**Review**

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# Fat and carbohydrate proportions influence on the insulin resistance; a systematic review and meta-analysis on controlled clinical trials

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## Abstract

The effect of dietary macronutrient proportion on insulin resistance is controversial. The objective of this study was to conduct a systematic review and meta-analysis on randomized controlled trials (RCTs) that examine the effects of replacing dietary fat with carbohydrate on insulin resistance. We searched PubMed, Google Scholar, Science Direct, and ISI Web of Science for RCTs until 2011. In total we found 15 articles that examine the effects of two kinds of prescribed diets low-fat, high-carbohydrate (LFHC) diet and high-fat low-carbohydrate (HFLC) diet on insulin resistance as regard the inclusion criteria. Meta-analysis of data from all 15 selected studies found that there is not significant difference between HFLC diet and LFLC diet (mean difference 0.01; 95% confidence interval [CI], -0.18 to 0.2; P > 0.05), but when two studies were excluded from the meta-analysis a significant difference was seen between HFLC diet and LFLC diet (mean difference 0.01; 95% CI, -0.17 to -0.02; P =0.009). Our findings suggested that HFLC diet significantly decreases insulin resistance compared with the LFLC diet. But we cannot conclude a LFHC diet is unfavorable compared with an HFLC diet for insulin resistant patients because in this study we have not determined the type of carbohydrate and fat intake, while dietary fat and carbohydrate composition may be a particularly important means of improving insulin sensitivity.

## Introduction

Insulin resistance was first defined in the 1970s. Reaven indicated that it was the underlying cause of a syndrome described by hyperinsulinemia, increased triglyceride, reduced high density lipoprotein (HDL) cholesterol, hypertension, hyperglycemia, and an increased risk of coronary heart disease (1). Several additional abnormalities have been identified, and the cluster of clinical and metabolic aspects is currently recognized as the insulin resistance or metabolic syndrome (2).

Different methods exist for the measurement of insulin sensitivity. The hyperinsulinemic euglycemic insulin clamp which is the gold standard and the intravenous glucose tolerance test, has been performed by different protocols in studies. Alternate procedures of insulin sensitivity, usually based on fasting insulin measurement, are also not standardized, so individuals with hyperinsulinemia may not have insulin resistance established

## Core tip

In this meta-analysis we found that high-fat low-carbohydrate (HFLC) diet significantly decreases insulin resistance compared with the low-fat, high-carbohydrate diet (LFHC). But we cannot conclude a LFHC diet is unfavorable compared with an HFLC diet for insulin resistant patients because in this study we have not determined the type of carbohydrate and fat intake, while dietary fat and carbohydrate composition may be a particularly important means of improving insulin sensitivity. We propose that the clinical trial studies will be designed that consider all above aspect to assess the amount and type of carbohydrate and fat on insulin resistance.

by insulin clamp method (3). Proportions of insulin sensitivity change broadly in healthy populations. Regardless of the method used, there is no approved cutoff for the designation of insulin-sensitive or insulin-resistant

individuals. Different methods to measure insulin sensitivity have greatly complicated the study of the nutritional factors of insulin resistance. Some of the determinants of an individual's insulin sensitivity are clear; physical fitness improves insulin sensitivity, adiposity (and especially abdominal fat accumulation) impairs it and dietary factors might influence insulin sensitivity (4). Many trace elements have been claimed to improve insulin sensitivity, among them magnesium, zinc, chromium, vanadium and vitamin D is also determined (5). Much interest has also focused on dietary macronutrients. Dietary macronutrient composition may play a role in determining insulin sensitivity and secretion. Several studies in humans have shown that the macronutrient content of the diet can also alter insulin action (6). Some studies have shown that isoenergetic diets containing a higher percentage of energy as fat produce insulin resistance (7), whereas other studies found no difference in insulin sensitivity after high-fat compared with high-carbohydrate diet (8). To summarize the available literature we conducted a meta-analysis of study on RCT that examined the effect of different proportion of macronutrient on insulin resistance.

## Methods
### Search strategy
We searched PubMed, Google Scholar, Science direct, and ISI web of science for randomized clinical trials until 2011, using following keywords: insulin resistance or insulin sensitivity combined with dietary fat or dietary carbohydrate or dietary macronutrients or proportion of fat to carbohydrate. Our search retrieved about 256 studies. All titles and if needed abstracts were reviewed by authors to find RCTs eligible to include in the study. Cohort study, case–control, and review articles were excluded. Our literature search identified 27 interventional studies. To ensure that they satisfied the inclusion criteria, the retrieved studies were assessed again by two independent authors.

### Inclusion criteria
Interventional studies (parallel or crossover RCTs) comparing the effect of two kinds of prescribed diets differing according to proportions of carbohydrate and fat under conditions that the prescribed total energy and protein intake did not differ significantly among groups of individuals with diabetes, patients with impaired glucose tolerance and persons with normal glucose tolerance were considered eligible. From 27 found trials, those not published in English and those conducted between children (ages -18 years) and those comparing the effect of another dietary factor such as fiber were excluded. Therefore, 15 articles remained in this meta-analysis.

### Data extraction
Surname of lead author, sample-size study design (randomized parallel, randomized crossover, or nonrandomized crossover intervention trial), participants' gender, age range and/or mean (SD), name, and characteristics of each diet, such as macronutrient composition, a weight-loss

diet, which was characterized as caloric restriction leading to weight reduction, and the method of insulin resistance assessment and study duration were recorded. Means ± SD of each group for the insulin resistance were extracted. The effect on insulin resistance, which is expressed as the mean difference between LFHC and HFLC diet groups in individual studies, was calculated by subtracting the change from baseline to final values in the HFLC-diet group from that in the LFHC-diet group. The standard error (SE) of change from baseline values was directly extracted from the reported data or estimated from the SEs of the baseline and final values in the LFHC and HFLC-diet groups, assuming a correlation of 0.5 between the baseline and final measures within each group, according to the formula of Follmann et al (9), as follows to estimate percent change, we divided each change from baseline values and its SE by the baseline value. When no baseline value was reported, as in some crossover studies, we summarized the intervention effect by the ratio of the difference in final values between LFHC and HFLC-diet groups to the final value in the HFLC-diet group and assumed that the baseline SE was equal to the final SE. This method of estimating percent change has limitations, especially in studies without washout periods, so we performed sensitivity analysis to examine the effect of these studies on the results.

### Statistical analysis
All percent changes were firstly pooled with a fixed-effects model. For each outcome measure, and influence analysis was conducted to detect an outlier (i.e., a single estimate with an extreme result), which influenced overall outcome. Study heterogeneity was statistically assessed by Q statistics. If heterogeneity was significant, the percent changes were secondarily re-pooled with random-effects model. Publication bias was assessed using Begg's test. The trim-and fill technique was used to investigate the impact of any suggested bias. We also calculated the weighted mean difference (WMD) in individual trials by multiplying each percent change by the inverse of its SE squared. We ecologically examined the reciprocal association among metabolic effect of the LFHC diet compared with the HFLC diet by Spearman's correlation analysis among WMDs. To investigate the effect of study traits, stratified analysis were done for the following possible confounders; study design (clinical trial or cross-sectional), the method of insulin resistance evaluation, recommendation a weight-loss or weight-maintenance diet, body mass index (BMI), the study duration and the carbohydrate proportion in the LFHC and HFLC diets. The STATA software version 11.2 (Stata Corp, College Station, TX) was used to perform analysis.

## Results
Fifteen articles were used for the meta-analysis (Figure 1) (4,6-8,10-20). Their characteristics and main outcomes are shown in Table 1. In various studies, several methods were used to measure insulin resistance so respectively two RCTs used of QUIKI method (12,13) three used of HOMA
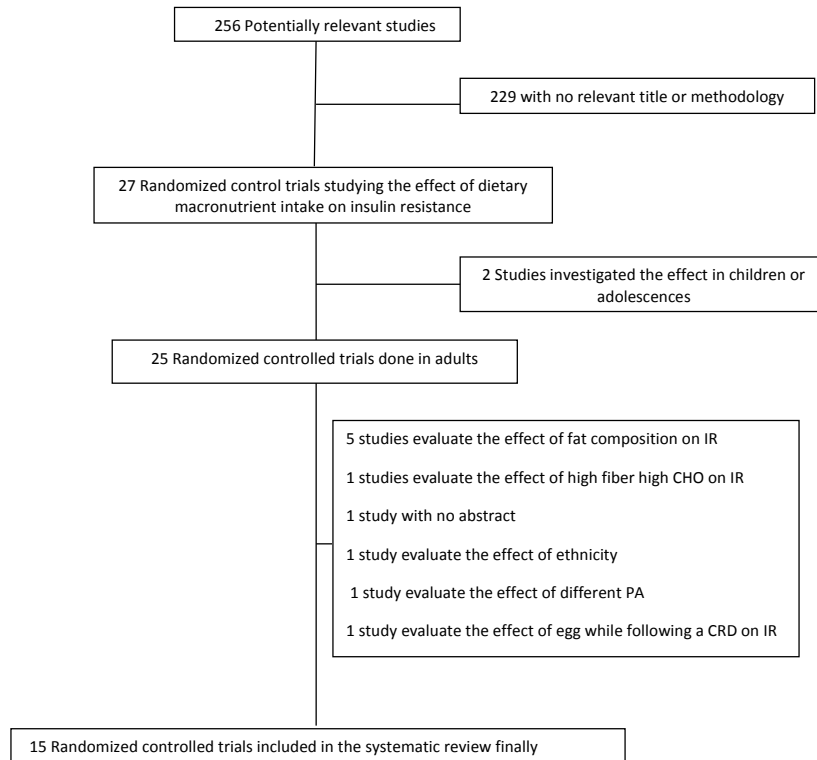
**Figure 1.** Flow of selection process.

method (4,15,19), one used of SSPG method (6), two used of GTT method (14,15) and seven used of clamp method (8,10,16-18,20). In these studies four different diets are prescribed; in first diet carbohydrate and fat were in WHO recommended range, in second diet carbohydrate and fat were above WHO recommended range, in third diet fat was in WHO recommended range and carbohydrate was above WHO recommended range and in last diet carbohydrate was in WHO recommended range and fat was above WHO recommended range. There was no significant difference between high carbohydrate low fat diet and low carbohydrate high fat diet (mean difference 0.01; 95% confidence interval [CI], -0.18 to 0.2; $P > 0.05$). However, heterogeneity was significant ($I^2 = 59.5\%$, $P = 0.003$) (Figure 2), thus we excluded two studies that led to higher heterogeneity (12,15) because of higher BMI than 35 kg/ $m^2$. After that, a significant difference was seen between HFHC diet and LFHC diet (mean difference -0.01; 95% CI, -0.17 to -0.02; $P < 0.05$) (Figure 2). Also stratified analysis which was conducted for the recommendation of weight-loss or weight-maintenance diet as possible confounders determined a significant difference between HFHC diet

**Table 1.** Descriptive statistics of studies included in the meta-analysis

| Author | HCLF | | LCHF | | Age (years) | Men (%) | BMI | Intervention period (week) |
|---|---|---|---|---|---|---|---|---|
| | n | C/F/P(%) | N | C/F/P (%) | | | | |
| Goree | 34 | 55/27/18 | 35 | 43/39/18 | 34.6±8.1 | 44.9 | 32.3±4 | 8 |
| Erik Kirk | 11 | 65/50/15 | 11 | 10/75/15 | 43.6±2.5 | 18 | 36.5±0.8 | 11 |
| Turdy | 12 | 55/25/20 | 13 | 30/50/20 | 29±17 | 60 | 22.1±0.3 | 10 |
| Samaha | 40 | 51/33/16 | 35 | 49/33/17 | 5.4±9 | 71 | 42.9±7.71 | 24 |
| Foster | 19 | 60/25/15 | 18 | 5/80/15 | 44.2±7 | 54 | 34.4±3.1 | 52 |
| Bisschop | 3 | 85/0/15 | 3 | 2/83/15 | 29-55 | 100 | 21-26 | 14 |
| Lovejoy | 16 | 55/30/15 | 15 | 35/50/15 | >18 | 0 | >25 | 6 |
| Parillo | 5 | 60/20/20 | 5 | 40/40/20 | 52.7±8.4 | 70 | 26.7±3.5 | 4 |
| Resenfalk | 6 | 55/25/20 | 7 | 55/30/15 | 34.9±9.8 | 46 | 25±3.5 | 12 |
| Anette Due | 15 | 60/25/15 | 15 | 50/35/15 | 28±0.7 | 43 | 31.2±0.3 | 24 |
| Shikny | 1131 | -/20/- | 1132 | 50/35/15 | 61.5±6.9 | 0 | 29.6±5.8 | 18 |
| Muzio | 50 | 65/22/13 | 50 | -/30/- | 52.1±16.7 | 27 | 37.1±2.1 | 20 |
| Borkman | 4 | >50/>20/<30 | 4 | 48/33/19 | 37±3 | 37 | 24±1.6 | 3 |
| Bradley | 72 | 60/20/20 | 12 | 20/60/20 | 39±10 | 37 | 33.6±3.7 | 8 |
| Laughlin | 28 | 60/25/15 | 29 | 40/42/18 | 50±10 | 42 | 32±1.8 | 16 |
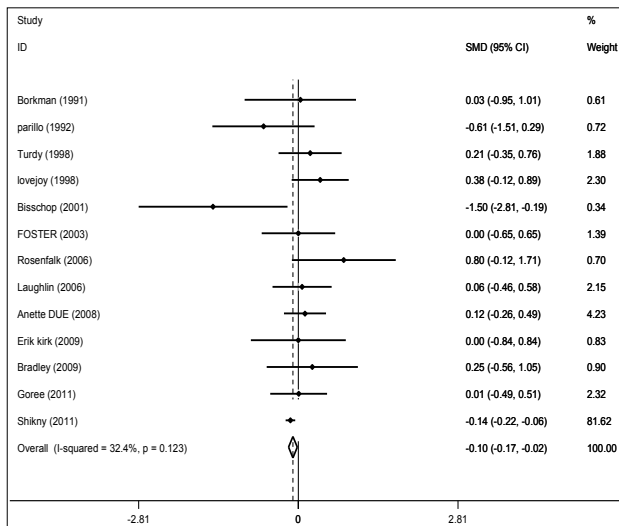
**Figure 2.** Forest plot showing overall effect of HFLC and LFHC diet on insulin resistance using random effects model.
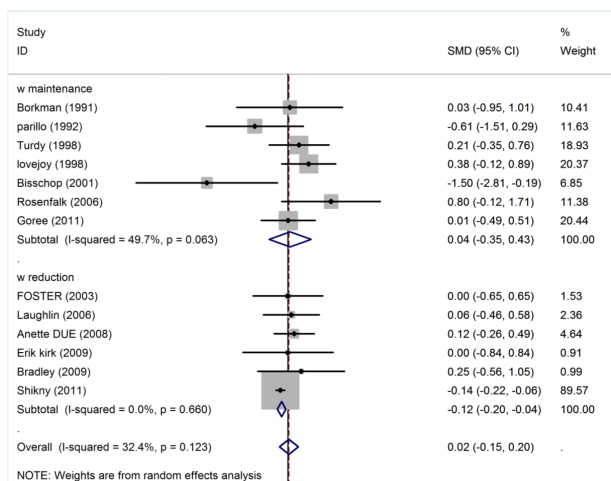


**Figure 3.** Forest plot showing overall effect of HFLC and LFHC diet on insulin resistance using random effects model based on weight change (with weight reduction vs weight maintenance).

and LFHC diet (mean difference -0.12 ; 95% CI, -0.04 to -0. 2; $P < 0.05$) (Figure 3). Data on publication bias and its likely effect on estimates of outcome was shown in Figure 4, which shows a relatively of publication bias (Egger's test, $P = 0.09$). According to results of the compensatory trim-and-fill method, the effect of publication bias would marginally underestimate the effect of the LFHC diet.

## Discussion

In the present meta-analysis we found, HFHC diet significantly decreases insulin resistance compared with the LFHC diet. This finding is in agreement with the findings of Gower and Goss, which showed a lower-carbohydrate, higher-fat diet increases insulin sensitivity in adults at risk of type 2 diabetes. They prescribed two diets with different macronutrient composition including lower-fat diet: 55%, 18%, and 27% and lower-carbohydrate diet: 43%, 18%, and 39%, of energy from carbohydrate, protein, and fat, re-
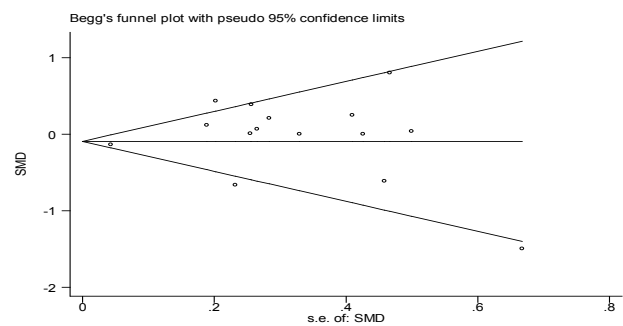


**Figure 4.** Begg's funnel plot (with pseudo 95% confidence interval) in mean difference (MD) versus SEs of correlation coefficients.

spectively for 8 weeks and concluded lower-carbohydrate, higher-fat diet decreases insulin resistance (21).

However, the findings of the current study do not support some previous research such as the study of Black et al, which examined the effects of diet macronutrient composition on insulin sensitivity and concluded 8 weeks of a higher carbohydrate/lower-fat (55% carbohydrate, 18% protein, 27% fat) diet versus lower-carbohydrate/higher fat (43:18:39) lead to higher insulin sensitivity in healthy normal glucose tolerant overweight/obese individuals (22). Another study, which is in contrast to our result, is the study by Black et al. They examined, macronutrient intake patterns in association with anthropometric and metabolic traits in individuals of BetaGene, a family-based investigation of obesity, insulin resistance, and B-cell dysfunction in Mexican Americans. They concluded that a high fat, low-carbohydrate dietary pattern might play a role in insulin resistance, obesity, and reduced b-cell function (22). Diets high in total fat are energy-dense and may be less satiating than carbohydrates, at least in some individuals. As a result, they tend to promote excess energy intake and are associated with an increased risk of obesity and insulin resistance (23). However as previous studies have indicated Mediterranean pattern diets that, not fat-restricted, exert favorable effects on insulin resistance, and diabetes risk (24). Hence, the type and components of dietary fat are important, especially with intake moderate fat (<30%) various types of dietary fat play a role in the alteration of diet-induced insulin resistance (25).

Polyunsaturated (PUFA), monounsaturated (MUFA), saturated fatty acids (SFA), and trans unsaturated fatty acids (TFA) are the main constituents of dietary fat (23). Adverse effects of TFA on insulin resistance in human are less clear. Studies in animal have exhibited that high ingestion of TFA induces insulin resistance in compared with low fat diets (8). Relationship between TFA intake and insulin resistance, probably related to increase in inflammatory cytokines (26).

Epidemiological investigations show a direct relationship between dietary SFA and insulin resistance or type 2 diabetes (T2DM) (27) and replacing MUFA with SFA may decrease insulin resistance (25). Different mechanisms are suggested for the influence of SFA on insulin resistance including (28); influencing on β cells, transcription factors

and key enzyme activities (29), activating specific serine kinases (30), and affecting inflammatory pathways.

The mechanisms that MUFA improve insulin sensitivity comprise changing cell membrane fatty acid composition (24) influencing on ion permeability and membrane fluidity, cytoprotective effects on beta cell function (26), and insulin receptor binding affinity.

The potential mechanisms were extracted of *in vitro* and animal study reveals that PUFA has anti-inflammatory properties, influence on toll-like receptors (TLRs) (14) and inhibit TLR-2 and TLR-4 also PUFA may change membrane fluidity, improve binding affinity of the insulin receptor, and enhance glucose transportation into cells *via* glucose carriers (25). Also PUFA affects on the regulation of peroxisome proliferator-activated receptors, hepatic nuclear factors, SREBP-1c, liver X receptors, retinoid X receptors, which are involved in lipid and carbohydrate metabolism (26).

These studies have not determined the type of carbohydrate and fat intake while as previously mentioned, dietary fat and carbohydrate composition may be a particularly important means of improving insulin sensitivity in the context of more moderate intakes of total fat (31).

In our review a significant difference between HFHC diet and LFHC diet was seen after stratified analysis that were done for the recommendation a weight-loss or weight-maintenance diet as possible confounders .

 A meta-analysis suggests that a total fat intake of <30% total energy facilitates weight loss among overweight individuals (32). Thus, high-fat diets may promote insulin resistance via their obesogenic potential. In the same way the context of energy balance and weight maintenance, may influence insulin sensitivity. Diets rich in low-energy-dense foods, including whole-grain cereals and cereal products and other foods rich in dietary fiber, promote satiety and may, as a consequence, facilitate appropriate energy intake (33), and by reducing the risk of obesity, such foods may be regarded as reducing the risk of insulin resistance. In addition, it is possible that the effects of weight loss overcame any lesser effect of dietary macronutrient intake (20). These are important practical considerations because most overweight individuals will rapidly achieve their maximum weight loss, and the appropriate dietary advice will be facilitates weight maintenance and ensures the greatest degree of insulin sensitivity.

## Limitations of the study
Our study has some limitations; first, we did not omit studies investigating the effect of high-carbohydrate diets that were also high in dietary fiber; it is possible that the additional phytochemicals (including fiber itself) with a substantial amount of carbohydrate influence the metabolic effects regardless of the change in carbohydrate, fat ratio. Second, few studies investigated long-term effects of changing the proportions of carbohydrate and fat on insulin resistance. Third, a variety of target populations have been studied, mostly in small studies, and for many of these studies (e.g. those enrolling patients with normal

glucose handling), it is perhaps unsurprising that no effect on insulin resistance was seen. Fourth, there are a number of methodological limitations among the studies including most of them enrolled a small number of patients, thus lacking the statistical power, and they have used different methods to assess insulin resistance that may affect on result.

## Conclusion
Our findings suggested that HFHC diet significantly decreases insulin resistance compared with the LFHC diet and LFHC diet. But we cannot conclude a LFHC diet is unfavorable compared with an HFLC diet for insulin resistant patients because in this study we have not determined the type of carbohydrate and fat intake, while dietary fat and carbohydrate composition may be a particularly important means of improving insulin sensitivity. We propose that the clinical trial studies will be designed that consider all above aspect to assess the amount and type of carbohydrate and fat on insulin resistance.

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