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# Low-Carbohydrate-Diet Score and its Association with the Risk of Diabetes: A Systematic Review and Meta-Analysis of Cohort Studies

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## ABSTRACT

The association between a low-carbohydrate diet (LCD) score and the risk of diabetes mellitus (DM) is contradictory. This study is a systemic review of cohort studies that have focused on the association between the LCD score and DM. We searched PubMed/Medline, Scopus, Embase, ISI Web of Science, and Google Scholar for papers published through January 2017 with no language restrictions. Cohort studies that reported relative risks (RRs) with 95 % confidence intervals (CI) for DM were included. Finally, 4 studies were considered for our meta-analysis. The total number of participants ranged from 479 to 85 059. Among 4 cohort studies, 8 081 cases with DM were observed over follow-up durations ranging from 3.6 to 20 years. A marginal significant association was observed between the highest LCD score and the risk of DM (RR = 1.17; 95 % CI: 0.9, 1.51). Moreover, the RRs for studies with energy adjustments showed a significant association (RR: 1.32; 95 % CI: 1.17, 1.49; $I^2$: 0 %). Based on our findings, study qualities score of less or equal to 7 had a significant influence on the pooled effect size (RR = 1.31, 95 %CI: 1.15, 1.49; $I^2$: 0 %), whereas the overall RR in the studies with quality score more than 7 was 1.09 (95 % CI: 0.73, 1.63). In conclusion, we have found that the highest LCD score was marginally associated with the risk of DM. However, more prospective cohort studies are needed to clarify the effects of the LCD score on the risk of DM.

## Introduction

Diabetes mellitus (DM) is a pivotal health problem that is increasing worldwide [1]. The world health organization (WHO) reported a prevalence of DM of 108 million in 1980, which dramatically increased to 422 million in 2014. Approximately half of all-causes of mortality are attributed to high blood glucose levels. The WHO has also predicted that DM will be the seventh leading cause of mor-

tality in 2030 [2]. Therefore, to reduce the global epidemic, it is essential to provide effective solutions for DM prevention [3].

DM is a multi-factorial metabolic disorder in which genetics and life style, particularly dietary habits, play prominent roles [4]. A combined healthy diet and physical activity can decrease the risk of DM by 30–60 % among various societies and ethnic groups [5]. However, as energy intake and dietary habits can influence glucose level and other biochemical parameters, the ideal proportion of macronutrients needed to prevent DM is a matter of debate [6].

In the majority of Asian countries, the most highest proportion of dietary energy is provided by carbohydrate sources [7]. Some studies have reported that diets with high amounts of carbohydrate or a high glycemic index are associated with an increased risk of DM and other metabolic disorders [8–10]. In many societies, low-carbohydrate diets are popular for promoting weight loss and controlling glucose levels; however, because such kinds of diet limit the intake of several healthy carbohydrate sources, such as whole grains, vegetables, fruits, refined grains and increase the consumption of protein and fat sources [11], some cohort studies have reported that adherence to such diets can increase the risk of DM [3, 12].

Macronutrient diet scores such as the LCD score can offer a comprehensive approach to the association between diet and chronic diseases. Each macronutrient could have various effects on the risk of DM [13], and these scores consider the proportion of all 3 macronutrients from total energy intake. A higher LCD score reflects higher intake of protein or fat and lower eaten carbohydrate, while the lower score shows the inverse [7]. Three studies reported that LCD scores are associated with an increased risk of DM [11, 12, 14], while others failed to find any associations [7, 13, 15]. To the best of our knowledge, no study has systematically examined the association between the LCD score and the risk of DM so far. In the present study, we therefore aim to summarize the association of the LCD score with the risk of DM in cohort studies.

## Methods and Materials

### Literature search

We searched 5 electronic databases including PubMed/Medline, Scopus, Embase, ISI web of science, and Google Scholar through January 2017 with no language restrictions. Key words were as follows:'low-carbohydrate- diet score' OR 'low carbohydrate diet score' OR 'low- carbohydrate diet score' AND 'diabetes' OR 'diabetic'. In addition, the reference lists from review and relevant articles were checked to find additional relevant publications. Screening of publications based on titles and abstracts as well as the assessment of full text papers were performed independently by 2 reviewers. Whenever there was a disagreement between 2 reviewers, it was resolved by consensus.

### Inclusion and exclusion criteria

Studies were included in the meta-analysis if they had (i) cohort study design and (ii) reported relative risks (RRs) with 95 % confidence intervals (CI) for DM. Grey literatures such as conference abstracts, thesis, and letters to the editor, studies with other designs and those in which the RRs for our exposure and outcome were not reported, were excluded.

### Quality assessment

Two reviewers independently assessed the full texts of included studies for methodological quality using the Newcastle Ottawa Scale [16]. Newcastle Ottawa scale consists of 8 items about selection, comparability and exposure with a maximum 9 score. In the present meta-analysis, papers with more than a median score were considered as high quality studies. Any discrepancies between 2 reviewers on the methodological quality of studies were resolved by discussion. Scores for quality assessment of each paper is presented in ▶ **Table 1**.

### Data extraction

Two investigators independently extracted data from eligible papers using a pre-designed form. First author's last name, publication year, study design, country, age range, gender, number of participants, cases, duration of follow-up, person-year, exposure, method of exposure assessment, outcome, reference vs. comparison group and risk estimates with 95 % CI as well as adjusted covariates were extracted. When a study reported several RRs for an outcome, the maximally adjusted models were considered.

### Statistical analysis

This meta-analysis was performed using maximally adjusted relative risks (RRs) to compare the highest vs. the LCD scores. Since the studies involved participants with varying characteristics, we used DerSimonian and Laird's random-effects model to examine within- and between-study variability. We reported the standard error for log (RR) of each size to weight effect on the relative contribution of each included study. Heterogeneity was estimated using the $I^2$ index. $I^2$ values greater than 50 % were considered to have high heterogeneity [17].

Subgroup analyses were performed for the duration of follow-up (less than 12, ≥ 12), energy adjustment (adjusted, non-adjusted), and study quality (more than 7, less than or equal to 7).

The robustness of the findings was checked using a sensitivity analysis, which was repeated after excluding one study at a time to assess the influence of each study on the overall effect size. To examine potential publication bias, the Egger test was used. All data analyses were carried out using Stata 12.0 software (Stata Corp LP, College Station, TX, USA).

## Results

### Systematic review findings

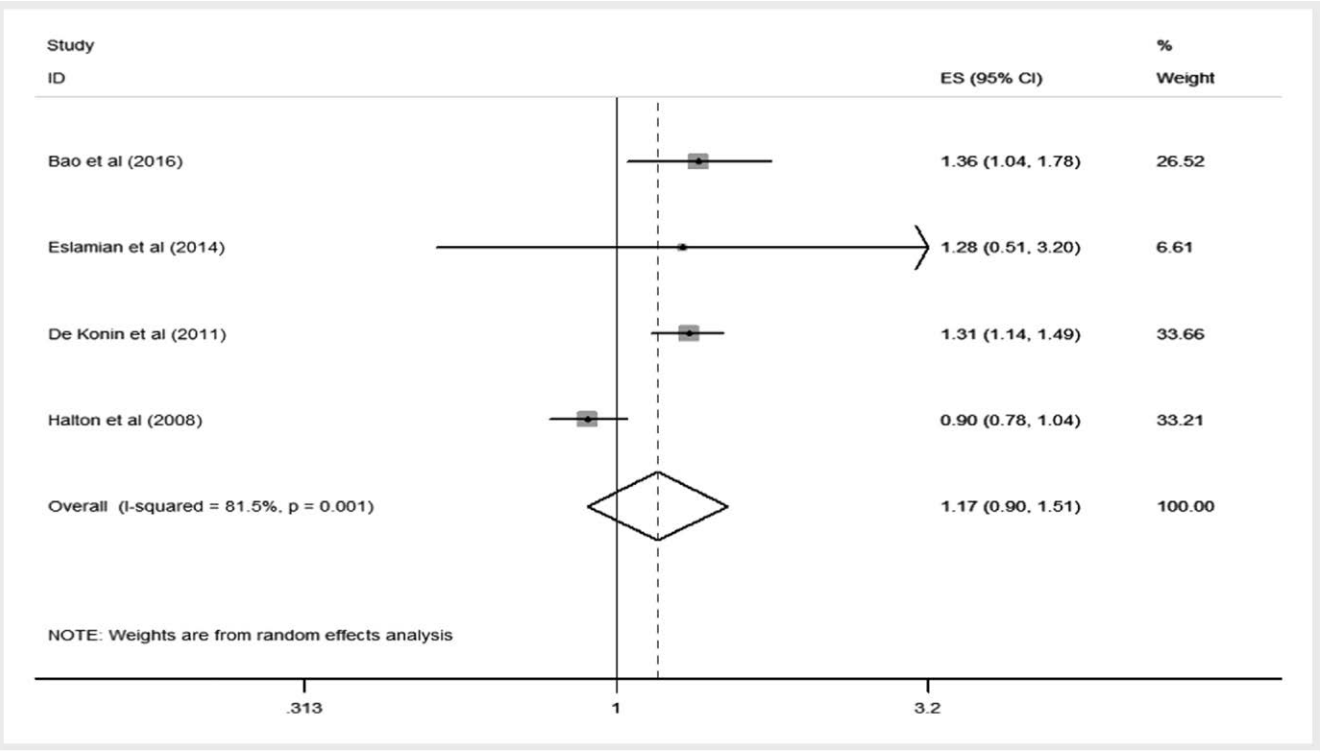
A primary literature resulted in 29 publications. However, we found 15 duplications. We excluded 15 duplicated ones and reached 14 studies. In the next step, 14 papers were assessed for relevance based on their titles and abstracts. After removing the irrelevant papers, 7 full texts of papers were examined. Papers were excluded if they contained irrelevant topics (n = 6) and not including our outcome (n = 1). According to our inclusion and exclusion criteria, cross-sectional studies (n = 2) were excluded when the full text articles were assessed for eligibility. Finally, 4 cohort studies were selected for a systematic review and meta-analysis (**Fig. 1S**).

▶ **Table 1** presents the characteristics of the studies that were included in the systematic review and meta-analysis. Of 4 studies,

▶ **Table 1** Main characteristics of studies examined for the association of low-carbohydrate diet score with risk of diabetes.

| First Author (Year) | Study name/ study design | Country | Age range | Gender | Sample size | Cases | Duration follow-up (years) | Person-year | Exposure assessment | Outcome (ascertainment) | Comparison | OR or RR (95% CI) | Adjustments | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bao et al. (2016) | Nurses Health Study II (NHSII)/ Cohort | USA | 24–44 | Women with history of GDM | 4.502 | 722 | 12 | 68.897 | FFQ | American Diabetes Association criteria: 1) one or more classic symptoms plus FBS >7.0 mmol/l or random plasma glucose >11.1 mmol/l), 2) no symptoms reported but 2 or more high BS on more than one occasion or 3) treatment with insulin or oral hypoglycemic agent | Q5 vs. Q1 (score 25 vs. score 5) | 1.36 (1.04, 1.78) | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 | 8 |
| Eslamian et al. (2014) | Tehran Lipid and Glucose study/ Cohort | Iran | 13.8 | Both | 479 | – | 3.6 | – | FFQ, 168-item | Joint Interim Statement (JIS): FBS ≥ 100 mg/dl or medical treatment | Q4 vs. Q1 | 1.28 (0.51, 3.20) | 1, 10, 11, 14 | 7 |
| de Koning et al. (2011) | Health Professionals Follow-Up study/ Cohort | USA | 40–75 | Men | 40.475 | 2 689 | 20 | 712.103 | FFQ, 131-item | National Diabetes Data Group | Q5 vs. Q1 (>19 vs.<7) | 1.31 (1.14, 1.49) | 1, 5, 8, 9, 10, 11, 13, 15 | 6 |
| Halton et al. (2008) | Nurses Health Study II (NHSII)/ Cohort | USA | 30–55 | Women | 85.059 | 4 670 | 20 | 1.606.716 | FFQ | American Diabetes Association criteria | Q10 vs. Q1 (median: 21.8 vs.5) | 0.90 (0.78, 1.04) | 1, 5, 8, 9, 10, 13 | 8 |

Adjustments: 1: age; 2: parity; 3: age at first birth; 4: race/ethnicity; 5: family history of diabetes; 6: oral contraceptives; 7: menopausal status; 8: cigarette smoking; 9: alcohol intake; 10: physical activity; 11: total energy intake; 12: glycemic index; 13: body mass index; 14: gender; 15: coffee intake; GDM: Gestational diabetes mellitus; FBS: Fasting blood sugar; Q: Quintile; NA: Not applicable




▶ **Fig. 1** Forest plot of the association between LCD score and the risk of diabetes.

which were published between 2008 and 2016, 3 were conducted in the U.S [11, 12, 15] and one in Iran [13]. The total number of participants ranged from 479 to 85 059 and they were aged between 13.8 and 75 years. Two studies focused on women [11, 15], one focused on men [12], and the remaining paper included both genders [13]. Except for one [13], all of the studies examined adults. Of the 4 papers, one cohort study [11] was performed exclusively on women with a history of Gestational DM (GDM). In all studies the tool for exposure assessment was the Food Frequency Questionnaire.

Throughout the follow-up duration, ranging from 3.6 to 20 years among 4 cohort studies, 8 081 cases with DM were observed. Three studies reported the person-year, which were between 68 897 and 1 606 716. To evaluate the association between the LCD score and the risk of DM, all papers reported adjusted RRs or ORs, which were adjusted more for age (n = 4) [11–13, 15], family history of DM (n = 3) [11, 12, 15], cigarette or alcohol use (n = 3) [11, 12, 15], total energy intake (n = 3) [11–13], and body mass index (BMI) (n = 3) [11, 12, 15]. Adjusted RRs for the risk of DM across the highest vs. the lowest score of LCD were between 0.90 and 1.36. ▶ **Table 1** presents the total quality score for each study. The included papers had a quality score between 6 and 8. All studies used high quality methodology (score ≥ 5).

The present systematic review found that 2 studies reported an association between the LCD score and the risk of DM [11, 12]. Based on their findings, the highest vs. the lowest LCD score had a noticeable impact and could increase the risk of DM. However, the 2 remaining studies did not find any significant associations [13, 15]. Because various cut-off points were considered for the LCD score in the eligible studies, it was difficult to report a certain LCD score that increases the risk of DM.

The different findings among the studies might be caused by differences in gender, age, individual characteristics, race, duration of follow-up, adjusted covariates, or study quality.

## Findings from the meta-analysis on LCD score and the risk of diabetes

Results from the meta-analysis on the association between the LCD score and the risk of DM are presented in ▶ **Fig. 1**. Overall, 4 effect sizes were included. The total number of participants in the cohort studies were 130 515, out of which 8 081 cases with DM were reported. A marginally significant association was observed between the highest LCD score and the risk of DM compared to the lowest score (overall RR = 1.17; 95 % CI: 0.90, 1.51).

The current meta-analysis, found a high between-study heterogeneity ($I^2$: 81.5 %; p < 0.001). To find the main parameter involved in the heterogeneity, subgroup analyses based on follow-up duration, energy adjustment, and study quality were performed (**Table 1S**). Since only one study was conducted on only men [12], we could not examine the association between the LCD score and the risk of DM in each gender.

According to the follow-up duration of cohort studies, a significant difference was found in the short-term studies (≤ 12 years) (1.35, 95 % CI: 1.05, 1.75; $I^2$: 0 %). After excluding one study, which was not adjusted for energy [15], the overall RR showed a substantial association (RR: 1.32; 95 % CI: 1.17, 1.49) and stratification by energy adjustment removed the heterogeneity ($I^2$: 0 %; p = 0.96). Based on our findings, all 4 studies had high methodological qual-

ity. However, after stratification by study quality (score >7, ≤7), the study quality of less than or equal to 7 had a significant influence on the pooled effect size (1.31, 95 % CI: 1.15, 1.49; $I^2$: 0 %), while in studies with the score of more than 7, the overall effect size was 1.09 (95 % CI: 0.73, 1.63, $I^2$: 85.8 %). Based on findings, energy adjustment had the strongest impact on between-study heterogeneity.

Sensitivity analysis indicated that excluding none of the studies altered the pooled effect size considerably (overall RR ranged from 1.06 to 1.31). To examine publication bias, we used the Egger's regression plot, which indicated that no publication bias existed for the association between the LCD score and the risk of DM (p = 0.54).

## Discussion

Based on the present meta-analysis, we found that the highest LCD score was marginally associated with the risk of DM compared to the lowest intake. Moreover, short-term cohort studies (≤ 12 years) also reported an association. Studies with energy adjustment also found that the LCD score increased the risk of DM by 32 %. Moreover, in studies with a score greater than 7 for methodological quality, no association was found; whereas, studies with a score lower than 7 showed a significant association.

To the best of our knowledge, no previous meta-analyses have examined the association between LCD score and the risk of DM. However, the relationship between the LCD score and the risk of metabolic disorders is a novel topic in the field of nutrition [7]. Prior studies have reported different impacts of each macronutrient on the risk of DM and other chronic diseases [18–21]. Some studies indicated that LCDs can increase the risk of DM associated with hyperglycemia and insulin resistance [22, 23] whereas such conclusions were not made in several other studies [24–27].

As LCDs consist of a high proportion of protein and fat and a low proportion of carbohydrate, it is thought that LCDs are helpful for controlling glycemic status. However, it is surprising that LCD diet can actually worsen the metabolic profile and even increase the incidence of DM [11, 12]. Although we found a marginal significant association between LCD score and risk of DM, from a clinical view point, 17 % rise in the risk of DM following adherence to an LCD, is noticeable. It seems reasonable to avoid high restriction of carbohydrate sources for DM prevention. It is worth noting that unlike a cohort study design, a cross-sectional study design cannot explicitly identify a cause-effect relationship and its direction. Cohort studies can provide the ground work for an intervention to prevent or treat various diseases [28]. Therefore, in the current meta-analysis, the 2 cross-sectional studies were not included.

The above-mentioned observations can be partially explained by the amounts and types of consumed macro- and micronutrients, when following an LCD. Substituting a considerable percentage of carbohydrates with protein and fat sources plays a focal role in changing the metabolic parameters [29]. Evidence shows that, although protein intake can activate insulin secretion [30, 31], the outcomes hinge on the sources of protein (animal, vegetable). Following a reduction in the proportion of carbohydrates from the total energy intake, the consumption of unhealthy foods such as processed meat and sources with high saturated fatty acids (SFAs) often increases and the consumed amount of fruits, vegetables, and dietary fibers decreases [7]. Two recent meta-analyses concluded that the consumption of red and processed meat was positively related to type 2 diabetes [32, 33]. In addition, substituting red and processed meat with other types of protein sources such as white meat, dairy, legumes and nuts can help to control glycemic status [12].

The present systematic review and meta-analysis, showed that only 2 cohort studies of the 4 papers assessed animal and vegetable LCD scores, separately [11, 12]. Therefore, it did not allow us to conduct a meta-analysis based on protein sources (animal or vegetable). Bao et al., reported that a low-carbohydrate dietary pattern with high animal protein and fat intake increased the risk of DM by 40 %, whereas the incidence of DM following the high consumption of vegetable protein and fat was not significant [11]. A study by de Koning et al., revealed similar results. This study found a substantial association between high animal sources and risk of DM (37 %), while the consumption of high vegetable sources with LCD showed protective effects. They also suggested that dairy products attenuated the risk of DM, while red and processed meats had progressive roles [12]. A limitation of these studies is that the type of fat intake was not considered. Overall, these findings reflect the effects of other consumed foods on the incidence of DM.

Some components such as heme iron, nitrites, and nitrates in animal protein (red and processed meat) might elevate the risk of DM [18]. Besides, subjects with a high consumption of animal proteins usually consume a higher proportion of SFAs which might raise the risk of developing type 2 diabetes and greater insulin resistance. Plausible mechanisms for the negative effects of SFAs are a reduction in cell membrane fluidity, changes in glucose transport, and expression of some genes [34]. However, vegetable protein sources are full in vitamins, minerals, poly-(PUFA) and mono-unsaturated fatty acids (MUFAs), and other beneficial nutrients, which can decrease the risk of DM or partially neutralize the harmful effects of other consumed foods [11]. Moreover, according to some metabolomics studies, a high animal protein diet vs. high vegetable protein diet causes greater serum levels of branched-chain amino acids, which are associated with the higher risk of DM and insulin resistance [35].

On the other hand, various types of fat intake influence the risk of DM differently. As previous studies have shown, substituting carbohydrates with MUFAs can decrease the risk of DM. The association between high saturated fat intake and risk of DM found in earlier studies [20] can be partially explained by the deleterious effects on glucose tolerance and insulin function. SFAs can affect insulin release, glucose oxidation, insulin sensitivity in skeletal muscle, and endogenous glucose [20]. The glycemic load and glycemic index also affects the association between the LCD score and the risk of DM. Among the 6 studies included in this study, one prospective study was adjusted for the glycemic index value [11]. Although the LCD score allows us to assess the impacts of the whole diet with the different percentages of macronutrients, the effects of different kind of carbohydrate sources with various glycemic loads or indices on the risk of DM or other diseases cannot be identified [36]. The consumption of carbohydrates with a high glycemic load and glycemic index can affect the risk of DM [35, 37]. A health professionals follow-up study displayed that adjusting the RR for glycemic load strengthened the association between the LCD score and

risk of DM. The study concluded that reducing the intake of foods with a high glycemic load in a low-carbohydrate diet could somewhat neutralize the harmful effects of red and processed meat [12]. Additionally, as carbohydrate sources (i. e., whole grain, vegetables, and fruits) are main sources of dietary fiber, a carbohydrate restriction decrease the whole grain intake, which then increases the risk of developing metabolic disorders such as DM [38, 39].

In the present systematic review and meta-analysis, differences in gender, age, duration of follow-up, covariates that were adjusted, and study quality might be responsible for the different findings among the studies. As all studies except one [13] focused on a relatively similar age range, a subgroup analysis based on mean age was not performed. However, after excluding the study that had been conducted on children and adolescents [13], no considerable changes were observed in the pooled effect size and heterogeneity. Among the parameters that were considered for the subgroup analyses, energy adjustment had the highest effect on removing heterogeneity. Total energy intake is the main factor affecting the aforementioned association. Studies with an energy adjustment showed that the highest LCD score, as compared to the lowest score increased the risk of DM by 32 %. However, owing to different cut-off points for the LCD score among the included studies, we could not identify a definite LCD score that had the greatest association with DM. As all 4 included studies obtained at least a median score from the quality assessment; this issue cannot affect the results. Nevertheless, different findings were observed in studies with a score lower or greater than 7.

Overall, even though the LCD score is a beneficial index by which to identify the association between diet and diseases, it cannot explain the association between low-carbohydrate intake and DM, thoroughly. It is therefore crucial to consider not only the sources of carbohydrate (complex, refined grains), glycemic load, and glycemic index but also the types of foods that are substituted.

The present study has some limitations. Owing to the different cut-off points for the LCD score in the 4 studies, we could not introduce a definite score that might be partially responsible for the risk of DM. The role of gender on this association also remained uncertain. In addition, because of the insufficient number of studies, the impact of protein sources along with a LCD was not examined. The strengths of the current study include identifying a main heterogeneity parameter and performing a meta-analysis of cohort studies for the first time on this topic. This study also revealed that, apart from the proportion of macronutrients, examining the types of each macronutrient is highly important for decreasing the risk of DM.

In conclusion, we have found that the highest LCD score increased the risk of DM compared to the lowest intake by 17 %. Studies with energy adjustment also found that the LCD score increased the risk of DM. Moreover, in studies with score more than 7 for methodological quality, no association was found whereas studies with a score less than or equal to 7 showed a significant association. However, because of limited number of studies in this field, more prospective cohort studies are needed to clarify the effects of the LCD score on the risk of DM.

## Author Contributions

The authors' responsibilities were as follows: B.L, L.A designed the research; N.N and L.A: conducted systematic research; N.N, L.A, B.L: extracted data; N.N, L.A: analyzed data; N.N, B.L and L.A: wrote manuscript; B.L, L.A: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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