                       | –                                        |                                          |
| Krebs 2012  | 12                          | 2000 deficit                            | 7400 (3057)                          | 6815 (1841)                                                           | 9.71                                     | 8.32                                     |
|             | 52                          |                                        | 7258 (2098)                          | 6784 (1792)                                                           | p = 0.012                                |                                         |                                          |
|             | 104                         |                                        | 7170 (1974)                          | 7093 (1851)                                                           | over 104 weeks                          | 11.24                                   | 8.71                                     |
| Larsen 2011 | 12                          | 6400 or 30% restriction                 | 6449 (2652)                          | 6029 (2652)                                                           | p = 0.22 for “group by time interaction”| 1.85                                     | 8.37                                     |
|             | 52                          | balance                                | 6664 (3233)                          | 6628 (3233)                                                           | 4.00                                     | 8.09                                     |
| Lasker 2008 | 16                          | 7100                                    | 6607 (1175)                          | 5875 (1955)                                                           | p > 0.10                                | 2.45                                     | 8.77                                     |
| Layman 2009 | 16                          | 7100                                    | 6730 (1659)                          | 6200 (1714)                                                           | p > 0.05                                | 3.16                                     | 6.93                                     |
|             | 52                          |                                        | 7118 (1793)                          | 6800 (1917)                                                           | p > 0.05                                | 6.32                                     | 4.69                                     |
| Lim 2010    | 12                          | 6500                                    | 7706 (868)                           | 7659 (1044)                                                           | –                                        |                                         |                                          |
|             | 24                          |                                        | 7367 (1372)                          | 6449 (1668)                                                           | 11.10                                    | 2.77                                     |
|             | 52                          |                                        | 7726 (1609)                          | 7124 (2287)                                                           |                                         |                                         |                                          |
|             | 64                          |                                        | 6841 (1348)                          | 6593 (1503)                                                           | 41.28                                    | 8.10                                     |
| Luscombe 2003 | 12                         | 6500                                    | 6358 (885)                           | 6663 (819)                                                            | p > 0.05                                |                                         |                                          |
|             | 16                          | 8200                                    | 8068 (1342)                          | 8235 (263)                                                            | p > 0.05                                | 6.18                                     | 4.14                                     |
| Parker 2002 | 8                           | 6720                                    | 6665 (771)                           | 6480 (977)                                                            | “not different”                         | 3.59                                     | 5.54                                     |
|             | 12                          | balance                                | 8522 (1178)                          | 7497 (1645)                                                           | “not different”                         |                                         |                                          |
A few studies reported change in BMI. As with weight, average BMI was lower after dieting in both diet groups, but with no difference detected at either 3–6 months across the 4 trials reporting this (Table 10; Figure S2A in Supporting Information S2), or in the one trial reporting this at 1–2 years (Table 11; Figure S2B in Supporting Information S2).

**Blood pressure.** At 3–6 months, the average DBP compared to baseline in each study was reduced in both the low CHO group (range: −10 to −1 mmHg) and in those on balanced diets (range: −14 to −1 mmHg). At 1–2 years, the average drop within studies compared to baseline ranged from 9 mmHg lower to no change in DBP with low CHO and a reduction across studies with balanced diets of 11 to 1 mmHg.

The meta-analyses of the mean difference in DBP change did not demonstrate a difference between the low CHO and balanced diets at 3–6 months (95%CI −1.53 to 1.36; 8 trials) (Table 10; Figure S2C in Supporting Information S2) and at 1–2 years (95%CI −1.68 to 1.62; 6 trials) (Table 11; Figure S2D in Supporting Information S2). (In one of the trials [26], the mean SBP value after three months in the low CHO group was reported as 103.1±13.7 mmHg (corresponding reported mean baseline value of 138.6±16.8 mmHg). We suspected this very low SBP value to be a typographical error, but did not receive a response after contacting the authors and therefore excluded this data from the meta-analysis.)

At 3–6 months, the average SBP in each study compared to baseline showed a drop in both the low CHO (range: −15 to −2 mmHg) and balanced diet groups (range: −16 to −1 mmHg) in all trials. At 1–2 years, average SBP decreased with low CHO (range: −10.6 to −0.9 mmHg) and either decreased or increased with balanced diets (range: −10 to 8 mmHg). The increase was observed in a small trial (n = 25) with 48% attrition when the trial ended after one year [31].

The meta-analysis of the mean difference in SBP change showed no difference after 3–6 months (−1.26 mmHg, 95%CI −2.67 to 0.15; 7 trials) (Table 10; Figure S2E in Supporting Information S2) and after 1–2 years (−2.00 mmHg, 95%CI −5.00 to 1.00; 6 trials) (Table 11; Figure S2F in Supporting Information S2).

**Blood lipids.** At 3–6 months, compared to baseline, average LDL and total cholesterol were inconsistent across trials with low CHO diets (range LDL: −0.62 to 0.3 mmol/L; total cholesterol: −0.71 to 0.1 mmol/L), while these values decreased with balanced diets in each of the 12 trials that reported these values (range LDL: −0.82 to −0.03 mmol/L; total cholesterol: −0.88 to −0.07 mmol/L). Average changes in HDL and TG from baseline varied with low CHO (range HDL: −0.07 to 0.1 mmol/L; TG: −0.64 to 0.01 mmol/L) and balanced diets (range HDL: −0.1 to 0.08 mmol/L; TG: −0.49 to 0.01 mmol/L). At 1–2 years, average lipid marker changes from baseline were inconsistent in both diet groups across trials, with variations in ranges of change that were similar to those reported at 3–6 months.

The meta-analyses of the mean differences in blood lipids between the low CHO and balanced diets were small in both follow-up categories, with narrow confidence intervals suggesting little or no difference in effect between the two diets (Tables 10 and 11; Figures S2G to S2N in Supporting Information S2).

**Fasting blood glucose.** From baseline to 3–6 months, average FBG decreased with low CHO (range −0.47 to −0.06 mmol/L) and balanced diets (range −0.52 to −0.1 mmol/L), and at 1–2 years average changes were variable with low CHO (range: −0.71 to 0.17 mmol/L) and balanced diets (range: −0.4 to 0.06 mmol/L). The meta-analysis showed no difference between low CHO and balanced diets in FBG change.
Table 10. Summary of findings for meta-analysis of low carbohydrate diets compared with balanced diets for overweight and obese adults: 3–6 months follow-up.

Patient or population: overweight and obese adults without type 2 diabetes
Settings: primary care
Intervention: low carbohydrate diets (includes high fat and high protein variants)
Comparison: balanced diets
Follow-up: 3–6 months after starting diet

| Outcomes                  | Balanced diets | Low carbohydrate diets | No. of participants (studies) | Quality of the evidence (GRADE) |
|---------------------------|----------------|-------------------------|------------------------------|--------------------------------|
| Illustrative range of change in average values from pre-diet levels by study: range across studiesa | The effect difference with low carbohydrate diets in randomised comparison to balanced diets (95%CI) |                              |                              |
| Weight loss               | Lower by 2.65 to 9.4 kg | 0.74 kg more weight lost | 1745                         | ★★★★                           |
|                           | (could be 1.49 lost to a gain of 0.01) | (14 studies) | moderate1,2                    |
| BMI                       | Lower by 1.6 to 2.4 kg/m² | 0.25 kg/m² lower BMI | 673                          | ★★★★                           |
|                           | (could be 0.64 lower to 0.13 higher) | (4 studies) | moderate3                      |
| Diastolic blood pressure  | Lower by 1 to 14 mmHg | 0.08 mmHg lower diastolic blood pressure | 1362 | ★★★★ |
|                           | (could be 1.53 lower to 1.36 higher) | (8 studies) | low4,5                          |
| Systolic blood pressure   | Lower by 1 to 16 mmHg | 1.26 mmHg lower systolic blood pressure | 1057 | ★★★★ |
|                           | (could be 2.67 lower to 0.15 mmHg higher) | (7 studies) | moderate6                      |
| LDL cholesterol           | From 0.03 lower to 0.82 mmol/L higher | 0.09 mmol/L higher LDL cholesterol | 1603 | ★★★★ |
|                           | (could be 0 to 0.18 mmol/L higher) | (12 studies) | moderate7                      |
| HDL cholesterol           | From 0.1 lower to 0.08 mmol/L higher | 0.03 mmol/L higher HDL cholesterol | 1603 | ★★★★ |
|                           | (could be 0.01 lower to 0.08 mmol/L higher) | (12 studies) | low8,9                          |
| Total cholesterol         | Lower by 0.07 to 0.88 mmol/L | 0.08 mmol/L higher total cholesterol | 1603 | ★★★★ |
|                           | (could be 0.02 lower to 0.17 mmol/L higher) | (12 studies) | moderate10                       |
| Triglycerides             | From 0.49 lower to 0.01 mmol/L higher | 0.05 mmol/L lower triglycerides | 1603 | ★★★★ |
|                           | (could be 0.14 lower to 0.04 mmol/L higher) | (12 studies) | low10,11                       |

CI: Confidence interval;
aNote this is the univariate average change observed between follow-up and baseline in the control group.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1Downgraded by 1 for risk of bias: 8 of 14 studies did not report adequate sequence generation and 13 studies did not report adequate allocation concealment. 4 studies had high total attrition (>20%) and 2 other studies had differential attrition.
2Not downgraded for inconsistency: no qualitative heterogeneity; some quantitative heterogeneity, to be expected.
3Downgraded by 1 for risk of bias: 7 studies did not report adequate sequence generation and 6 studies reported on allocation concealment and 1 study had high total attrition (>20%).
4Downgraded by 1 for risk of bias: 2 studies did not report adequate sequence generation and 2 other studies had differential attrition.
5Downgraded by 1 for inconsistency: Mean differences were on opposite sides of the line of no difference (I² 51%).
6Downgraded by 1 for risk of bias: 5 of 8 studies did not report adequate sequence generation and 7 studies did not report adequate allocation concealment. 2 studies had high total attrition (>20%).
7Downgraded by 1 for risk of bias: 5 of 12 studies did not report adequate sequence generation and 11 studies did not report adequate allocation concealment. 3 studies had high total attrition (>20%) and 2 other studies had differential attrition.
8Downgraded by 1 for risk of bias: 6 of 12 studies did not report adequate sequence generation and 11 studies did not report adequate allocation concealment. 3 studies had high total attrition (>20%) and 2 studies had differential attrition.
9Downgraded by 1 for inconsistency: Mean differences were on opposite sides of the line of no difference (I² 63%).
10Downgraded by 1 for inconsistency: Mean differences were on opposite sides of the line of no difference (I² 72%).
doi:10.1371/journal.pone.0100652.t010

at either 3–6 months (0.05 mmol/L, 95%CI −0.05 to 0.15; 10 trials; Figure S2O in Supporting Information S2) or 1–2 years (0.0 mmol/L, 95%CI −0.16 to 0.16; 6 trials; Figure S2P in Supporting Information S2).

Trials in participants with type 2 diabetes

Total weight loss. Average weight loss was evident at 3–6 months with low CHO (range: 2.79 to 5.5 kg) and isoenergetic balanced diets (range: 3.08 to 5.4 kg), and similarly with both diets at 1–2 years (range low CHO diets: 2 to 3.9 kg; range balanced
diets: 2.1 to 6 kg) in all trials. The meta-analysis of the mean difference in weight loss between the low CHO and balanced diets did not demonstrate a difference at 3–6 months (0.82 kg, 95%CI 2.91 to 2.90; 5 trials) (Table 12; Figure 5); and at 1–2 years (0.91 kg, 95%CI 2.08 to 3.89; 4 trials) (Table 13; Figure 6).

A single trial found no difference in BMI change between the low CHO (high fat variant) and balanced diets at 3–6 months (Figures S3A and S3B in Supporting Information S3).

Markers of glycaemic control. At 3–6 months, compared to baseline, changes in average HbA1c varied across studies with low CHO diets (range: 2.0.54 to 0%), and decreased in each study with balanced diets (range: 2.0.51 to 2.0.3%). At 1–2 years, average HbA1c changes from baseline were inconsistent in both diet groups across trials (range low CHO: 2.0.23 to 0.1%; balanced: 2.0.28 to 0.4%).

The meta-analyses of the mean difference in HbA1c change did not demonstrate a difference between the low CHO and balanced diets at 3–6 months (95%CI 2.1.77 to 3.30; 4 trials) (Table 12; Figure S3G in Supporting Information S3) and at 1–2 years (95%CI 2.1.95 to 2.13, 4 trials) (Table 13; Figure S3H in Supporting Information S3).

The average SBP in each study compared to baseline showed a drop in both the low CHO (range: 2.9 to 2.1 mmHg) and balanced diets (range: 2.8 to 3.7 mmHg) at 3–6 months, with varied changes at 1–2 years (range low CHO: 2.9 to 2.2 mmHg; balanced: 2.11 to 3.7 mmHg).

The meta-analysis of the mean difference in SBP change showed no difference after 3–6 months (95%CI 2.3.14 to 4.36; 4 trials) (Table 12; Figure S3I in Supporting Information S3) and after 1–2 years (95%CI 2.3.10 to 3.72; 4 trials) (Table 13; Figure S3J in Supporting Information S3).

Blood lipids. At 3–6 months, blood lipids (LDL, HDL, total cholesterol, TG) showed variable changes from baseline in both low CHO and balanced diets. Overall, changes from baseline were inconsistent between the diet groups and for both follow-up categories. The changes on meta-analysis were small suggesting little or no difference in effect between the two diets (Table 12 and 13; Figures S3K to S3R in Supporting Information S3).

| Study or Subgroup      | Low CHO | Balanced | Mean Difference | Mean Difference |
|------------------------|---------|----------|----------------|----------------|
|                        | Mean    | SD       | Total          | Mean           | SD     | Total          | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 1.1.1 High fat variant | Aude 2004 | -6.2     | 1.8            | 22             | -3.4   | 2              | 23      | 11.7%               | -2.80 [-3.91, -1.69] |
|                        | De Luis 2009 (1) | 90.4   | 19.7           | 52             | 87.5   | 10.1           | 66      | 1.5%                | 2.90 [-2.98, 8.78]   |
|                        | De Luis 2012 (2) | 91.4   | 17.4           | 147            | 88.6   | 16.8           | 158     | 3.1%                | 3.40 [-0.42, 7.22]   |
|                        | Frisch 2009 | -7.2    | 5.4            | 100            | -6.2   | 4.8            | 100     | 10.1%               | -1.00 [-2.42, 0.42]  |
|                        | Kiemsdal 2010 | -5.7    | 11.1           | 100            | -4.8   | 11.1           | 102     | 4.3%                | -0.90 [-3.96, 2.16]  |
|                        | Lin 2006    | -2.85   | 2.94           | 40             | -2.65  | 3.63           | 49      | 10.3%               | 0.00 [-1.38, 1.36]   |
|                        | Sacks 2009  | -5.6    | 5.6            | 201            | -5.8   | 5.4            | 201     | 11.9%               | 0.20 [-0.88, 1.28]   |
|                        | Subtotal (95% CI) | 686    | 720            | 61.6%          | -0.62  | [-1.79, 0.54]  |         |                      |                      |
| Heterogeneity: Tau² = 1.71; Chi² = 24.29, df = 7 (P = 0.001); I² = 71% |

Test for overall effect: Z = 1.05 (P = 0.30)

| Study or Subgroup      | Low CHO | Balanced | Mean Difference | Mean Difference |
|------------------------|---------|----------|----------------|----------------|
|                        | Total (95% CI) | 854    | 891            | 100.0%         | -0.74 [-1.49, 0.01] |
| Heterogeneity: Tau² = 0.93; Chi² = 27.93, df = 13 (P = 0.009); I² = 53% |

Test for overall effect: Z = 1.94 (P = 0.05)

Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%

(1) End value data
(2) End value data

Figure 3. Forest plot of low carbohydrate versus balanced diets in overweight and obese adults for weight loss (kg) at 3–6 months. doi:10.1371/journal.pone.0100652.g003
Discussion

This review, including 19 RCTs with 3209 participants showed there is probably little or no difference in changes in weight and cardiovascular and diabetes risk factors with low CHO weight loss diets compared to isonenergetic balanced weight loss diets. This was in both overweight and obese adults without diabetes and those with diabetes, with follow-up for up to two years. When reported, energy intake was similar in the diet groups being compared, but participants did not adhere fully to the prescribed macronutrient goals for both diets in most trials.

Overweight and obese adults without type 2 diabetes

Weight loss. Participants lost weight in both groups, with similar before and after average loss after 3–6 months, and 1–2 years follow-up. There was little or no difference in weight loss and change in BMI between the low CHO and balanced weight loss diets in the two follow-up periods. The similar reported mean energy intakes in the low CHO and balanced diet groups and the corresponding similar average weight loss in the diet groups supports the fundamental physiologic principle of energy balance, namely that a sustained energy deficit results in weight loss regardless of macronutrient composition of the diet [43].

Norms for defining “stable weight” are gaining less than or equal to 2 kg and losing less than 2 kg [44] indicating that both low CHO and balanced weight loss diets (or energy-restricted diets) result in meaningful weight loss. Clearly, the goal of any healthy weight loss strategy should be to achieve weight loss and to subsequently maintain this over the long-term. The 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults state that strategies for weight maintenance after

Table 11. Summary of findings for low carbohydrate diets compared with balanced diets for overweight and obese adults at 1–2 years follow-up.

| Outcomes                  | Balanced diets                                                                 | Low carbohydrate diets                                                                 | No. of participants (studies) | Quality of the evidence (GRADE) |
|---------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------|---------------------------------|
| Weight loss               | Lower by 3.5 to 10.9 kg                                                       | 0.48 kilograms more weight lost                                                        | 1025                         | ★★★★★                         |
| BMI                       | Lower by 1.5 kg/m²                                                            | (could be 1.44 lost to a gain of 0.49 kg)                                              | (7 studies)                  | moderate                        |
| (at 1 year)               | (could be 0.94 lower to 0.14 higher)                                          | (1 study)                                                                               | low                          |
| Diastolic                 | Lower by 1 to 11 mmHg                                                         | 0.03 mmHg lower diastolic blood pressure                                               | 914                          | ★★★★                          |
| blood pressure            | (could be 1.68 lower to 1.62 mmHg higher)                                     | (6 studies)                                                                              | moderate                     |
| Systolic                  | From 10 lower to 8 mmHg higher                                                 | 2 mmHg lower systolic blood pressure                                                    | 914                          | ★★★★                          |
| blood pressure            | (could be 5 lower to 1 mmHg higher)                                           | (6 studies)                                                                              | moderate                     |
| LDL cholesterol           | From 0.79 lower to 0.06 mmol/L higher                                         | 0.07 mmol/L higher LDL cholesterol                                                     | 915                          | ★★★★                          |
| HDL cholesterol           | From 0.03 lower to 0.15 mmol/L higher                                         | 0.04 mmol/L higher HDL cholesterol                                                     | 986                          | ★★★★                          |
| Total cholesterol         | From 0.76 lower 0.13 mmol/L higher                                            | 0.06 mmol/L higher total cholesterol                                                   | 915                          | ★★★★                          |
| Triglycerides             | From 0.44 lower to 0.06 mmol/L higher                                         | 0.06 mmol/L lower triglycerides                                                        | 915                          | ★★★★                          |

CI: Confidence interval;
*Note this is the univariate average change observed between follow-up and baseline in the control group.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.
1Downgraded by 1 for risk of bias: 5 of 7 studies did not report adequate sequence generation and only 1 reported adequate allocation concealment. 5 studies were judged to have a high or unclear risk of attrition bias.
2Downgraded by 1 for imprecision: difference in mean BMI change ranges from a reduction of –0.94 to an increase of 0.14 kg/m² (approximately equivalent to 2 to 4 kilograms).
3Downgraded by 1 for risk of bias: the study did not report adequate allocation concealment and reasons for attrition differed between groups.
4Downgraded by 1 for risk of bias: 4 of 6 studies did not report adequate sequence generation and 5 studies did not report adequate allocation concealment. 2 studies had high total attrition (>20%), 1 of which also had differential attrition.
doi:10.1371/journal.pone.0100652.t011
successful loss differ from the strategies for achieving weight loss and make recommendations in this regard [44].

**Impacts on markers of cardiovascular risk.** Weight loss improves markers of cardiovascular risk [45–47]. According to the 2013 AHA/ACC/TOS Guideline [44], based largely on systematic reviews, clinically meaningful changes in CVD risk indicators are associated with a loss of at least 2.5 kg, or 2% of body weight, achieved with lifestyle interventions over one to four years. This document states that at a 5% weight loss, a weighted mean reduction in DBP of about 2 mmHg and in SBP of about 3 mmHg is observed [44]. Correspondingly, the weight loss in both diet groups in our review was accompanied by reductions in average DBP and SBP in all trials. In line with the weight loss findings, there is probably little or no difference in SBP changes after 3–6 months and there may be little or no difference in DBP changes between the low CHO and balanced diet groups. After 1–2 years, there is probably little or no difference in changes in DBP and SBP between the diet groups. These judgements are based on both the meta-analyses and the quality of the evidence for these outcomes per length of follow-up category.

When considering blood lipid changes, a weight loss of 5 kg to 8 kg is reported to result in LDL cholesterol reduction of approximately 0.13 mmol/L and an increase in HDL cholesterol of between 0.05 to 0.08 mmol/L [44]. In overweight and obese adults with and without CVD risk who lose 3 kg on a lifestyle intervention, a weighted reduction in serum TG of approximately 0.17 mmol/L is observed [44]. In the trials in our review, effects on blood lipids and FBG with low CHO and balanced diets were variable, with greater and lesser average changes in LDL, HDL and TG than the observations described above. When comparing low CHO and isoenergetic balanced diets, the pooled mean differences across the trials and quality of evidence indicate that there is probably little or no difference in changes in LDL, HDL and total cholesterol and there may be little or no difference in TG change at 3–6 months. Similarly, after 1–2 years, there is probably little or no difference in serum LDL and total cholesterol and TG between the diet groups. Meta-analysis of HDL cholesterol difference was 0.04 mmol/L higher with low CHO diets compared to balanced diets after 1–2 years, but the difference was not clinically meaningful, and no difference was detected for LDL.

The primary reason for the moderate grade of evidence in most outcomes at 3–6 months and 1–2 years is the risk of selection, performance and attrition bias in most included trials. For serum triglycerides, inconsistency (as discussed above) in effects resulted in further downgrading to low quality indicative of less confidence in the findings. Similarly, for DBP at 3–6 months, inconsistency in the mean differences across the different trials resulted in further downgrading to low quality evidence. This inconsistency could not be explained by the different variants of the low CHO diet. Most of the inconsistency can be ascribed to two trials [32,41] with similar weights in the meta-analysis (19.5% and 15.5%, respectively) that produced significant opposite mean differences for DBP. Klemsdal and colleagues [32] found that the low CHO diet reduced DBP more than the balanced diet (–3.40 mmHg, 95%CI 2.02 to 6.78). They reported that this observation should be interpreted with some caution, since blood pressure was a secondary endpoint in the study and the effect on SBP did not differ between the two groups. This effect was no longer significant at one year. In contrast, Wycherley and colleagues [41] reported a greater reduction in DBP with the balanced diet compared to the low CHO diet (4.00 mmHg, 95%CI 0.58 to 7.42). Similarly, this difference in effect was not found for SBP and disappeared at one year. The heterogeneity may also be attributable to differences in dietary adherence, as well as mean baseline DBP in one trial [27] that could be judged as being imbalanced (85.8 and 80.7 mmHg in low CHO and balanced diet groups, respectively). Although not reported, it could be argued that differences in the sodium and potassium content of the intervention diets may explain some of the variable effects on DBP.

**Overweight and obese adults with type 2 diabetes mellitus**

**Weight loss.** Both low CHO diets and balanced weight loss diets showed similar weight loss on average after 3–6 months and...
Table 12. Summary of findings for low carbohydrate diets compared with balanced diets for overweight and obese adults with type 2 diabetes mellitus at 3–6 months follow-up.

| Outcomes                  | Balanced diets | Low carbohydrate diets | No. of participants (studies) | Quality of the evidence (GRADE) |
|---------------------------|----------------|-------------------------|-------------------------------|--------------------------------|
| Weight loss               | Lower by 3.08 to 5.4 kg | 0.82 kg less weight lost | 599                           | ⬠ibaba ⬠ibaba ⬠ibaba ⬠ibaba |
| HbA1c                     | Lower by 0.3 to 0.51% | 0.19% higher HbA1c      | (5 studies)                   | low¹²                             |
| Diastolic blood pressure  | From 3 lower to 1.63 mmHg higher | 0.77 mmHg higher diastolic blood pressure | 545                       | ⬠ibaba ⬠ibaba                          |
| Systolic blood pressure   | Lower by 0.06 to 8 mmHg | 0.61 mmHg higher systolic blood pressure | 545                       | ⬠ibaba ⬠ibaba                          |
| LDL cholesterol           | From 0.11 lower to 0.09 mmol/L higher | 0.06 mmol/L higher LDL cholesterol | 599                      | ⬠ibaba ⬠ibaba ⬠ibaba ⬠ibaba         |
| HDL cholesterol           | From 0.01 lower to 0.03 mmol/L higher | 0.01 lower HDL cholesterol | 679                      | ⬠ibaba ⬠ibaba ⬠ibaba ⬠ibaba         |
| Total cholesterol         | Lower by 0.01 to 0.31 mmol/L | 0.04 mmol/L higher total cholesterol | 670                      | ⬠ibaba ⬠ibaba ⬠ibaba ⬠ibaba         |
| Triglycerides             | From 0 to 0.45 mmol/L lower | 0.20 mmol/L lower triglycerides | 252                      | ⬠ibaba ⬠ibaba ⬠ibaba ⬠ibaba         |

CI: Confidence interval; aNote this is the univariate average change observed between follow-up and baseline in the control group. GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. ¹Downgraded by 1 for imprecision: difference in mean weight loss ranges from a loss of 1.25 to a gain of 2.9 kilograms. ²Downgraded by 1 for risk of bias: 1 out of 5 studies did not report adequate sequence generation and 3 out of 5 studies did not report adequate allocation concealment. ³Downgraded by 1 for risk of bias: 1 of 5 studies did not report adequate sequence generation and 3 out of 5 studies did not report adequate allocation concealment. 4Downgraded by 1 for imprecision: difference in mean systolic blood pressure ranges from a reduction of 3.14 to an increase of 4.36 mmHg. ⁵Downgraded by 1 for risk of bias: 1 of 4 studies did not report adequate sequence generation and 3 of 4 studies did not report adequate allocation concealment. ⁶Downgraded for risk of bias: 3 of 4 studies did not report adequate sequence generation and 2 studies did not report adequate allocation concealment. ⁷Downgraded by 1 for imprecision: confidence interval range is 0.5 mmol/L.

doi:10.1371/journal.pone.0100652.t012

after 1–2 years. Meta-analysis and quality of evidence indicate that in overweight and obese adults with type 2 diabetes there may be little or no difference in weight loss after 3–6 months and 1–2 years. The earlier discussion of the long-term effects of dieting on weight loss is also applicable in this population.

Impacts on glycaemic control and cardiovascular risk. Weight loss is associated with improvements in glycaemia in overweight and obese adults with type 2 diabetes. According to the 2013 AHA/ACC/TOS Guideline, 2% to 5% weight loss achieved with one to four years of lifestyle intervention results in modest reductions in FBG and lowering of HbA1c by 0.2% to 0.3% [44]. Along with weight loss in both diet groups in our included trials, both low CHO and balanced diet groups showed similar reductions in average HbA1c in most trials after 3–6 months. At 1–2 years average HbA1c change was more variable. Comparing these changes by combining data across trials indicated that there is probably little or no difference in changes in HbA1c between the two diets at 3–6 months and 1–2 years. The meta-analysis at 3–6 months of two small trials [25,40] showed similar findings for FBG concentrations. Only one of these trials went on to report FBG at 15 months and had the same finding [25].

Effects on DBP with low CHO and balanced diets were variable in most trials, showing both reductions and increases. Both the low
CHO and balanced weight loss diets demonstrated reductions in average SBP in all trials after 3–6 months, but effects were variable with both diets after 1–2 years. Based on both the meta-analyses and the quality of the evidence, there is probably little or no difference in DBP change between the two diets and there may be little or no difference in SBP change after 3–6 months. After 1–2 years, there is probably little or no difference in changes in both DBP and SBP.

Effects on blood lipids with low CHO and balanced diets were variable between included trials, as was seen in the non-diabetic population. Considering the meta-analyses and the quality of the evidence, there is probably little or no difference in changes in LDL, HDL and total cholesterol after 3–6 months and 1–2 years when comparing the two diets. There may be little or no difference in changes in TG concentrations after 3–6 months and 1–2 years.

As in the non-diabetic overweight and obese population, the presence of risk of selection, performance and attrition bias in most included trials were the primary reasons for the moderate grade of evidence in most outcomes in the diabetic population. For weight loss at 3–6 months and 1–2 years follow-up, imprecision of the effect estimates resulted in further downgrading to low quality evidence. Similarly, the evidence for triglycerides for both follow-up categories and for SBP at 3–6 months was downgraded due to imprecision of the effect estimates. These imprecise estimates possibly relate to the smaller samples in the diabetes population.

Adherence

Assessment of adherence to energy prescriptions across the 19 trials was problematic due to the different methods used to express prescriptions and the lack of reported energy intake data in some trials. The dietary intake methodology used also varied between the included trials, with trials using food records/diaries, single or multiple 24 hour recalls, food frequency questionnaires or combinations of these methods.

From the calculated adherence scores it was clear that strict adherence to prescribed macronutrient goals failed with both diets in most trials and generally declined with longer follow-up. This diminished adherence after the first few months has been well documented in weight loss trials [48–51] and is more likely in weight loss diets involving extreme dietary changes such as drastic restrictions of entire food groups. This is supported by the fact that trials of low CHO diets have reported a very low incidence of urinary ketosis after six months [49–51], which suggests that most overweight participants in weight loss trials struggle to sustain a low intake of CHO. It could thus be argued that overweight participants following reduced energy weight loss diets in trials tend to revert to their usual macronutrient intakes over time, but may nonetheless, be able to lose weight if they are able to maintain the energy deficit. The novelty factor attached to a particular diet, media attention, and the opinion of the researchers involved could possibly affect the adherence of participants to any type of diet. It is clear from this and other research [52] that one of the pertinent issues in the treatment of overweight and obesity relates to the improvement of behavioural adherence to reduced dietary energy intake. It should be noted that the adherence score is based on calculations using mean reported intakes of macronutrients (% of total energy) and thus does not consider the variation around the mean.

Overall completeness and applicability of evidence

The findings of our review need to be interpreted in light of the presence of risk of bias or lack of power or both in many of the included trials, the possibility that adherence to dietary macronutrient goals were not optimal and that there was inter-trial variation in quantity (and type) of fat consumed. The interpretation of many weight loss trials is limited by a lack of blinded ascertainment of the outcome, small samples, large loss to follow-up, potentially limited generalisability and a lack of data on adherence to assigned diets [53]. These limitations all apply to the...
Strengths of our review include the clear definitions used in relation to the energy content and macronutrient composition of treatment and control diets, as well as the restriction of included studies to those testing diets only thereby reducing the risk of confounding by co-interventions. By considering only isoenergetic comparisons we also avoided the problem of the effect of energy imbalance between the comparison groups being confounded with any potential effect of macronutrient manipulation on the outcomes being investigated. Furthermore, we only included studies with follow-up of 12 weeks or more to allow for sufficient time to detect weight and CVD risk factor changes and assessed outcomes at defined lengths of follow-up. These methods differentiate our systematic review from previous reviews on this topic.

Our results show that the weight loss in overweight and obese subjects with or without diabetes on isoenergetic low CHO or balanced weight loss diets was similar at 3–6 months and at 1–2 years. Thus, the weight loss is the result of a reduction in total dietary energy intake rather than manipulation of macronutrient contribution. It follows that when considering dietary strategies for weight loss, less emphasis should be placed on an ‘ideal’ macronutrient composition and more emphasis on reduction in total energy intake, as well as improvement of behavioural adherence to reduced energy intake. This will go a long way to ensure that weight loss is achieved and maintained to gain health benefits.

Table 13. Summary of findings for low carbohydrate diets compared with balanced diets for overweight and obese adults with type 2 diabetes mellitus at 1–2 years follow-up.

| Patient or population: overweight or obese adults with type 2 diabetes | Settings: primary care | Intervention: low carbohydrate diets (high fat and high protein variants combined) | Comparison: balanced diets | Follow-up: 1–2 years after starting diet |
|---|---|---|---|---|
| Outcomes | Balanced diets | Low carbohydrate diets | No. of participants (studies) | Quality of the evidence (GRADE) |
| Illustrative range of change in average values from pre-diet levels by study: range across studies* | The effect difference with low carbohydrate diets in randomised comparison to balanced diets (95%CI) | | |
| Weight loss | Lower by 2.1 to 6 kg | 0.91 kg less weight lost | 492 | ⬠⬠⬠⬠ |
| | (could be 2.08 lost to a gain of 3.89) | (4 studies) | low | |
| HbA1c | From 0.28% lower to 0.4% higher | 0.01% higher HbA1c | 492 | ⬠⬠⬠⬠ |
| | (could be 0.28 lower to 0.3 higher) | (4 studies) | moderate | |
| Diastolic blood pressure | From 6 lower to 2.5 mmHg higher | 0.09 mmHg higher diastolic blood pressure | 492 | ⬠⬠⬠⬠ |
| | (could be 1.95 lower to 2.13 higher) | (4 studies) | moderate | |
| Systolic blood pressure | From 11 lower to 3.7 mmHg higher | 0.31 mmHg higher systolic blood pressure | 492 | ⬠⬠⬠⬠ |
| | (could be 3.1 lower to 3.72 higher) | (4 studies) | moderate | |
| LDL cholesterol | From 0.3 lower to 0.04 mmol/L higher | 0.10 mmol/L higher LDL cholesterol | 492 | ⬠⬠⬠⬠ |
| | (could be 0.06 lower to 0.27 higher) | (4 studies) | moderate | |
| HDL cholesterol | Higher by 0.02 to 0.19 mmol/L | No difference in HDL cholesterol | 492 | ⬠⬠⬠⬠ |
| | (could be 0.09 lower to 0.08 higher) | (4 studies) | moderate | |
| Total cholesterol | From 0.3 lower to 0.35 mmol/L higher | 0.10 mmol/L higher total cholesterol | 492 | ⬠⬠⬠⬠ |
| | (could be 0.09 lower to 0.08 higher) | (4 studies) | moderate | |
| Triglycerides | Lower by 0.1 to 0.3 mmol/L | 0.08 mmol/L lower triglycerides | 198 | ⬠⬠⬠⬠ |
| | (could be 0.49 lower to 0.26 higher) | (3 studies) | low | |

*Note this is the univariate average change observed between follow-up and baseline in the control group.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1Downgraded by 1 for risk of bias: 2 of 4 studies did not report adequate allocation concealment. 1 study had high total attrition (>20%) and 2 studies had differential attrition.

2Downgraded by 1 for imprecision: The 95% confidence interval includes both a loss of 2.08 kg and a gain of 3.89 kg.

3Downgraded by 1 for risk of bias: 2 of 4 studies did not report adequate allocation concealment, 2 studies had high total attrition (>20%), 2 studies had differential attrition.

4Downgraded by 1 for risk of bias: 1 of 3 studies did not report adequate allocation concealment. 2 studies had high total attrition (>20%), 2 studies had differential attrition.

5Downgraded by 1 for imprecision: confidence interval range is about 0.7 mmol/L.

doi:10.1371/journal.pone.0100652.t013
benefits. Guidance on macronutrient composition to meet nutritional requirements and prevent disease [12–15] remains integral to healthy sustainable weight management.

The small size and short duration of weight loss trials often account for their lack of definitive evidence of the effectiveness of dietary interventions on CVD risk. By contrast sound observational data, population-level interventions and “natural experiments” in whole populations have demonstrated a reduction in population risk with adoption of recommended, balanced dietary strategies to lower cardiovascular risk. For example, over the past three decades, levels of population cardiovascular risk factors have declined in Finland, with the greatest change being dietary behaviour (reduction in total and saturated fat and increased vegetables and fruit intake). These declines explain most of the observed decline in CHD mortality in the Finnish middle-aged population over this period [54]. Mortality due to coronary heart disease was reduced in Poland over a ten year period by partly replacing dietary saturated fats with polyunsaturated fats while maintaining a low intake of trans fatty acids [55]. A large prospective cohort study in 30 to 49 year old Swedish women (n = 43396; average follow-up 15.7 years) reported significantly increased incidence of cardiovascular disease overall (n = 1270) with a one tenth decrease in carbohydrate intake or increase in protein intake, or a two unit increase in the low carbohydrate-high protein score [9].

Our systematic review did not address macronutrient quality of the diets, specifically the quality of CHO and fat, which along with total macronutrient quantities and proportions, explains the effects of diet on cardiovascular risk [56]. The replacement nutrient is central to these effects. When foods high in CHO are avoided and replaced with high protein foods, reliance on animal protein sources becomes necessary since most foods with significant amounts of plant protein are also high in CHO (e.g. legumes). This reliance on animal protein will result in a greater intake of both total and especially saturated fat leading to higher serum HDL and LDL cholesterol over time. Substitution of saturated fat with polyunsaturated fats reduces coronary heart disease risk [57,58], while substitution with high glycaemic index CHO increases risk [59]. LDL-cholesterol is a causal risk factor for heart disease and reducing LDL cholesterol has been shown to be effective in reducing risk of heart disease irrespective of the presence of prior heart disease, age, sex, hypertension and diabetes [60–62]. Mendelian randomisation studies have demonstrated a 54% reduction in coronary heart disease risk per 1 mmol/l lower serum LDL cholesterol over a lifetime [62]. Treatment of elevated cholesterol levels reduces coronary heart disease risk, with clinical trials demonstrating a 24% reduction in risk per 1 mmol/l reduction in LDL over 5 years [60]. Furthermore, the role of ultra-processed products in the etiology and treatment of obesity and NCD is a pertinent consideration in this area [63,64]. The inconsistent changes in blood lipids and markers of diabetes risk with both diets in the trials may be attributable to differences in the quality of macronutrients in the intervention diets, for example, different intakes of saturated fat and/or types of carbohydrates (low or high glycaemic), an issue which was beyond the scope of our review. These inconsistences may also be attributable to participants not fully adhering to the prescribed total macronutrient goals for each of the diets, as evident from the adherence data.

Any dietary guidelines for health should be sustainable in the long-term, specifically in terms of ease of adherence, availability and affordability of foods, as well as social and cultural acceptability. Bearing this in mind, the dietary approach for weight management should be one that is nutritionally sound, not harmful and feasible to maintain over time. Such diets can be tailored to the needs of individuals on the basis of each individual’s complete health and risk profile, for example existing lipid abnormalities and comorbidities, as well as food preferences, socioeconomic circumstances and personal and cultural preferences, thereby improving the chances of longer term success. Suitably qualified healthcare professionals should guide the tailoring of dietary advice for individuals. Monitoring and follow-up by a healthcare professional during a dietary weight loss intervention is known to positively affect outcomes [16]. The demonstrated value of combining dietary and other positive lifestyle interventions such as increased physical activity for weight loss and reduction of cardiovascular risk, is also important to keep in mind [65,66].

![Figure 6. Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes for weight loss (kg) at 1–2 years.](doi:10.1371/journal.pone.0100652.g006)
Potential biases in the review process
Three prominent electronic databases were searched and two authors carried out the various steps in the review (screening and selecting, extracting, risk of bias assessment, analysing, collation and interpretation). Although we planned not to include non-English randomised controlled trials, we did not come across any potentially eligible studies that we needed to exclude based on language.

Conclusions
Trials show weight loss in the short-term irrespective of whether the diet is low CHO or balanced in terms of its macronutrient composition. There is probably little or no difference in weight loss and changes in cardiovascular risk factors up to two years of follow-up when overweight and obese adults, with or without type 2 diabetes, are randomised to low CHO diets and isoenenergetic balanced weight loss diets.

Supporting Information
PRISMA Checklist S1

Support Information S1 A critical summary of existing systematic reviews.

Support Information S2 Forest plots of meta-analyses in overweight and obese adults without type 2 diabetes mellitus. Figure S2A: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults for body mass index (kg/m²) at three to six months. Figure S2B: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults for body mass index (kg/m²) at one year. Figure S2C: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults for systolic blood pressure (mmHg) at three to six months. Figure S2D: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults for diastolic blood pressure (mmHg) at three to six months.

Support Information S3 Forest plots of meta-analyses in overweight and obese adults with type 2 diabetes mellitus. Figure S3A: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for body mass index (kg/m²) at three to six months. Figure S3B: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for body mass index (kg/m²) at two years. Figure S3C: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for fasting blood glucose (mmol/L) at three to six months. Figure S3D: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for HDL cholesterol (mmol/L) at three to six months. Figure S3E: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for LDL cholesterol (mmol/L) at three to six months. Figure S3F: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for total cholesterol (mmol/L) at three to six months. Figure S3G: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for triglycerides (mmol/L) at three to six months. Figure S3H: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for glycosylated hemoglobin (%) at three to six months. Figure S3I: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for HDL cholesterol (mmol/L) at 15 months. Figure S3J: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for systolic blood pressure (mmHg) at three to six months. Figure S3K: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for LDL cholesterol (mmol/L) at three to six months. Figure S3L: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for HDL cholesterol (mmol/L) at three to six months. Figure S3M: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for HDL cholesterol (mmol/L) at three to six months. Figure S3N: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for HDL cholesterol (mmol/L) at one to two years. Figure S3O: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults with type 2 diabetes mellitus for triglycerides (mmol/L) at one to two years. Figure S3P: Forest plot of low carbohydrate versus balanced diets in overweight and obese adults for fasting blood glucose (mmol/L) at one to two years.

Acknowledgments
We acknowledge Elizabeth Pienaar for searching EMBASE.
Conceived and designed the experiments: CN AS MS TY PG JV. Performed the experiments: CN AS. Analyzed the data: CN AS.

References

1. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, et al. (2011) The global obesity pandemic: shaped by global drivers and local environments. Lancet 378: 804–814.

2. World Health Organization (2004) Global strategy on diet, physical activity and health. World Health Assembly Resolution 57.17. Geneva: World Health Organization.

3. World Health Organization (2010) Global status report on noncommunicable diseases 2010. Geneva: World Health Organization.

4. Abogum D, Smiley CD, Adam T, Orwepom M, Strong K (2007) The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 370: 1929–1938.

5. World Health Organization (2008) The global burden of disease: 2004 update. Geneva: World Health Organization, 2008. Geneva: World Health Organization.

6. Atkins Nutritional (2011) New Atkins. http://sa.atkins.com/. Atkins Nutritional.

7. WebMD (2012) The Atkins Diet. http://www.webmd.com/diet/atkins-diet-overview#webMD.

8. Noakes TD, Brinkworth GD (2004) Long-term low-carbohydrate and high-fat intake can manage obesity and associated conditions: Occasional survey. S Afr Med J 103: 826–830.

9. Lajugui P, Sandin S, Lof M, Trichopolous D, Adami HO, et al. (2012) Low-carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. BMJ 344: e0026.

10. Noto H, Goto A, Tsujimoto T, Noda M (2013) Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. Nutr Metab Cardiovasc Dis 23: 455–460.

11. Sjogren P, Becker W, Warenjo E, Olsson E, Byberg L, et al. (2010) Mediterranean and carbohydrate-restricted diets and mortality among elderly men: a cohort study in Sweden. Ann J Clin Nutr 92: 967–974.

12. Australian National Health and Medical Research Council and the New Zealand Ministry of Health (2006) Nutrient Reference Values for Australia and New Zealand: Including Recommended Dietary Intakes. Canberra: Australian National Health and Medical Research Council and the New Zealand Ministry of Health.

13. EFSA Panel on Dietetic Products Nutrition and Allergies (NDA) (2010) Dietary Reference Values Parma: European Food Safety Authority (EFSA).

14. Institute of Medicine Food and Nutrition Board (2002/2005) Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, DC: National Academies Press.

15. NNR Project Group (2004) Nordic Nutrition Recommendations NNR 2004. Working Group on Diet and Nutrition, NKF, Nordic Committee of Senate Officials for Food Issues, EK-Livs.

16. Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, et al. (2009) Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 360: 859–873.

17. Higgins D, Green S, editors (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.1 [updated March 2011]. London: John Wiley & Sons, Ltd.

18. Renger AC (2002) Characterizing and displaying multivariate data. Methods of Multivariate Analysis. Hoboken NJ: John Wiley, pp. 43–81.

19. The Nordic Cochrane Centre: The Cochrane Collaboration (2011) Review Manager (RevMan) 5.1 ed. Copenhagen: The Cochrane Collaboration, 2011.

20. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539–1558.

21.GRADE Working Group (2004–2007) GRADEprofiler (GRADEpro). 3.2.2 ed. The Nordic Cochrane Centre: The Cochrane Collaboration (2011) GRADEprofiler (GRADEpro).

22. Glenton C, Santesso N, Rosenbaum S, Nilsen ES, Rader T, et al. (2010) Presenting the results of Cochrane Systematic Reviews to a consumer audience: a qualitative study. Med Decis Making 30: 566–577.

23. Rencher AC (2002) Characterizing and displaying multivariate data. Methods of Multivariate Analysis. Hoboken NJ: John Wiley, pp. 43–81.

24. Wrote the paper: CN AS MS TY PG JV. Contributed reagents/materials/analysis tools: CN AS MS TY PG JV. Wrote the paper: CN AS MS TY PG JV.
body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 88: 1617–1623.
49. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, et al. (2003) A randomized trial of a low-carbohydrate diet for obesity. New England Journal of Medicine 348: 2082-2090.
50. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Wittev S, et al. (2008) Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 359: 229–241.
51. Yancy WS, Jr., Olsen MK, Guyton JR, Bakst RP, Westman EC (2004) A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 140: 769–777.
52. Allison S, Kim S, Bersamin A, King AG, Gardiner CD (2008) Dietary adherence and weight loss success among overweight women: results from a TTO Z weight loss study. Int J Obes (Lond) 32: 985–991.
53. Simons-Morton DG, Oharazane E, Cutler JA (2006) Obesity research - limitations of methods, measurements, and medications. JAMA 295: 626-629.
54. Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Mannisto S, et al. (2010) Effect of low-carbohydrate diet on postprandial lipids in type 2 diabetic patients. Diabetes Care 33: 2168-2173.
55. Zatonski WA, Willett W (2005) Changes in dietary fat and declining coronary heart disease in Poland: population based study. BMJ 331: 187–189.
56. Mensink RP, Zock PL, Kester AD, Katan MB (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. N Engl J Med 349: 239–249.
57. Jakobson MU, O’Reilly EJ, Heimtall BM, Pereira MA, Balter K, et al. (2009) Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 89: 1425–1432.
58. Maasfrank D, Schuha R, Wallace S (2009) Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 7: e1000252.
59. Jakobson MU, Detlefsen C, Joensen AM, Stegger J, Tjønneland A, et al. (2010) Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. Am J Clin Nutr 91: 1764–1768.
60. Bairey C, Kech S, Kearney PM, Blackwell L, Buck G, et al. (2005) Efficiency and safety of niacin-flavoring treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 366: 1267-1278.
61. Cohen JC, Boerwinkle E, Mosley TH, Jr, Hobbs HH (2006) Sequence variations in PCSK9, LDLR, and ApoB affect low-density lipoprotein cholesterol and myocardial infarction risk. N Engl J Med 354: 1245–1254.
62. Ferrante BA, Yoo W, Alesh I, Mahajan N, Mirovskaa KK, et al. (2012) Effect of long-term exposure to lower density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol 60: 2631–2639.
63. Monteiro CA, Moubarac JC, Cannon G, Ng SW, Popkin B (2013) Ultra-processed products are becoming dominant in the global food system. Obes Rev 14 Suppl 2: 21–28.
64. Ismaeil KA, O'Sullivan C, Saari D (2004) Comparison of a low-fat diet to a Mediterranean diet on biomarkers of metabolic syndrome in Emirati adults. Journal of Nutrition 139: 1061–1067.
65. Ashton EL, Pommeroy S, Foster JE, Kaye RS, Nester PJ, et al. (2000) Diet high in monounsaturated fat does not have a different effect on arterial elasticity than a low-fat, high-carbohydrate diet. Journal of the American Dietetic Association 100: 337-342.
66. Baha NH, Sasaia S, Torbay N, Habbal Z, Azar S, et al. (1999) High protein vs high carbohydrate hyperoxygenic diet for the treatment of obese hyperinsulinemic subjects. Int J Obes Relat Metab Disord 23: 1202–1206.
67. Bradley U, Spence M, Courtney CH, McKinley MG, Enni CN, et al. (2009) Low-fat versus low-carbohydrate weight reduction diets: effects on weight loss, insulin resistance, and cardiovascular risk: a randomized controlled trial. Diabetes 58: 2741–2748.
68. Boardman J, Verca S, Tranchina MR, Cotrone S, Ceresa G (2009) Effects of hypothalamic very-low-carbohydrate diets on body composition and food intake in obese subjects. Am J Physiol Regul Integr Comp Physiol 297: R1282–R1290.
69. Braden J, Nirta P, Orm M, Johansson J, Ekelund U, et al. (2011) Low-carbohydrate diet with postprandial insulin levels in type 2 diabetes. Diabetologia 54: 2168-2173.
70. Yancy WS, Jr., Foster JE, Kaye RS, Nester PJ, et al. (2000) Diet high in monounsaturated fat does not have a different effect on arterial elasticity than a low-fat, high-carbohydrate diet. Journal of the American Dietetic Association 100: 337-342.
71. Brown SP, Sapp S, Brancatelli G, Ascherio A, Colditz GA, et al. (2009) Low-carbohydrate, high-fat diet vs low-fat diet in overweight or obese individuals. Int J Obes (Lond) 33: 175–182.
72. Brehm SJ, Apovian CM,刻 M, Szatrowski TP, Smith SR, et al. (2003) A comparison of low-carbohydrate and low-fat diets for weight loss in obese adults. N Engl J Med 348: 1833–1840.
100. Miller M, Beach V, Sorkin JD, Mangano C, Dobmeier C, et al. (2009) Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA 297: 969–977.

101. Layman DK, Evans E, Baum JJ, Selyer J, Erickson DJ, et al. (2005) Dietary Protein and Exercise Have Additive Effects on Body Composition during Weight Loss in Adult Women. The Journal of Nutrition 135: 1903-1910.

102. Sebregts EH, Falger PR, Bar FW, Kester AD, Appels A (2003) Cholesterol reduction, mainly of VLDL subclasses, and C-reactive protein levels of hypertriglyceridemic weight loss in women participating in a Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 343: 1454-1459.

103. Shaper GD, Kristal AR, Withell LH (1998) Weight loss in women participating in a Mediterranean-style diet. Am J Clin Nutr 54: 821-828.

104. Chen YD, Coalston AM, Zhou MY, Holleburn CR, Reaven GM (1995) Why do low-fat/high-carbohydrate diets accentuate postprandial lipemia in patients with NIDDM? Diabetes Care 18: 10–16.

105. Ehrmann-Moes M, Boehm U, Wittmann R, Thomas U, Ditschuneit HH (2010) Enhanced weight loss with protein-enriched meal replacements in subjects with the metabolic syndrome. Diabetes Metab Res Rev 26: 393–405.

106. Trexyon L, Chen S, Hong K, Yan E, Carpenter CL, et al. (2008) A controlled trial of protein enrichment of meal replacements for weight reduction with retention of lean body mass. Nutrition Journal 7: 23.

107. Gardner CD, Kiazzend A, Ahlasan S, Kim S, Stafford RS, et al. (2007) Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA 297: 969–977.

108. Larsen TM, Dalskov SM, van Baak M, Jebb SA, Papadaki A, et al. (2010) Diets compared with high fat, low fat, or low carbohydrate restriction for weight loss, cardiovascular risk factors, and weight maintenance. New England Journal of Medicine 363: 2102–2113.

109. Hockaday TD, Hockaday JM, Mann JJ, Turner RC (1978) Prospective comparison of modified fat/high-carbohydrate with standard low-carbohydrate dietary advice in the treatment of diabetes: one year follow-up study. Br J Nutr 39: 357–362.

110. Rico M, Ozenez M, Corella D, Saez G, Estruch R, et al. (2007) Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Arch Intern Med 167: 1195–1203.

111. Wasterkar RD, Marsh RD, Sneddon M, Mihalyko M, Wasterkar B, et al. (2009) Comparison of the effects of four commercially available weight-loss programmes on lipoprotein cardiovascular risk factors. Public Health Nutrition 12: 1700–1704.

112. Walker KZ, O'dea K, Nicholson GC, Muir KG (1995) Dietary composition, body weight, and NIDDM. Comparison of high-fiber, high-carbohydrate, and low-carbohydrate diets. Diabetes Care 18: 401–403.

113. Dansinger ML, Gleason JA, Griffin JI, Selker HP, Scharf EJ (2005) Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 293: 43–53.
173. Leidy HJ, Carnell NS, Mattes RD, Campbell WW (2007) Higher protein diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. Diabet Med 24: 1430–1435.

174. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, et al. (2010) Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. Ann Intern Med 153: 147–157.

175. Fleming RM (2002) The effect of high-, moderate-, and low-fat diets on weight loss and cardiovascular disease risk factors. Prev Cardiol 5: 110–118.

176. Due A, Larsen TM, Hermansen K, Stender S, Holst JJ, et al. (2008) Reduction of low-density lipoprotein cholesterol and triglycerides by a low-fat diet. J Lipid Res 49: 2078–2081.

177. Noakes M, Kegoh JB, Foster PR, Clifton PM (2005) Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. Am J Clin Nutr 81: 1299–1306.

178. Patterson RE, Hutchinson F (2004) Dietary adherence in the Women’s Health Initiative Dietary Modification Trial. Journal of the American Dietetic Association 104: 654–658.

179. Raatz SK, Torkelson CJ, Redmon JB, Reck KP, Kwong CA, et al. (2005) Reduced glycemic index and glycemic load diets do not increase the effects of energy restriction on weight loss and insulin sensitivity in obese men and women. Journal of Nutrition 135: 2387–2393.

180. Rodriguez-Hernandez H, Morales-Amaya UA, Rosales-Valdez R, Rivera-Hinojosa F, Rodriguez-Moran M, et al. (2009) Prevention of cardiovascular risk factor elevations in healthy premenopausal women. Prev Med 49: 509–517.

181. Skov AR, Toubro S, Ronn B, Holm L, Astrup A (1999) Randomized trial on protein vs carbohydrate restriction for the treatment of obesity. Int J Obes Relat Metab Disord 23: 528–536.

182. Seshadri P, Samaha FF, Stern L, Chicano KL, Daily DA, et al. (2005) Free fatty acids, insulin resistance, and corrected QT intervals in morbid obesity: effect of weight loss during 6 months with different dietary interventions. Obes Surg 15: 254–259.

183. Skov AR, Toubro S, Ronn B, Holm L, Astrup A (2000) Insulin sensitivity after a reduced-fat diet and a monoene-enriched fatty acid diet in type 2 diabetic subjects. Diabet Med 17: 390–403.

184. Due A, Larsen TM, Hermansen K, Stender S, Holst JJ, et al. (2008) Reduced glycemic index and glycemic load diets do not increase the effects of energy restriction on weight loss and insulin sensitivity in obese women. Obesity (Silver Spring) 15: 421–429.

185. Seshadri P, Samaha FF, Stern L, Chicano KL, Daily DA, et al. (2003) A low-carbohydrate as compared with a low-fat diet in severe obesity. New England Journal of Medicine 348: 1997–2003.

186. Skov AR, Toubro S, Ronn B, Holm L, Astrup A (1999) Randomized trial on protein vs carbohydrate restriction for the treatment of obesity. Int J Obes Relat Metab Disord 23: 528–536.

187. MacManus K, Antinoro L, Sacks F (2001) A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. Int J Obes Relat Metab Disord 25: 1503–1511.

188. Rodriguez-Hernandez H, Morales-Amaya UA, Rosales-Valdez R, Rivera-Hinojosa F, Rodriguez-Moran M, et al. (2009) Prevention of cardiovascular risk factor elevations in healthy premenopausal women. Prev Med 49: 509–517.

189. Ben-Avraham S, Harman-Boehm I, Schwarzfuchs D, Shai I (2009) Dietary fat modifications and blood pressure in subjects with the metabolic syndrome in the LIPGENE dietary intervention study. Br J Nutr 104: 1600–1604.

190. Brinkworth GD, Noakes JD, Brinkworth GD, Kegoh JB, Clifton PM (2006) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 90: 23–32.

191. Dacie V, Lamac B, Charest A, Tremblay AJ, Couture P (2012) Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 61: 76–83.

192. Brinkworth GD, Noakes JD, Brinkworth GD, Kegoh JB, Clifton PM (2006) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 90: 23–32.

193. Dacie V, Lamac B, Charest A, Tremblay AJ, Couture P (2012) Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 61: 76–83.

194. Brinkworth GD, Noakes JD, Brinkworth GD, Kegoh JB, Clifton PM (2006) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 90: 23–32.

195. Dacie V, Lamac B, Charest A, Tremblay AJ, Couture P (2012) Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 61: 76–83.

196. Brinkworth GD, Noakes JD, Brinkworth GD, Kegoh JB, Clifton PM (2006) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 90: 23–32.

197. Dacie V, Lamac B, Charest A, Tremblay AJ, Couture P (2012) Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 61: 76–83.

198. Brinkworth GD, Noakes JD, Brinkworth GD, Kegoh JB, Clifton PM (2006) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 90: 23–32.

199. Dacie V, Lamac B, Charest A, Tremblay AJ, Couture P (2012) Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 61: 76–83.

200. Brinkworth GD, Noakes JD, Brinkworth GD, Kegoh JB, Clifton PM (2006) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. Am J Clin Nutr 90: 23–32.

201. Dacie V, Lamac B, Charest A, Tremblay AJ, Couture P (2012) Effect of short-term low- and high-fat diets on low-density lipoprotein particle size in normolipidemic subjects. Metabolism 61: 76–83.
208. Shikany JM, Margolis KL, Pettinger M, Jackson RD, Limacher MC, et al. (2010) Outcome expectations of a Low-Carbohydrate Diet on Appetite Hormones: A Randomized Controlled Trial Circulation 127: AP167.

207. Moore SD, King AC, Kiernan M, Gardner CD (2010) Effect of dietary carbohydrate restriction versus low-fat diet on flow-mediated dilation. Metabolism 59: 1769–1777.

206. McAuley KA, Hopkins CM, Smith KJ, McLay RT, Williams SM, et al. (2005) Comparison of high-fat and high-protein diets with a low-carbohydrate diet in insulin-resistant obese women. Diabetologia 48: 8–16.

205. Due A, Toubro S, Skov AR, Astrup A (2004) Effects of medium- or high-protein diets, on body weight in overweight subjects: a randomised 1-year trial. Int J Obes Relat Metab Disord 28: 1283–1290.

204. McAuley KA, Hopkins CM, Smith KJ, McLay RT, Williams SM, et al. (2005) Long-term effects of weight loss with a very low carbohydrate and low fat diet on flow-mediated dilation. Metabolism 54: 461–467.

203. Malec M, et al. (2010) A low-fat, high-complex carbohydrate diet supplement-associated with obesity or insulin resistance in humans. Eur Rev Med Pharmacol Sci 9: 161–165.

202. Malec M, et al. (2010) The effect of a low-carbohydrate, ketogenic diet program compared to a low-fat diet on insulin resistance in patients with metabolic syndrome. J Nutr 140: 1595–1601.

201. Malec M, et al. (2010) Effects of dietary fat modification on insulin sensitivity and on other risk factors of the metabolic syndrome–LIPGENE: a European randomized dietary intervention study. Int J Obes (Lond) 35: 800–809.

200. Malec M, et al. (2010) Long-term effects of popular dietary approaches on weight loss and features of insulin resistance. Am J Clin Nutr 94: 75–85.

199. Malec M, et al. (2010) Clinical efficacy of two hypocaloric diets that vary in overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab 12: 204–209.

198. Malec M, et al. (2010) The effect of a low-carbohydrate diet on adipocytokines and inflammatory markers: A randomized controlled trial. Circulation 127: AP166.

197. Malec M, et al. (2010) Relatively high-protein or ‘low-carb’ energy-restricted diets for body weight loss and body weight maintenance after significant weight loss in healthy overweight and obese subjects: does diet composition matter? Am J Clin Nutr 90: 1203–1214.

196. Malec M, et al. (2010) Low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab 12: 204–209.

195. Malec M, et al. (2010) Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. Diabetologia 48: 8–16.

194. Malec M, et al. (2010) Long-term effects of weight loss with a very low carbohydrate and low fat diet on flow-mediated dilation. Metabolism 54: 461–467.

193. Malec M, et al. (2010) Long-term effects of weight loss with a very low carbohydrate and low fat diet on flow-mediated dilation. Metabolism 54: 461–467.