A systematic review and meta-analysis comparing heterogeneity in body mass responses between low-carbohydrate and low-fat diets

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Keywords: inter-individual response, randomized control trial, ketogenesis, weight loss, personalized nutrition

Running title

Individual responses to different diets

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Conflict of Interest

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STUDY IMPORTANCE

What is already known about this subject?

- Both low-CHO and low-fat diets are popular amongst people who desire to reduce body mass and improve glycemic control.
- In the context of personalized and stratified nutrition, there is increasing interest in whether the responses to these diets differ between individuals.

What are the new findings in your manuscript?

- We synthesised the available dietary intervention trials and, for the first time, used a novel response variance comparison approach to see if individual differences in responses were similar or not between the two diets.
- We were unable to detect any clinically-relevant differences in individual response heterogeneity between the two diets.

How might your results change the direction of research or the focus of clinical practice?

- Our results indicate that more evidence is needed to support the notion of differences in response heterogeneity between low-CHO and low-fat diets.

ABSTRACT

An important notion in personalized medicine is that there is clinically relevant treatment response heterogeneity. Low-carbohydrate (CHO) and low-fat diets are widely adopted to reduce body mass. To compare individual differences in responses between two dietary interventions, a formal statistical comparison of response variances between study arms in a randomised controlled trial (RCT) is crucial. We compared change variances in RCTs for the body mass responses to low-CHO dietary interventions vs change variances for the low-fat groups (typically considered as the comparator intervention). A literature search identified relevant RCTs (*n*=25, 3340 participants). We extracted the means and standard deviations (SD) of body mass change in low-CHO and low-fat study arms to calculate the variances of individual responses. These were meta-analysed in a random effects model and converted to the SD for individual responses (SDir). The pooled SDir for body mass response was 1.4 kg (95%CI: –1.1 to 2.3) with a wide 95% prediction interval of –6.3 to 10.4 kg. We conclude that evidence is insufficient to suggest the response heterogeneity to low-carbohydrate diets differs from that observed with low-fat diets.

Keywords: inter-individual response, randomized control trial, ketogenesis, weight loss, personalized nutrition

INTRODUCTION

Low-carbohydrate (CHO) diets are common amongst people attempting to achieve weight (body mass) loss, and in the management of glycemic control in type 2 diabetes (1, 2, 3). Furthermore, interest in the more extreme low-CHO dietary approach, the ketogenic diet (<50 g CHO·day^{-1}), has increased over the last 10-20 years. There is some evidence that low-CHO diets elicit greater reductions in body mass than the traditional low-fat diet (4), although other evidence suggests that the loss of fat mass is marginally greater with low-fat diets (5). The authors of a recent commentary concluded that any difference in the body mass loss achieved between prescribed diets was not clinically meaningful in interventions exceeding one year, which is a crucial finding, given the chronic nature of obesity (6).

Popular approaches to achieve body mass loss include personalized and stratified nutrition, which tailor dietary strategies to optimize their effectiveness for specific individuals and populations, respectively (7). However, before a 'personalized' approach can be advocated, it is important to consider whether individuals respond differently to identical dietary interventions, referred to as "response heterogeneity" (8). Whilst ostensible differences in individual response may *appear* to exist in the treatment arm of a randomized control trial (RCT), a more robust approach is to compare response heterogeneity formally between different interventions, or an intervention and a comparator in the RCT (9, 10). Nonetheless, individual response variation is often reported from findings observed solely in an intervention group (11).

The standard deviation (SD) of responses derived solely from data in the intervention arm is not a robust estimate of response heterogeneity because it includes the confounding influence of within-subject variation, which is also present in another treatment or comparator arm (8, 9, 10). Recognition of this fact therefore questions several common practices, such as highlighting

individual responses only from the intervention group and correlating baseline status with response to identify 'responders' and 'non-responders' (i.e. "dichotomania"; (12)). A more robust approach to quantifying response heterogeneity is by comparing the SDs of pre-post changes between study arms in the RCT; differences between treatment and comparator response variability would appear as a higher SD of change in the treatment *versus* comparator group (8, 9).

It is important to note that within-subjects variability is not merely short-term test-retest measurement error but also includes the random variability that occurs over the much longer time periods in a weight-loss study, e.g. 6 to 52 weeks (8). Further, inter-individual response variation should be quantified relative to a minimal clinically important difference (MCID; e.g. weight-loss sufficient to improve health) before determinants of individual response can be identified or interpreted (9). If the inter-individual response variation does not exceed the MCID then 'true' inter-individual variation is not likely to be clinically important and as such any influence of hypothesized predictors of response also may not be clinically relevant.

The above "response variance comparison" approach has not yet been applied to explore the response heterogeneity in low-CHO compared to low-fat diets. Previous findings regarding other physiological responses have reported no greater change variance in intervention samples relative to the comparator (11, 13, 14, 15). While others have described a greater change variance in body composition metrics following exercise interventions vs a comparator group (16, 17). It is vital that any specific inter-individual variation in response to low-CHO diets (vs any such variation in low fat diets) is explored to inform personalized nutrition and optimize effectiveness. Therefore, we conducted a systematic review and meta-analysis to quantify the 'true' inter-individual response variation in RCTs on the body mass response following low-CHO and low-fat dietary interventions.

METHODS

Literature search strategy

The literature was previously searched for an earlier published review (18) and was subsequently updated to include studies published since that time. Detailed information of the previously used search strategy is available in Smith, Gonzalez (18). In brief, a range of databases (PubMed, Web of Science, Medline and SPORTDiscus) were searched with the following terms: "carbohydrate*" AND "body mass" OR "adiposity" OR "energy intake" OR "metabolic dysregulation" OR "cardiovascular disease"**.** Trials registered at 'clinicaltrials.gov' were also examined for potentially relevant studies. During the screening of potentially eligible papers, references lists were also examined for further relevant studies. Searches were restricted to English language papers only, published between 1990 and 2019.

Inclusion criteria

Studies of interest were randomized controlled trials of low-CHO diets *versus* at least one comparator condition (n.b. these comparators are not necessarily 'true' control diets in terms of a complete absence of dietary intervention or habitual dietary intake but rather included relevant comparisons of standardized low-fat hypocaloric diets typically used in weight-loss studies). Participants were aged 18 years and over, inclusive of both sexes, all levels of adiposity, and both healthy populations and those with established disease states (e.g. type 2 diabetes). Exposure duration was an intervention period of at least 3 months to ensure any body mass loss can be attributed to the dietary interventions and is not a results of short-term test-retest measurement error. Regarding the intervention condition; a threshold of 150 g CHO·day^{-1} was defined as a low CHO intake, based on the guidelines outlined by Burke, Hawley (19), while a ketogenic diet was defined as <50 g CHO·day^{-1} as agreed by the Academy of Nutrition and Dietetics and the British Dietetic Association (20, 21). Importantly, classification of intake

was based on the actual CHO consumption achieved by participants and not the prescribed intake (i.e. this review is primarily concerned with the variability in body mass response when the adhering to the specified diet, not variability in adherence to the specified diet). If the achieved dietary intake was not detailed, or this could not be calculated, studies were excluded. Studies prescribing a drug in either the intervention or comparator arm were also excluded. Notably, studies included in the previous review (18) were refined to only include parallel groups designs and a CHO intake meeting the defined criteria.

Data extraction

The mean change and SD of the change in body mass pre-post intervention were extracted for both intervention and comparator study groups. Where it was not possible to extract the required information from the manuscript, the authors were contacted for clarification. In studies providing standard error of the mean or confidence intervals (CI) for body mass change, the SD was calculated using reported approaches (22). When data from multiple sub-samples were reported either within individual studies or across different published papers, the issue of "double counting" was addressed by calculating pooled estimates of sample size, means and SDs according to equations reported by the Cochrane Collaboration (23). For one dataset, there were multiple publications divided according to duration of follow-up (24, 25, 26). A sensitivity analysis of this particular dataset (pooled and individual) was undertaken.

Data synthesis/ meta-analysis

Statistical analysis was conducted with Stata software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). A random-effects meta-analysis using a restricted maximum likelihood (REML) model along with the Knapp-Hartung method to reduce type-one error was conducted for the mean body mass change across studies to establish a mean treatment effect. For each study, the 'true' individual response variance was

quantified as the change in body mass in the intervention group minus the control group (SD^2_I – SD^2_C). The standard error (SE) for this variance was then calculated for each study as $\sqrt{[2(SD_{Exp}^4 /DF_{Exp} + SD_{Con}^4 /DF_{Con})]}$, where DF_{Exp} and DF_{Con} are the degrees of freedom of the SD in the intervention and control groups, respectively. The individual response variances and their SEs for each study were meta-analysed using a REML and the Knapp-Hartung method to give a pooled point estimate for the inter-individual variability (SDir) in body mass change. A 95% CI was calculated for both the mean body mass change and individual response variance. The tau statistic (τ) was used to calculate between-study heterogeneity.

To quantify the expected range of response variances expected for a future study, a 95% prediction interval was calculated using the tau statistic and the SE. The methods outlined by Swinton, Hemingway (10) were used to estimate the expected percentage of responders to a future similar intervention based on the pooled estimates of mean treatment effect and response SD, as well as a defined MCID. The threshold of the MCID was defined as 2.5 kg, as being both the smallest absolute reduction in fat mass associated with any clinical benefit (27), alongside being outside the typical range of fluctuation associated with acute hydration status under standardized conditions (28). This MCID is also a small meaningful change in body mass that could reasonably be expected in our minimum dietary duration of 3 months. A Funnel plot and Egger's regression analysis was used to scrutinize the presence of small study effects (publication) bias. Methodological risk of bias was examined according to the Cochrane guidelines (29), with each criteria judged as having a low, high, or unclear risk of bias. Risk of bias was independently assessed by two members of the research team, with discrepancies discussed and agreed upon. A risk of bias summary is presented in **figure 1** and **figure 2**, created with RevMan software (Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2014).

RESULTS

Study selection

Thirty-three studies which met inclusion criteria were identified. One study was excluded as it reported duplicate data to another study (30). It was not possible to extract the SD directly from the manuscript for eight of these studies. The authors of these papers were contacted and three responses were received of which two were able to provide raw data. The study which was unable to provide raw data was excluded along with the remaining five papers for which no response was received (31, 32, 33, 34, 35, 36). An additional study was excluded as it was not possible to obtain information regarding the number of participants in comparator and intervention groups that were used in reported body mass data (37). Therefore, 25 studies comprising 3340 participants were included in the final analysis. The included studies had follow-up periods ranging from 3 to 24 months, with sample sizes from 22 to 609. Studies predominantly replaced CHO with protein and fat to achieve a lower CHO intake, with the comparator groups typically undertaking a 'low-fat, high-CHO diet'. One study encompassed a 2-month very low energy diet (488 kcal/ day) followed by a 14-month period over which body mass regain was monitored (38). For this study the total body mass loss over the 16-month period was calculated as the body mass lost in the initial two months added to that regained over the 14-month dietary intervention. **Table 1** details the key characteristics of included studies. The majority of studies were deemed to display a low-to-unclear risk of bias (**Figures 1 and 2**).

Study outcomes

The pooled mean group difference in body mass change following the intervention (intervention minus comparator) was –1.3 kg (95% CI –2.1 to –0.5; **Figure 3A**). The between-study heterogeneity (τ) was 1.6 kg. The 95% prediction interval in mean body mass loss was -

4.8 to 2.2 kg, tau-squared was 2.7 kg. The pooled point estimate for the inter-individual variability in body mass change (SDir) was 1.4 kg (95% CI: –1.1 to 2.3; **Figure 3B**). The between-study heterogeneity (τ) was 3.6 kg and tau-squared was 13.4 kg. The 95% prediction interval for the overall SDir revealed that a future trial could have a SDir between –6.3 and 10.4 kg. A sub-group analysis was conducted stratifying studies according to CHO intake in the intervention group. For studies with an intervention group classified as a Ketogenic (n = 5) the SDir was –2.1 kg (95% CI: –4.1 to 2.9; Prediction interval, -5.2 to 4.3), while for the remainder of studies (n = 20) the SDir was 1.7 kg (95% CI: –1.0 to 2.5). Sensitivity analyses revealed little influence on the SDir of the analysis approach (i.e. intend-to-treat or completers) nor of multiple papers published from the same data set but reported in separate papers in completers' analyses. The Funnel plot and results of the Eggers regression analysis indicated little evidence of small study effect (publication) bias (slope = -0.23, P = 0.47) (Appendix A). We also undertook a sensitivity analysis to explore whether the magnitude of SDir was associated with the magnitude of mean treatment effect (39). We ran a meta-regression on the variances for individual response in each study with the mean treatment effect of each study as a predictor, and then converted to the SDir. The resulting meta-regression slope was shallow and not statistically significant (-1.2 kg/kg (95%CI: -1,8 to 0.56).

Using the approach described by Swinton, Hemingway (10) and Atkinson, Williamson (8), the pooled estimate of SDir of 1.4 kg was used to estimate the proportion of the population of interest who could be defined as exceeding the MCID of 2.5 kg in a future study. This proportion was estimated to be 20%. Nevertheless, the wide confidence and prediction intervals associated with the SDir also makes the estimate of this proportion somewhat imprecise.

DISCUSSION

This review examined whether published trials of low-CHO diets show any greater individual differences in the amount of weight-loss achieved compared to low-fat diets. Our approach was to calculate, for each study, the difference in pre-post change variance between the study arms (9, 10). Our results indicate that there is not enough sufficiently precise evidence to indicate any greater or lesser inter-individual variation in body mass response between low-CHO and low-fat diets. This finding is in agreement with previous studies also reporting a clinically trivial individual response variation in maximal oxygen uptake (11) and weight-loss (14) following exercise interventions or slightly lower, rather than higher, variability in the treatment *versus* control group in a range of different clinical trials (13, 15). Nevertheless, we highlight that in these latter studies, the comparator group was closer to being a "do nothing" control than in our study in which we compared two dietary interventions, although, low fat is typically designated the comparator group in these studies.

The overall SDir of 1.4 kg (–1.1 to 2.3) alongside the SDir of those studies classified as ketogenic, –2.1 kg (95% CI: –4.1 to 2.9) and non-Ketogenic, 1.7 kg (95% CI: –1.0 to 2.5) are all small and, in the case of ketogenic studies, negative. We also highlight the fact that the lower confidence limits of these estimates are negative in sign. This indicates a lack of evidence for inter-individual response variability directly particularly attributable to low-carbohydrate diets (i.e. the variability is at least no more than restricting the other major macronutrient) and relative to the inevitable random within-subjects variability in body mass that naturally occurs over periods of several months or more. Further, the overall SDir is similar to the pooled mean group difference in body mass change of –1.3 kg (95% CI: –2.1 to –0.5). The 95% CIs and prediction intervals (–6.3 to 10.4 kg) are wide and overlap zero considerably, highlighting the imprecision in the estimate of inter-individual response variability. This evidence in combination suggests there is insufficient evidence for any greater or lesser 'true' inter-

individual response variation to low-CHO diets relative to the comparable low-fat diets in the trials conducted to date.

The negative SDir reported in the Ketogenic studies is probably attributable to an absence of 'true' treatment heterogeneity combined with random sampling error given that there were only five studies, which also involved small sample sizes (8). We cannot completely rule-out the possibility that subsets of individuals may respond differently to a clinically relevant level to a low CHO diet, but we maintain that this is unlikely, especially if any differences in subsets at baseline is adjusted for using an appropriate ANCOVA model (6, 7). More trials with greater sample sizes will improve the precision of response heterogeneity estimates in the future. Nevertheless, our findings indicate that there is currently insufficient evidence to conclude that different individuals have innately different response characteristics to either dietary intervention, rendering the mean treatment effect as the most informative statistic when contrasting dietary interventions. Importantly, although no difference in individual response variation was detected between low-CHO and low-fat dietary interventions, clinicians and dieticians are still required to treat individuals with obesity. Consequently, whilst not anticipating any innate difference in individual variation between low-CHO and low-fat diets, clinicians may be advised to consider that individual variation to dietary composition may be context dependent.

In an attempt to explain the lack of inter-individual response variation, we considered whether the comparator groups were assigned to a high-CHO diet or a 'true' control of maintaining habitual CHO intake. This threshold of a 'high' CHO diet was taken to be >240 g CHO·day^{-1} based on the mean reported CHO intake in the comprehensive report published by the Scientific Advisory Committee on Nutrition for the United Kingdom government (40). Intake in the comparator group exceeded 240 g CHO·day^{-1} in only one study (41), so the lack of individual variation to low-CHO dietary interventions is not due to a varied or 'high' CHO intake in the

comparator group. Further, fat intake in the comparator, low fat diets was 49 ± 8 g total fat·day^{-1} suggesting the lack of individual response variation was not as a result of a highly varied fat consumption in the comparator diets.

Limitations

The comparator groups were heterogenous in nature, with the absence of a typical control group comprising a 'habitual' diet in any of the studies. Hence, the low-CHO diets are not compared to identical control diets, instead the majority of studies have used a low-fat diet as their comparator group. As such, we are unable to determine the presence or absence of 'true' individual response variation in each of the two diets individually, but rather that there is no difference in response variation between low-CHO and low-fat diets. However, comparing the low-CHO diet to an absence of dietary intervention may in fact be of less practical relevance as an individual is more likely to select a specific dietary intervention (e.g. low-CHO or low-fat) in attempt to lose weight, rather than adhere to a habitual diet.

A wide range of participants were included in the inclusion criteria for each study. It is possible that this participant heterogeneity influences mean intervention effects and inter-individual response variability. Nevertheless, all studies were randomised controlled trials so that, by design, the heterogeneity in participant's status at baseline should be balanced between the study arms, depending on the robustness of randomisation procedures in each study. In studies where there were more than 2 interventions, these were combined to avoid double counting of the intervention group, although this may mask any potential effect of different 'higher' CHO doses. However, even in studies using multiple comparator groups, none of these exceeded 240 g CHO·day^{-1} (42, 43, 44, 45) and so there is unlikely any influence of these marginal differences in CHO intake. Data from four eligible studies were not included in analysis due to a lack of response from the authors to obtain the necessary SD, or an inability to find the raw data from

an older study. We assume this lack of author response was random, however it was the case that no response was received for two studies by the same author. The studies included in this review were mainly conducted in free-living situations and therefore the SDir may differ in response to feeding studies in a controlled environment. However, free-living scenarios are arguably more important to consider, reflecting the practical implementation of low-CHO diets in real-world scenarios applicable to daily living.

Conclusions

Based on the available literature there is insufficient evidence at present to expect any greater or lesser 'true' inter-individual variation in body mass change in response to low-CHO vs low-fat dietary interventions. Ideally, properly-powered trials should be designed specifically to compare the treatment response heterogeneity between low-CHO, low-fat and a suitable habitual comparator diets.

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Conflict of Interest

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APPENDIX

A. *Regression-based Egger test for small-study effects*

FIGURE LEGENDS

Figure 1. Risk of bias graph. Risk of bias for each item presented as percentages across all included studies.

Figure 2. Risk of bias summary. Risk of bias for each item presented individually for each included study.

Figure 3. Forest plots for (A) mean treatment effects and (B) pooled point estimate for the inter-individual variability in body mass change, where “0” represents studies involving a non-Ketogenic dietary intervention and “1” is used for studies classified as having a Ketogenic intervention group.