Long-term Low-carbohydrate Diets and Type 2 Diabetes Risk: A Systematic Review and Meta-analysis of Observational Studies

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Objective: Low-carbohydrate diets have favorable short-term effects on body weight and risk factors for cardiovascular disease. However, they are potentially associated with an increased long-term risk of mortality. Our objective was to elucidate their effects on the incidence of diabetes.

Methods: Several databases (MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov) were searched for relevant articles that were published prior to May 2015. Cohort studies with a follow-up period of at least one year were included. Identified articles were systematically reviewed, and those with pertinent data were selected for inclusion in a meta-analysis. The pooled risk ratio (RR) with 95% confidence interval (CI) for the incidence of diabetes was calculated using the random-effects model with inverse-variance weighting.

Results: We included 13 studies in a systematic review, followed by a meta-analysis using pertinent data. Among the 440,669 people that were included in 11 cohort studies, 27,887 (6.3%) cases of diabetes were documented. The risk of incident diabetes among individuals with a low-carbohydrate diet was not significantly different from that of individuals with a high-carbohydrate diet: the pooled RR was 1.03 (95% CI, 0.91–1.16).
Conclusion: Low-carbohydrate diets did not show any benefit on the risk of diabetes. However, this analysis is based on limited observational studies, and large-scale trials examining the complex interactions between low-carbohydrate diets and long-term outcomes are needed.

Keywords: low-carbohydrate diet, diabetes mellitus, type 2 diabetes risk, meta-analysis

Introduction
A growing body of short-term evidence has suggested that low-carbohydrate diets are effective for weight loss and the amelioration of cardiovascular disease (CVD) risk factors. However, individuals on low-carbohydrate diets tend to regain weight over the long term. In addition, low-carbohydrate diets tend to result in a reduced intake of fiber and fruits and an increased intake of protein from animal sources, cholesterol, and saturated fat, all of which are risk factors for mortality and CVD. Our recent analysis has suggested that low-carbohydrate diets are associated with a significantly higher mortality and potentially increased risk of CVD, although the causes of premature death, such as diabetes-related death, remain to be elucidated.

Since obesity is a major risk factor for diabetes, it is speculated that low-carbohydrate diets might prevent diabetes, although the results of previous limited meta-analyses have been mixed. In light of the worldwide diabetes epidemic and the widespread popularity of low-carbohydrate diets, explorations of their long-term preventative effects on health are of clinical importance in terms of weight control. Moreover, such studies are crucial in the areas of public health, since a modest increase in the risk of morbidity and mortality translates into a substantial social burden. These circumstances prompted us to investigate, with greater precision, the effects of low-carbohydrate diets on the incidence of diabetes by scrutinizing pertinent original reports and combining their data in an attempt to obtain meaningful clues for evaluating the benefits and harm associated with dietary modifications.

Materials and Methods
Search
Searches of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov from their inception until May 12, 2015, were performed. Studies evaluating the risk of diabetes among subjects with a low-carbohydrate intake, compared with subjects with a high-carbohydrate intake, were identified using a combination of the following keywords: “low-carbohydrate diet” or “carbohydrate-restricted diet” or “carbohydrate intake”, and “diabetes”, and “risk” or “incidence”. The reference lists of pertinent articles were also inspected.

Selection
We assessed all the identified studies describing the effects of low-carbohydrate diets on the risk of diabetes based on original data analyses to determine their eligibility for inclusion in a qualitative analysis. The inclusion criteria in the meta-analysis were as follows: published full-text reports, randomized controlled trials (RCTs), or observational studies with a long-term follow-up period of at least one year reporting the relative risks, i.e. hazard ratios (HRs), risk ratios (RRs), or odds ratios with confidence intervals (CIs) after adjustments for major confounders for diabetes. Studies on gestational diabetes were excluded.

Validity and quality assessment
To ascertain the validity of the eligible studies, the quality of each report was appraised according to the CONSORT statement and the STROBE statement, as appropriate. The quality of the studies that were included in the meta-analysis were further evaluated using the Newcastle-Ottawa Scale, with a score of 5 or less indicating a high risk of bias.

Data abstraction
We reviewed each full-text report to determine its eligibility and extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the subjects (including age, gender,
and geographical region), the study design, publication year, follow-up period, diabetes ascertainment, and risk parameters. Any disagreement was resolved by a consensus among the investigators.

**Quantitative data synthesis**

If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. The reports were summarized both qualitatively and quantitatively.

We pooled the relative risk in the individuals with lowest-carbohydrate intake (designated as low-carbohydrate diet), with those with highest-carbohydrate intake (designated as high-carbohydrate diet) as a referent, according to either the proportion of the total energy intake or the intake amount.

In the meta-analysis, each adjusted relative risk with low-carbohydrate intake was combined and the pooled RR with a 95% CI was calculated using the random-effects model with inverse-variance weighting. If a study reported the relative risks separately for men and women, an overall estimate for the study was calculated from the two relative risks using the fixed-effects model with inverse-variance weighting; these single estimates were then used in the subgroup analysis evaluating the individual contribution of gender. Heterogeneity among the studies was evaluated using I² statistics. The possibility of a publication bias, which can result from the non-publication of small studies with negative findings, was assessed visually using a funnel plot for asymmetry. RevMan (version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for these calculations. All the procedures were in accordance with the guidelines for the meta-analysis of observational studies in epidemiology and the PRISMA statement.

**Results**

**Search results**

A total of 3,080 articles were identified during our search; of these, 22 were assessed with respect to their eligibility for inclusion in our review, which was aimed at determining the influence of low-carbohydrate diets on the incidence of diabetes (Figure 1). No RCTs were identified. Nine articles were excluded from the systematic review because of overlapping populations. Out of these 22 articles, a total of 13 cohort studies were appraised in the systematic review and meta-analysis.

The 13 selected articles included in the systematic review were moderately heterogeneous in terms of population demographics, carbohydrate intake parameters, and the assessment of confounding factors. The population sample sizes in these studies ranged from 8,370 to 85,059. The majority of the articles were published from European countries and the United States (US).

Table 1 shows the characteristics of each study that were included in the meta-analysis according to the year of publication. The caloric proportion or the amount of carbohydrate intake in the low and the high carbohydrate diets is depicted in Table 2. The adjustment factors and the risk of bias among the studies are summarized in Tables 2 and 3, respectively. A regression coefficient of the multiple logistic model was provided in one article, and total energy intake, a major confounding factor, was not stated in one study, which was not included in the subsequent meta-analysis. Few of the studies re-examined carbohydrate intake over the follow-up period. The protein source was included in the analysis in 3 studies.
## Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Source</th>
<th>Country, region/cohort</th>
<th>Follow-up, years</th>
<th>N (women, %)</th>
<th>Age, years</th>
<th>Incident diabetes, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer, 2000</td>
<td>US</td>
<td>6</td>
<td>35,988 (100)</td>
<td>5–69</td>
<td>1,141</td>
</tr>
<tr>
<td>Hodge, 2004</td>
<td>Australia</td>
<td>4</td>
<td>36,787 (59)</td>
<td>40–69</td>
<td>365</td>
</tr>
<tr>
<td>Villegas, 2007</td>
<td>China</td>
<td>4.6</td>
<td>64,227 (100)</td>
<td>40–70</td>
<td>1,608</td>
</tr>
<tr>
<td>Halton, 2008</td>
<td>US</td>
<td>20</td>
<td>85,059 (100)</td>
<td>30–55</td>
<td>4,670</td>
</tr>
<tr>
<td>Schulze, 2008</td>
<td>Germany</td>
<td>8–11</td>
<td>25,067 (61)</td>
<td>35–65</td>
<td>844</td>
</tr>
<tr>
<td>de Koning, 2011</td>
<td>US</td>
<td>20</td>
<td>40,475 (0)</td>
<td>40–75</td>
<td>2,689</td>
</tr>
<tr>
<td>Similä, 2012</td>
<td>Finland</td>
<td>12</td>
<td>25,943 (0)</td>
<td>50–69</td>
<td>1,098</td>
</tr>
<tr>
<td>Alhazmi, 2013</td>
<td>Australia</td>
<td>6</td>
<td>8,370 (100)</td>
<td>45–50</td>
<td>311</td>
</tr>
<tr>
<td>Ericson, 2013</td>
<td>Sweden</td>
<td>12</td>
<td>24,841 (61)</td>
<td>45–74</td>
<td>1,567</td>
</tr>
<tr>
<td>Sluijs, 2013</td>
<td>8 European countries</td>
<td>12</td>
<td>29,238 (62)</td>
<td>35–70</td>
<td>12,403</td>
</tr>
<tr>
<td>Nanri, 2015</td>
<td>Japan</td>
<td>5</td>
<td>64,674 (57)</td>
<td>40–69</td>
<td>1,191</td>
</tr>
</tbody>
</table>

## Table 2. Methodological assessments of the included studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Referent</th>
<th>Comparator</th>
<th>Adjustment factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer, 2000</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Age, total energy intake, BMI, waist-to-hip ratio, education, pack-years of smoking, alcohol intake, and physical activity</td>
</tr>
<tr>
<td>Hodge, 2004</td>
<td>Quartile 4</td>
<td>Quartile 1</td>
<td>Age, sex, country of birth, physical activity, family history of diabetes, alcohol intake, education level, weight change in the last 5 years, energy intake, BMI, and WHR</td>
</tr>
<tr>
<td>Villegas, 2007</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Age, kilocalories per day consumed, body mass index, waists-to-hip ratio, smoking status, alcohol consumption, physical activity, income level, education level, occupation, and diagnosis of hypertension</td>
</tr>
<tr>
<td>Halton, 2008</td>
<td>Decile 10</td>
<td>Decile 1</td>
<td>Age, BMI, smoking, postmenopausal hormone use, physical activity, alcohol intake, family history of type 2 diabetes in a first-degree relative and protein, cereal fiber, and total calories</td>
</tr>
<tr>
<td>Schulze, 2008</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Age, education, occupational activity, sport activity, smoking, alcohol intake, and total energy intake</td>
</tr>
<tr>
<td>de Koning, 2011</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Age, smoking, physical activity, coffee intake, alcohol intake, family history of T2DM, total energy intake, and BMI</td>
</tr>
<tr>
<td>Similä, 2012</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Age, intervention group, BMI, smoking, physical activity, intake of total energy, and coffee consumption</td>
</tr>
<tr>
<td>Alhazmi, 2013</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Area of residence, education, current smoking status, physical activity, self-rated health as good, menopausal status, BMI, alcohol consumption, total energy intake, saturated fatty acid, and mono-unsaturated fatty acid</td>
</tr>
<tr>
<td>Ericson, 2013</td>
<td>Tertile 3</td>
<td>Tertile 1</td>
<td>Age, sex, diet method version, season, BMI, education, alcohol intake, smoking, total energy intake, and leisure-time physical activity</td>
</tr>
<tr>
<td>Sluijs, 2013</td>
<td>Quartile 4</td>
<td>Quartile 1</td>
<td>Center, age, sex, education, physical activity, BMI, menopausal status, smoking status, alcohol consumption, energy intake, dietary protein, polyunsaturated: saturated fat ratio, and fiber</td>
</tr>
<tr>
<td>Nanri, 2015</td>
<td>Quintile 5</td>
<td>Quintile 1</td>
<td>Age, study area, smoking status, alcohol consumption, family history of diabetes mellitus, total physical activity, history of hypertension, total energy intake, coffee consumption, and BMI</td>
</tr>
</tbody>
</table>

RR: relative risk, OR: odds ratio, HR: hazard ratio.
<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Representativeness of the exposed cohort</td>
<td>Selection of the non-exposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Demonstration that outcome of interest was not present at start of study</td>
</tr>
<tr>
<td>Meyer, 2000&lt;sup&gt;27&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Hodge, 2004&lt;sup&gt;28&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Villegas, 2007&lt;sup&gt;30&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Halton, 2008&lt;sup&gt;31&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<tr>
<td>Schulze, 2008&lt;sup&gt;32&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>de Koning, 2011&lt;sup&gt;33&lt;/sup&gt;</td>
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<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Similä, 2012&lt;sup&gt;34&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<tr>
<td>Alhazmi, 2013&lt;sup&gt;35&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<tr>
<td>Ericson, 2013&lt;sup&gt;36&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
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<tr>
<td>Sluijs, 2013&lt;sup&gt;37&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Nanri, 2015&lt;sup&gt;38&lt;/sup&gt;</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
</tbody>
</table>

<sup>a</sup>: A maximum of 2 stars can be awarded for this item. A study controlling for age receives one star, and a study controlling for other major risk factors for diabetes receives an additional star.

<sup>b</sup>: A study with a follow-up period ≥5 years receives one star.

<sup>c</sup>: A study with a follow-up rate >90% receives one star.
The risk of bias among the studies included in the meta-analysis was relatively low.

**Qualitative summary**

The methodologies of all the studies included in our analysis were good in quality. The studies included in the systematic review were conducted in the US, European countries, and Asia Pacific Rim countries, and their follow-up durations were generally long enough for the outcome to occur. Although the majority of the enrolled subjects were middle-aged and free of chronic disease at baseline, healthcare professionals were predominant in the US cohorts and might not have been truly representative of the average population in the community.

In two cohorts consisting exclusively of men\textsuperscript{33,34} and another cohort,\textsuperscript{36} the risks of diabetes were significantly elevated among the subjects with low-carbohydrate diets (relative risk range, 1.15–1.31). In contrast, the risks in women\textsuperscript{30,31,38} were significantly lower (relative risk range, 0.63–0.79). The results in the other studies were inconclusive. A dose-response analysis was reported in 9 studies: a significant positive trend for men was observed in two,\textsuperscript{33,34} and a significant negative trend for women was observed in another two.\textsuperscript{31,38} Two studies that evaluated the effects of protein source consistently suggested that the risk of diabetes might be enhanced in subjects with animal-based dietary patterns, whereas it might be decreased in plant-based diets\textsuperscript{31,33} or an animal-based diet.\textsuperscript{38}

**Quantitative summary (meta-analysis)**

A total of 11 articles that provided sufficient information were included in the meta-analysis (Figure 1). The majority of the diagnosis ascertainment were based on self-reports. The follow-up rate was more than 90% in most of the studies. Carbohydrate intake was assessed using the residual method in 5 studies\textsuperscript{30,34,35,37,38} and by the density method in 3 studies.\textsuperscript{31–33} The method was not specified in the remaining reports. Of the 440,669 people (women, 68%) in the 11 cohort studies, 27,887 (6.3%) cases of incident diabetes were reported. Figure 2 illustrates the risk of diabetes among those adhering to low-carbohydrate diets, which was not statistically significant (pooled RR, 1.03; 95% CI, 0.91–1.16; $P = 0.65$; $I^2 = 79\%$).

Since the heterogeneity among the reports was statistically significant, we conducted a subgroup analysis according to the possible predictors in search of its source. The pooled RRs of the studies conducted in Europe,\textsuperscript{32,34,36,37} the US,\textsuperscript{27,31,33} Australia,\textsuperscript{28,35} and Asia\textsuperscript{30,38} were 1.12 (1.04–1.20), 1.07 (0.98–1.18), 1.10 (0.78–1.55) and 0.80 (0.70–0.90), respectively, and the differences among these subgroups were statistically
The RR of the studies using either dietary method were not significantly different (residual method, 0.96 [0.89–1.04]; density method, 1.08 [0.98–1.19]; P for difference = 0.06). The RR of the studies with a follow-up period shorter than 11 years and those with a follow-up period longer than 11 years were 0.92 (0.83–1.00) and 1.10 (1.03–1.17), respectively; this difference was statistically significant (P = 0.001). The pooled RR for men was significantly higher, while that for women was significantly lower (1.24 [1.12–1.36] vs. 0.79 [0.74–0.87], P for difference < 0.00001). We were unable to perform a subgroup analysis according to the body-mass index because the mean values were not stated or estimable in the majority of the reports. No apparent publication bias was apparent, as assessed using a funnel plot (data not shown).

Discussion

Our systematic review and meta-analyses of worldwide reports suggested that low-carbohydrate diets were associated with a non-significant risk of diabetes over the long term (period of one year or more). These findings support the hypothesis that the short-term (period of less than one year) benefits of low-carbohydrate diets for weight loss are potentially of little clinical benefit. In light of the fact that the number of people with obesity is increasing exponentially worldwide and that obesity is one of the leading risk factors of diabetes, our finding has substantial clinical and public implications on a global scale and points to a need for the further investigation of the long-term health effects of low-carbohydrate diets and other nutritional factors.

The strength of our present study is that the analysis was mainly based on updated long-term large population-based data originating from multiple nations and was thus more comprehensive than the data reported in previous articles. This finding was consistent with the pooled RR of the cross-sectional studies (data not shown). The included data were high quality and apparently had a sufficient power to detect differences in the risk of diabetes, and each result was adjusted for multiple confounders. Although the dietary assessment and the diagnosis of diabetes were mainly self-reported, the relative validity of carbohydrate measures using the Food Frequency Questionnaire has generally been reported to be moderate to good, and a high validation of the diagnosis of diabetes was confirmed in most of the included studies. The heterogeneity of the results of the component studies was relatively high: the large I² values indicated that the range of plausible risk estimates was wide, generally because of the diversity of the study designs, geographical locations, population backgrounds, ethnicities, and adjustments for potential confounders between studies. A subgroup analysis suggested that the major source of heterogeneity might have been the region, since the main dietary source and types of carbohydrate, the dietary practices, the population characteristics and the prevalence of obesity differ across regions. The length of the follow-up and the gender of the patients may have been other sources of heterogeneity, but these hypotheses cannot be statistically tested because of a lack of data.

Evidence has been accumulating to suggest that low-carbohydrate diets and their combination with high-protein diets are effective for weight loss and may have favorable short-term effects on the risk of diabetes and metabolic risk factors. Low-carbohydrate diets may be nutritionally safe and valid insofar as the carbohydrates are simple and refined and the main source of protein is from plants. The effect of low-carbohydrate diets may vary according to gender and region as well: such diets were reportedly associated with a lower risk of type 2 diabetes or lower cardiovascular and total mortality in Asian women. Despite these facts, our current study and a previous meta-analysis did not find a long-term health benefit when such nutritional quality was not considered. In fact, a recent meta-analysis has suggested protective effects of a low dietary glycemic index and a low glycemic load and a cohort study documented a significant association between rice intake and an increased risk of type 2 diabetes. Low-carbohydrate diets reportedly tend to result in the reduced intake of fiber and fruits and the increased intake of protein from animal sources, cholesterol, and saturated fat. In two US cohorts, subjects with diets high in animal protein
and fat had higher relative risks of diabetes than those with diets high in vegetable protein and fat at any given proportion of carbohydrate intake. In addition, a recent study showed that red meat intake was positively associated with the risk of diabetes. The beneficial effect of plant protein and fat may have been offset by the adverse effect of animal protein and fat in our calculations. The form of fat might also have affected the risk of diabetes.

Little is known about the consequences of low-carbohydrate diets with respect to other chronic health problems, such as cancer, kidney disease, osteoporosis, and mental conditions. The biology that underlies the positive correlation between low-carbohydrate diets and all-cause death has not yet been fully explained. Further studies to clarify this mechanism are eagerly awaited. Given the facts that low-carbohydrate diets are potentially unsafe and that calorie restriction has been demonstrated to be effective for weight loss regardless of nutritional composition, it might be premature to universally advocate low-carbohydrate diets for the time being. Further detailed studies to evaluate the effect of the source of protein and the nature of the carbohydrates are urgently needed.

Limitations
Our analysis should be interpreted in the context of the following limitations. The observational studies were scarce and were moderately heterogeneous as discussed; thus, a residual confounding bias may have existed and the result may not be generalizable, although we cannot assess this hypothesis. Next, we cannot definitely prove causality, particularly using observational studies, because of possible confounding factors and biases that may not have been fully adjusted for, which may have rendered the results less valid. In our analysis, the adjustment in each component study was adequate and fair. Confounding by treatment indication might bias the effect of diets. However, most of the target populations were free of chronic disease at baseline, and it is unlikely that the dietary habits had been modulated according to their previous health status. The dietary patterns may have varied over the course of the follow-up periods, but the dietary information was not updated in many of the studies, possibly affecting the magnitude of the risk as suggested by the subgroup analysis of the follow-up periods. Furthermore, the effects of individual nutritional components are difficult to distinguish. Despite these limitations, however, observational studies provide good available evidence regarding potential benefit and harm, and the temporal sequence of the events is appropriate. Regarding the external validity, it is also important to realize that the participants of the studies may not represent the general populations, mainly because the majority of the studies were performed in Western countries and healthcare professionals were the predominant subjects.

Even with these limitations, our analysis should provide physicians and healthcare practitioners with an incentive to pay attention to the potential effects on health in relation to low-carbohydrate diets. Of note, low-carbohydrate diets might be beneficial for Asian women as suggested in the subgroup analysis.

Conclusion
Our meta-analysis based on observational studies suggested that low-carbohydrate diets did not show any benefit on the risk of diabetes. However, the included studies were limited and heterogeneous. Our findings underscore the imminent need for large-scale trials on the complex interactions between macronutrients intake and long-term diabetes risk.

Acknowledgments
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