Efficacy of a meal sequence in patients with type 2 diabetes: a systematic review and meta-analysis

Yukiko Okami 1,2, Hideki Tsunoda 2,3, Jun Watanabe 2,4,5, Yuki Kataoka 2,6,7,8

ABSTRACT

Introduction This systematic review investigated the efficacy of a meal sequence, the carbohydrate-later meal pattern (CL), on type 2 diabetes mellitus (T2DM).

Research design and methods We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov until April 2020 to perform meta-analyses using random-effects models. Primary outcomes were hemoglobin A1c (HbA1c) and quality of life. Secondary outcomes were plasma concentrations of glucose, insulin and incretin 120 min after a meal, and any adverse outcomes. The revised Cochrane risk-of-bias tool and Grading of Recommendations, Assessment, Development, and Evaluation approach were used to assess the quality of individual studies and the body of evidence, respectively. The present study was registered in the UMIN Clinical Trials Registry.

Results We included 230 participants in eight trials, including both trials that examined long-term changes (more than 2 months and less than 2 years) and short-term changes (in 2-hour postprandial values). CL resulted in a slight to no difference in HbA1c (mean difference [MD] = –0.21% in the intervention group; 95% CI = –0.44% to –0.03%), plasma glucose (MD = 4.94 mg/dL; 95% CI = –8.34 mg/dL to +18.22 mg/dL), plasma insulin (MD = –3.63 µU/mL; 95% CI = –11.88 µU/mL to +4.61 µU/mL), plasma GLP-1 (MD = +0.43 pmol/L; 95% CI = –0.69 pmol/L to +1.56 pmol/L), and plasma GIP (MD = –2.02 pmol/L; 95% CI = –12.34 pmol/L to +8.31 pmol/L). All of these outcomes were of low-certainty evidence or very low-certainty evidence. None of the trials evaluated quality of life or adverse events.

Conclusions There was no evidence for the potential efficacy of recommending CL beyond standard dietary advice on T2DM.

Trial registration number UMIN000039979.

INTRODUCTION

Postprandial hyperglycemia is an independent risk factor for type 2 diabetes mellitus, and the control of postprandial glucose excursions has been suggested to reduce the progression of atherosclerosis and cardiovascular events. 1,2 The number of patients with diabetes worldwide is expected to increase to 366 million by 2030,3 and those with type 2 diabetes always initially require lifestyle guidance, including diet and exercise. Current dietary strategies to attenuate postprandial glucose are based on total energy intake and consumption and the amount or type of carbohydrate consumed despite the difficulties associated with adhering to a healthy diet by some patients. 4

SIGNIFICANCE OF THIS STUDY

What is already known about this subject?
- The number of patients with diabetes worldwide is expected to increase and those with type 2 diabetes always initially require lifestyle guidance, including diet and exercise.
- Current dietary strategies to attenuate postprandial glucose are based on total energy intake and consumption and the amount or type of carbohydrate consumed despite the difficulties associated with adhering to a healthy diet by some patients.

What are the new findings?
- We conducted a systematic review and meta-analysis in order to confirm whether the meal sequence, the carbohydrate-later meal pattern, would affect outcomes of diabetes.
- Carbohydrate-later meal patterns may result in a slight to no difference in hemoglobin A1c after 2 months to 2 years. Similarly, carbohydrate-later meal patterns may result in a slight to no difference in plasma glucose, insulin, and incretin 120 min after meals.
- There was no evidence for the potential efficacy of recommending carbohydrate-later meal patterns beyond standard dietary advice on type 2 diabetes.

How might these results change the focus of research or clinical practice?
- These results suggest that the meal sequence will not be strongly prioritized in clinical practice.
- Further large scale, well-designed controlled trials of the meal sequence are warranted.
A meal sequence, the carbohydrate-later meal pattern, was focused on as an easy and effective strategy to reduce postprandial glucose excursions in previous trials. This pattern means the order of eating within a meal. In other words, before consuming starchy or high glycemic index (GI) foods, eat carbohydrate-free or low GI foods first, such as proteins, fats, and vegetables. However, there have not yet been any systematic reviews that have examined the efficacy of this pattern, the meal sequence, to improve diabetes in randomized controlled trials (RCTs). Therefore, the meal sequence has never been presented in the diabetes guidelines as solid evidence.

A systematic review of the effects of changing the order in which carbohydrates are consumed on improvements in diabetes is very important for establishing whether this strategy may be used in future clinical practice. Therefore, the purpose of the present study was to systematically review evidence in order to confirm whether the meal sequence, the carbohydrate-later meal pattern, would improve diabetes.

**MATERIALS AND METHODS**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Online supplemental table S1 shows the PRISMA 2009 checklist. Detailed methods are described in UMIN000039979 in the UMIN Clinical Trials Registry (https://upload.umin.ac.jp/cgi-bin/ctr_e/ctr_view.cgi?recptno=R000045533).

**Eligibility criteria for included studies**

We included all RCTs that examined the efficacy of meal sequence in patients with type 2 diabetes or pre-diabetic conditions. The details were as follows.

We included all RCTs irrespective of the publication status, including individual and crossover RCTs. All other non-RCTs were excluded. Studies in any language from any country and any follow-up periods were accepted for screening. Men and women of all ages were included. Studies on healthy subjects, patients with type 1 diabetes, and patients after surgery (eg, postgastrectomy patients) were excluded. Carbohydrate-later meal patterns were used as intervention criteria. Carbohydrates included rice, bread, and noodles; precarbohydrate meals included all sources of protein, fat, vitamins and minerals, and dietary fiber. If interventions other than the meal sequence were used, we only included cases in which the meal sequence alone was assessable (eg, typical diet instructions+meal sequence instructions vs typical diet instructions). The duration of the intervention was one or more meals, and the time of the meal was any time. However, supplements were excluded. The control group was defined as the carbohydrate-first meal pattern or a random meal sequence (no intervention for the meal sequence) and included typical dietary instructions. As criteria for inclusion, energy intakes by the intervention and control groups were similar, and any RCTs that required only the intervention group to eat something before the consumption of a carbohydrate were excluded.

**Outcome measures**

The following primary outcomes were measured:

1. Hemoglobin A1c (HbA1c) (national glycohemoglobin standardization program (NGSP)) follow-up.
2. Physical component summary score (short form (SF) 36, SF12, and SF8).
3. Mental component summary score (SF36, SF12, and SF8).

Secondary outcomes were as follows:

1. Plasma glucose 120 min after a meal.
2. Plasma insulin 120 min after a meal.
3. Plasma incretin (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino trope polypeptide (GIP)) 120 min after a meal.
4. All adverse events.

In accordance with current guidelines, the present study used HbA1c, which reflects long-term blood glucose levels, as the primary outcome and postprandial blood glucose levels as the secondary outcome.

**Search methods for study identification**

**Electronic searches**

To identify relevant trials, we searched the following electronic databases on 15 April 2020:

1. The Cochrane Central Register of Controlled Trials (CENTRAL).
2. MEDLINE via Ovid.
3. Embase via ProQuest.

See online supplemental method S1 for details on search strategies.

**Searches of other resources**

We also searched the following registries to identify completed but unpublished trials and investigate reporting bias.

1. WHO International Clinical Trials Platform Search Portal (ICTRP).
2. ClinicalTrials.gov.

See online supplemental method S1 for details on search strategies.

The references of both extracted studies and international guidelines were also checked. We contacted authors if the extracted studies lacked the necessary information.

**Data collection and analysis**

**Study selection**

Two independent reviewers screened the titles and abstracts identified in the search. All of the extracts from the two reviewers were subjected to a full-text review. They then decided independently whether to
include the full text in the review. When it was an abstract-only study or when it was unclear whether it met the criteria for review, we contacted the original authors. Disagreements between the two reviewers were discussed and resolved among themselves. We discussed with a third reviewer where necessary. We followed a predefined protocol to screen abstracts and full texts and used predefined criteria in the registered protocol. One lead author (YO) checked all included studies and the exclusion criteria for all records subjected to the full-text screening procedure. Therefore, the decision did not systematically differ.

Data extraction and management
Data extraction in the present study was performed independently by two reviewers. Disagreements between the two reviewers were discussed and resolved among themselves. We discussed with a third reviewer where necessary and contacted the original author. If data for extraction were not available in the original paper, we contacted the authors to obtain them. Regarding the data extraction form, we used a prechecked form with 10 randomly selected studies. Please refer to online supplemental method S1 for details on extracted information.

Assessment of the risk of bias of included studies
Two reviewers conducted the study independently using the Risk of Bias 2 tool. Disagreements between the two reviewers were discussed and resolved by themselves. We discussed with a third reviewer where necessary.

Measures of the treatment effect
Regarding continuous outcomes (HbA1c, plasma glucose, plasma insulin, and plasma incretin), the mean difference (MD) with 95% CI was shown. HbA1c measured in Japan Diabetes Society (JDS) units was converted to NGSP units using the following formula: NGSP (%) = 1.02 * JDS (%) + 0.25. GLP-1 and GIP measured in pg/mL were converted to pmol/L using the following formulas: GLP-1 (pmol/L) = GLP-1 (pg/mL) / 3297.6 * 1000; GIP (pmol/L) = GIP (pg/mL) / 4983.5 * 1000. All MDs and 95% CIs used absolute changes not relative changes.

Dealing with analyses
To integrate the means and SD of continuous variables, we followed the methods of the Cochrane handbook. Units of randomization: regarding crossover tests, we asked the authors for the first half of the data, used only the first half if available or used reported values if not available, and reflected them in the Risk of Bias 2 tool. Multiple identical outcome assessments: the main outcome was HbA1c concentrations after the intervention, and if there were multiple endpoint measurements, the endpoint was 120 min later for the short-term intervention (assessment of one meal) and the longest follow-up period for the long-term intervention.

Dealing with missing values
Dropouts
Following the recommendations of The Cochrane Handbook, imputation was not performed. We conducted a meta-analysis of the data presented by the original authors.

Missing values
We contacted the original authors.

Missing statistics
If only SEs were reported, a SD was obtained from the SE of a mean by multiplying by the square root of the sample size: SD = SE * square root of N. 

Assessment of heterogeneity
We initially evaluated heterogeneity visually using a forest plot. We then calculated I² values (I² values of 0%–40%: may not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may be substantial). The Cochrane χ² test (Q-test) was performed for I² values, and a p value <0.10 was considered to be significant.

Assessment of publication bias
We searched the Clinical Trials registry site (ClinicalTrials.gov, ICTRP) for studies that were completed but not yet published. The funnel plot assessed publication bias for the primary outcome (online supplemental figure S1).

Data synthesis
We pooled data using a random-effects model. The DerSimonian and Laird method was used in the random-effects meta-analysis. All analyses were conducted using Review Manager software (RevMan V.5.4.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Subgroup analysis and investigation of heterogeneity
We aimed to identify possible causes of heterogeneity. The following prespecified subgroup analyses of the primary outcomes were planned: (1) types of carbohydrates (rice or other than rice); (2) types of foods containing a small amount of carbohydrates with low GI (vegetables or other than vegetables); (3) duration of the follow-up (long- or short-term); and (4) meal types (breakfast, lunch, or dinner).

Sensitivity analysis
The following prespecified sensitivity analyses of primary outcomes were planned:
(1) repeating the analysis using a fixed-effects model instead of random-effects model; and (2) excluding studies with ‘the analysis including imputed data’.

Summary of findings table
The main results of our review are presented in the summary of findings table, which includes an overall
grading of evidence related to each of the main outcomes using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, based on the recommendations of the Cochrane Handbook.

Registration and the differences between the protocol and review
We registered the protocol in UMIN000039979 in the UMIN Clinical Trials Registry (https://upload.umin.ac.jp/cgi-bin/ctr_e/ctr_view.cgi?recptno=R000045533).

The following is a list of items that were planned in the protocol but were ultimately not implemented (not possible to implement or did not need to be implemented).

► Because the number of included trials was smaller than expected, we decided not to account for the duration of intervention as an inclusion criterion because of no strong justification, currently evaluating both short-term postprandial effects and effects of advice for a habitual diet. For the same reason, we did not perform stratified analysis by gender and did not use funnel plots for inference of publication or small-study bias though we generated them (online supplemental figure S1).

RESULTS

Search results
After removing duplicates, we identified 3924 records during the search conducted in April 2020 (figure 1). We included 13 trials in the qualitative synthesis and detected one unpublished trial and four completed trials without clear data on outcomes. Ultimately, 230 participants in eight trials were included in the quantitative synthesis. These trials included both trials that examined long-term changes after 2 months or longer and trials that examined short-term changes in 2-hour postprandial values.

Table 1 and online supplemental table S2 summarize the published studies included in the qualitative synthesis.

Primary outcomes

HbA1c
Data from three trials comprising 147 participants that measured HbA1c were pooled in our meta-analysis (table 2, figures 2 and 3A). Carbohydrate-later meal patterns may result in a slight to no difference in HbA1c (MD, 0.21% lower in the intervention group; 95% CI 0.44% lower to 0.03% higher; p=0.09; low-certainty evidence). No significant heterogeneity was indicated.

Figure 1 PRISMA flow diagram. CENTRAL, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica Database; ICTR, International Clinical Trials Platform Search Portal; MEDLINE, Medical Literature Analysis and Retrieval System On-Line; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
As a subgroup analysis, we included rice only as the carbohydrate source; however, no change was observed in HbA1c with the intervention (online supplemental figure S2A). In the sensitivity analysis, although we also calculated a fixed effect model instead of a random effects model, the results were the same as those for the random effects model. In the sensitivity analysis, we also calculated a fixed effect model instead of a random effects model, the results were the same as those for the random effects model.

Quality of life
We searched for quality of life indicator outcomes, specifically the physical and mental component summary scores based on the 12-item medical outcomes study short form health survey (SF-12), SF-36, or SF-8 but were unable to find a single outcome.

Secondary outcomes
Plasma glucose
Data from six trials that measured plasma glucose 120 min after meals in 143 participants were pooled for the meta-analysis (table 2, figure 3B, online supplemental figure S3). Carbohydrate-later meal patterns may result in a slight to no difference in plasma glucose (MD, 4.94 mg/dL higher in the intervention group; 95% CI, 8.34 mg/dL lower to 18.22 mg/dL higher; p=0.47; low-certainty evidence). No significant heterogeneity was indicated (tau²=1.35; I²=0%) (table 2, figure 3B). Subgroup analyses were conducted by lunch and dinner. We also performed stratified analyses by a short-term intervention (120 min after a meal) and the carbohydrate source of rice only or non-rice, but none of which showed significant changes in blood glucose levels due to the intervention (online supplemental figure S2D–H).

Plasma insulin
Data from five trials that measured plasma insulin after 120 min of meals in 136 participants were pooled for the meta-analysis (table 2, figure 3C, online supplemental figure S4). All trials measured blood insulin levels in μIU/mL. Evidence for the effects of carbohydrate-later meal patterns on plasma insulin was uncertain (MD, 3.63 μIU/mL lower in the intervention group; 95% CI 11.88 μIU/mL lower to 4.61 μIU/mL higher; p=0.39; very low-certainty evidence). Significant heterogeneity was observed (tau²=38.90; I²=68%) (table 2, figure 3C). As a subgroup analysis, we only examined the short-term intervention (120 min after the meal) and rice only or non-rice as the carbohydrate source, none of which resulted in a significant insulin change with the intervention (online supplemental figure S2I–K).

Plasma incretin
Data from three trials that measured plasma concentrations of GLP-1 and GIP 120 min after meals in 120 participants (table 2, figure 3D,E, online supplemental figure S5). Carbohydrate-later meal patterns may result in a slight to no difference in plasma GLP-1 (MD, 0.43 mg/dL higher in the intervention group; 95% CI 0.69 mg/dL lower to 1.35 mg/dL higher; p=0.39; low-certainty evidence). Significant heterogeneity was indicated (tau²=4.50; I²=59%) (table 2, figure 3D). Subgroup analyses were conducted by lunch and dinner. We also performed stratified analyses by a short-term intervention (120 min after a meal) and the carbohydrate source of rice only or non-rice, but none of which showed significant changes in plasma incretin levels due to the intervention (online supplemental figure S2F–H).

### Table 1: Summary of published studies including a qualitative synthesis

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Men/women, n</th>
<th>Age, years</th>
<th>BMI, kg/m²</th>
<th>Diabetes history, years</th>
<th>Follow-up period</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bae et al (2019)</td>
<td>Korea</td>
<td>5/10</td>
<td>Mean 62.9 (SD 4.3)</td>
<td>Mean 24.8 (SD 3.5)</td>
<td>Mean 13.8 (SD 6.7)</td>
<td>180 min</td>
<td>ITT</td>
</tr>
<tr>
<td>Imai et al (2019)</td>
<td>Japan</td>
<td>7/8</td>
<td>Mean 61.7 (SD 11.6)</td>
<td>Mean 24.7 (SD 4.3)</td>
<td>Mean 5.3 (SD 8.8)</td>
<td>120 min</td>
<td>ITT</td>
</tr>
<tr>
<td>Imai et al (2011)</td>
<td>Japan</td>
<td>48/53</td>
<td>Mean 63.4 (SD 11.7)</td>
<td>Mean 23.4 (SD 4.1)</td>
<td>Mean 7.3 (SD 8.3)</td>
<td>2 years</td>
<td>ITT</td>
</tr>
<tr>
<td>Imai et al (2012)</td>
<td>Japan</td>
<td>–</td>
<td>Mean 65.7 (SD 9.6)</td>
<td>–</td>
<td>–</td>
<td>72 hours (3 days)</td>
<td>ITT</td>
</tr>
<tr>
<td>Imai et al (2013)</td>
<td>Japan</td>
<td>6/13</td>
<td>Mean 65.5 (SD 9.4)</td>
<td>Mean 22.5 (SD 3.1)</td>
<td>Mean 16.4 (SD 10.2)</td>
<td>72 hours (3 days)</td>
<td>ITT</td>
</tr>
<tr>
<td>Imai et al (2014)</td>
<td>Japan</td>
<td>–</td>
<td>Mean 69.1 (SD 6.7)</td>
<td>–</td>
<td>–</td>
<td>ITT</td>
<td></td>
</tr>
<tr>
<td>Kuwata et al (2016)</td>
<td>Japan</td>
<td>9/3</td>
<td>Mean 59.7 (SD 9.7)</td>
<td>Mean 25.3 (SD 4.1)</td>
<td>Mean 3.6 (SD 5.5)</td>
<td>240 min</td>
<td>ITT</td>
</tr>
<tr>
<td>Shukla et al (2017)</td>
<td>USA</td>
<td>7/9</td>
<td>Mean 57.7 (SD 7.6)</td>
<td>Mean 32.8 (SD 3.3)</td>
<td>Mean 3.8 (SD 2.4)</td>
<td>180 min</td>
<td>ITT</td>
</tr>
<tr>
<td>Shukla et al (2018)</td>
<td>USA</td>
<td>7/9</td>
<td>Mean 57.7 (SD 7.6)</td>
<td>Mean 32.8 (SD 3.3)</td>
<td>Mean 3.8 (SD 2.4)</td>
<td>180 min</td>
<td>ITT</td>
</tr>
<tr>
<td>Shukla et al (2019)</td>
<td>USA</td>
<td>4/11</td>
<td>Mean 52.4 (SD 3.4)</td>
<td>Mean 34.2 (SD 1.1)</td>
<td>NA</td>
<td>180 min</td>
<td>ITT</td>
</tr>
<tr>
<td>Trico et al (2016)</td>
<td>Italy</td>
<td>13/7</td>
<td>Mean 64.5 (SD 21.4)</td>
<td>Mean 30.6 (SD 3.5)</td>
<td>Less than 5</td>
<td>8 weeks</td>
<td>PP</td>
</tr>
<tr>
<td>Yabe et al (2019)</td>
<td>Japan</td>
<td>–</td>
<td>Mean 49.5 (SD 5.9)</td>
<td>Mean 25.9 (SD 2.1)</td>
<td>NA</td>
<td>22–26 weeks (6 months)</td>
<td>PP</td>
</tr>
</tbody>
</table>

*Studies included in the qualitative synthesis.
BMI, body mass index; ITT, intention-to-treat; PP, per-protocol.
Given the effect size of −0.21% in HbA1c (as an absolute value) over 2 months or longer, the meal sequence may not need to be positively taught in clinical practice. In the current diabetes guidelines, diet and exercise therapy are fundamental for the management of diabetes.6–8 A systematic review of obese patients with type 2 diabetes reported that a weight loss of 5% or more resulted in reduction of HbA1c by 0.91% after 1 year,17 and total energy intake and appropriate BMI were emphasized as the most important factors. Although there is no clear evidence on nutrient intake proportions, a RCT reported that a low-carbohydrate diet resulted in reduction of HbA1c by 0.6% after 6 months.18 Regarding lipids, a previous systematic review reported that a diet with increased monounsaturated fatty acids produced reduction of HbA1c by 0.21% after 6 months compared with a diet that decreased it.19 Furthermore, a systematic review on exercise therapy reported that exercise for more than 12 weeks lowered HbA1c by 0.67%.20 The reduction of HbA1c by 0.21% due to the meal sequence in the present

## DISCUSSION

Regarding primary outcomes, carbohydrate-later meal patterns may result in a slight to no difference in HbA1c after 2 months to 2 years. Similarly, for secondary outcomes, carbohydrate-later meal patterns may result in a slight to no difference in plasma glucose, insulin, and incretin 120 min after meals.

### All adverse events

We searched for any adverse event outcomes through the intervention; however, none of the trials reported this outcome.

### Table 2 Summary of findings

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of participants (studies) followed up</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c concentrations (NGSP)</td>
<td>147</td>
<td>Low†</td>
<td>The mean HbA1c (%) ranged from 6.1% to 7.7%</td>
</tr>
<tr>
<td>Physical component summary score (SF36, SF12, SF8)</td>
<td>NR</td>
<td></td>
<td>Risk with the carbohydrate-first meal pattern or random meal sequence</td>
</tr>
<tr>
<td>Mental component summary score (SF36, SF12, SF8)</td>
<td>NR</td>
<td></td>
<td>Risk difference with the carbohydrate-later meal pattern§</td>
</tr>
<tr>
<td>Plasma glucose 120 min after meals</td>
<td>143</td>
<td>Low†</td>
<td>Mean plasma glucose (mg/dL) 120 min after all meals ranging from 97.1 to 281.5 mg/dL</td>
</tr>
<tr>
<td>Plasma insulin 120 min after meals</td>
<td>136</td>
<td>Very low†‡</td>
<td>Mean plasma insulin (μIU/mL) 120 min after all meals ranging from 6.6 to 94.5 μIU/mL</td>
</tr>
<tr>
<td>Plasma GLP-1 120 min after meals</td>
<td>76</td>
<td>Low†</td>
<td>Mean plasma GLP-1 (pmol/L) 120 min after all meals ranging from 3.2 to 22.3 pmol/L</td>
</tr>
<tr>
<td>Plasma GIP 120 min after meals</td>
<td>44</td>
<td>Low†</td>
<td>Mean plasma GIP-1 (pmol/L) 120 min after all meals ranging from 24.1 to 76.5 pmol/L</td>
</tr>
<tr>
<td>All adverse events</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence.**

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is markedly different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be markedly different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.

*Downgraded due to the risk of bias.

† The sample size was small. The sample size did not meet the criteria of the optimal information size (OIS) (400). OIS was 400 if alpha D0.05, beta D0.2, delta D0.2.

‡ The I² statistic was higher than 60%, showing great heterogeneity and the direction of the effect was different.

§ The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GIP: glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, hemoglobin A1c; MD, mean difference; NGSP, national glycohemoglobin standardization program; NR, not reported; RCTs, randomized controlled trials; SF, short form.

dL lower to 1.56 mg/dL higher; p=0.45; low-certainty evidence). Carbohydrate-later meal patterns may result in a slight to no difference in plasma glucose, insulin, and incretin 120 min after meals.
A study was not as large as those by diet and exercise in these studies. In addition, a previous systematic review found that HbA1c lowering ≤0.3% had no effect, whereas HbA1c lowering ≥0.5% had a −13% (95% CI −20% to −5%) effect on major cardiovascular events. Therefore, a reduction of HbA1c by 0.21% is not considered to be a value with a certain effect and, thus, the meal sequence may not need to be intensively taught in clinical practice.

As a clinical implication, it may be better to prioritize conventional diet and exercise therapy. The clinical utility of the meal sequence remains unclear. In actual clinical practice, there are time and cost restrictions on dietary guidance. In the current dietary guidelines for diabetes care, dietitians and other healthcare providers initially prioritize the energy balance for patients with type 2 diabetes, particularly obese patients. In other words, they provide guidance to reduce total energy intake and increase physical activity. They then recommend an exercise strategy based on aerobic exercise, resistance exercise, or a combination. If more time is available or in consideration of other diseases, such as dyslipidemia, hypertension, and renal disease, a change in nutrient intake proportions and food intake may also be advised. The results of the present study suggest that the efficacy of the meal sequence on diabetes do not outweigh the importance of a known total energy balance (including energy restrictions, appropriate BMI, and exercise regimens), nutrient intake, and food content. Instructions by the meal sequence are not harmful. However, in consideration of the time and costs associated with counseling patients with diabetes, it may be more beneficial to prioritize conventional diet and exercise.

Since the results of the present study had a low certainty of evidence, they need to be interpreted with caution. Due to the very small number of RCTs on the meal sequence, the present results showed a low certainty of evidence. Although many RCTs have examined the efficacy of consuming some foods or nutrients (including supplements) before meals, they were excluded from this systematic review because of differences in total energy intake between the intervention and control groups, which made rigorous comparisons difficult. In order to increase the reliability of results, it is of the greatest importance to initially increase the sample size of trials examining the efficacy of the meal sequence on type 2 diabetes. Studies using the continuous glucose monitoring may be mandatory to decipher whether or not meal sequencing could be useful. It may also be possible to conduct higher quality RCTs in the future by rigorous randomization, the blinding of researchers, and

**Figure 2** (A) Risk of bias graph for HbA1c. (B) Risk of bias summary for HbA1c. (A) Review of author judgements on the risk for each bias item presented as percentages across trials. (B) Review of author judgements on the risk for each bias item in the trials. HbA1c, hemoglobin A1c.
the publication of protocols. Since the present results were based on patients with type 2 diabetes only, the generalizability of the results obtained to include healthy subjects and patients with type 1 diabetes is not possible. Similarly, since five out of the eight RCTs included in the present study were conducted on Asians, it remains unclear whether the same results may be obtained from a Western population, and this aspect also made it difficult to generalize the present results.

The limitations of the present study were as follows. First, we planned to include quality of life as a primary outcome because a balanced evaluation of interventions requires an analysis of both benefits and adverse effects; however, they were not reported by any of the RCTs included. Unlike trials in which medication was the intervention, trials in which dietary guidance was the intervention were more likely to lack these aspects. In long-term RCTs, a decrease in quality of life (eg, decreased social relationships and depressive tendencies) due to the inability to freely take in meals is expected. Therefore, quality of life needs to be evaluated in the design of future RCTs. Second, it is possible that underestimation of HbA1c may have occurred due to the inevitable decrease in compliance when looking at long-term effects. In addition, the decrease in compliance due to long-term intervention may have also contributed to the lower certainty of evidence. We could not identify any feeding trials that provided meals to improve compliance. The present study evaluated trials that tested an intervention of providing dietary advice. However, since no meaningful change was observed in plasma glucose at 2 hours in the short term, the order of meals may result in a slight to no difference.
in diabetes improvement as a whole. Third, there were very few RCTs examining the efficacy of meal sequence on HbA1c, and the wide range of intervention periods in the included articles made interpretation difficult. More importantly, the small number of RCTs produced results that were low certainty for both primary and secondary outcomes. We estimated ‘average’ effects from those limited number of trials. Therefore, some patients with diabetes may possibly gain benefit by carbohydrate-later meal patterns but many others may not. This study has not been able to clarify such a possibility distinct from no effect. Fourth, there were trials whose design was a cross-over RCT and for which data from only the first half or the corresponding t-test results and correlation coefficients needed for the calculations were not available. Incorporating data from the latter part of the study may be affected by carryover effects from the first half. However, we expected this carryover effects to lead to an underestimation of the results.

The strength of the present study was its carefully and rigorously designed screening, extraction, and scoring process based on the Cochrane Handbook.14 The present study is of importance because it is the first systematic review to examine the efficacy of the meal sequence on type 2 diabetes.

In conclusion, there was no evidence for the potential efficacy of recommending carbohydrate-later meal patterns beyond standard dietary advice on type 2 diabetes. These results suggest that the meal sequence will not be strongly prioritized in clinical practice. Further large-scale well-designed RCTs are warranted.

Author affiliations
1NCD Epidemiology Research Center, Shiga University of Medical Science, Otsu, Japan
2Systematic Review Workshop Peer Support Group (SRWS-PSG), Osaka, Japan
3Department of Family Medicine, University of Pittsburgh Medical Center Shadyside, Pittsburgh, Pennsylvania, USA
4Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke, Japan
5Division of Community and Family Medicine, Jichi Medical University, Shimotsuke, Japan
6Department of Internal Medicine, Kyoto Min-Iken Asukai Hospital, Kyoto, Japan
7Section of Clinical Epidemiology, Department of Community Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
8Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan

Acknowledgements I would like to express our deepest gratitude to the Systematic Review Workshop Peer Support Group (SRWS-PSG) for their cooperation in the present study.

Contributors YO, JW, and YK contributed substantially to the conceptualization, methodology, data analysis, interpretation, and writing of the manuscript; YO and HT were primarily engaged in study identification, study selection, data extraction, and evaluation. YO will be the guarantor of the entire content, will take full responsibility for the study and/or conduct of the study; will have access to the data, and will have control over the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Although this study involved human subjects, ethical approval was not obtained again for the present study because it had been approved in the individual original studies included in the systematic review. Participants in each study confirmed that they had given informed consent before participating in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data to support the results of this study can be obtained from the original study. However, some values that were not published in the original paper can be obtained from the corresponding author upon request. In such cases, permission must be obtained from the corresponding author of the original paper at the same time.

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ORCID iD
Yukiko Okami http://orcid.org/0000-0002-5651-7872

REFERENCES


Method S1. Search strategy

CENTRAL

#1 [mh "Diabetes Mellitus, Type 2"]
#2 diabet*:ti,ab,kw
#3 #1 OR #2
#4 [mh "Gastric Emptying"]
#5 [mh "Postprandial Period”]
#6 "intake sequence*":ti,ab,kw
#7 "meal sequence*":ti,ab,kw
#8 ("meal adj order*"):ti,ab,kw
#9 ("meal adj pattern*"):ti,ab,kw
#10 "postprandial insulin":ti,ab,kw
#11 "postprandial glycemia":ti,ab,kw
#12 "postprandial glucose":ti,ab,kw
#13 "postprandial rise":ti,ab,kw
#14 "dietary instruction*":ti,ab,kw
#15 ("Before adj Carbohydrate*"):ti,ab,kw
#16 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 [mh "Dietary Carbohydrates"]
#18 [mh starch]
#19 [mh "Glycemic Index"]
#20 [mh "Glycemic Load”]
#21 [mh meals]
#22 [mh eating]
#23 carbohydrate*:ti,ab,kw
#24 starch*:ti,ab,kw
#25 "Glycemic Index":ti,ab,kw
#26 "Glycemic load":ti,ab,kw
#27 glycemia:ti,ab,kw

#28 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#29 #3 AND #16 AND #28

**MEDLINE (via Ovid)**

#1 exp Diabetes Mellitus, Type 2/
#2 diabet*.mp.
#3 1 or 2
#4 exp Gastric Emptying/
#5 exp Postprandial Period/
#6 intake sequence*.mp.
#7 meal sequence*.mp.
#8 (meal adj order*).mp.
#9 (meal adj pattern*).mp.
#10 postprandial insulin.mp.
#11 postprandial glycemia.mp.
#12 postprandial glucose.mp.
#13 postprandial rise.mp.
#14 dietary instruction*.mp.
#15 (Before adj Carbohydrate*).mp.
#16 or/4-15
#17 exp Dietary Carbohydrates/
#18 exp starch/
#19 exp Glycemic Index/
#20 exp Glycemic Load/
#21 exp meals/
#22 exp eating/
#23 carbohydrate*.mp.
#24 starch*.mp.
#25 Glycemic Index.mp.
#26 Glycemic load.mp.
#27 glycemia.mp.
#28 or/17-27
#29 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or random*.ab. or trial.ab. or groups.ab.
#30 exp animals/ not humans.sh.
#31 29 not 30
#32 3 and 16 and 28
#33 31 and 32

EMBASE (via ProQuest)

S1 (EMB.EXACT.EXPLODE("non insulin dependent diabetes mellitus"))
S2 (ab(diabet*) OR ti(diabet*))
S3 (S1 OR S2)
S4 (EMB.EXACT.EXPLODE("stomach emptying"))
S5 (EMB.EXACT.EXPLODE("postprandial state"))
S6 (ab(intake sequence*) OR ti(intake sequence*))
S7 (ab(meal sequence*) OR ti(meal sequence*))
S8 (ab(meal NEAR order*) OR ti(meal NEAR order*))
S9 (ab(meal NEAR pattern*) OR ti(meal NEAR pattern*))
S10 (ab(postprandial insulin) OR ti(postprandial insulin))
S11 ((ab(postprandial glycemia) OR ti(postprandial glycemia)))
S12 ((ab(postprandial glucose) OR ti(postprandial glucose)))
S13 ((ab(postprandial rise) OR ti(postprandial rise)))
S14 ((ab(dietary instruction*) OR ti(dietary instruction*)))
S15 ((ab(Before NEAR Carbohydrate*) OR ti(Before NEAR Carbohydrate*)))
S16 (S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15)
S17 (EMB.EXACT("carbohydrate intake"))
S18 EMB.EXACT.EXPLODE("starch")
S19 (EMB.EXACT.EXPLODE("glycemic index"))
S20 (EMB.EXACT.EXPLODE("glycemic load"))
S21 EMB.EXACT.EXPLODE("meal")
S22 EMB.EXACT.EXPLODE("eating")
S23 ((ab(carbohydrate*) OR ti(carbohydrate*)))
S24 ((ab(starch*) OR ti(starch*)))
S25 ((ab(Glycemic Index) OR ti(Glycemic Index)))
S26 ((ab(Glycemic load) OR ti(Glycemic load)))
S27 ((ab(glycemia) OR ti(glycemia)))
S28 (S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27)
S29 ((ab(random*) OR ti(random*)) OR (ab(placebo*) OR ti(placebo*)) OR (ab(double NEAR/1 blind*) OR ti(double NEAR/1 blind*)))
S30 (S3 AND S16 AND S28)
S31 S30 AND S29

**ICTRP**

Advanced search

#1 Conditions: ("Diabetes Mellitus" OR diabet*)

AND

#2 Intervention: (((intake OR meal) AND (sequence OR order OR pattern)) OR (postprandial AND (insulin OR glycemia OR glucose OR rise)) OR "dietary instruction") AND (carbohydrate OR starch OR "Glycemic Index" OR "Glycemic load" OR glycemia)

#3 #1 AND #2

Recruitment status is ALL.
clinicaltrials.gov

Advanced search

(((intake OR meal) AND (sequence OR order OR pattern)) OR (postprandial AND (insulin OR glycemia OR glucose OR rise)) OR "dietary instruction") AND (carbohydrate OR starch OR "Glycemic Index" OR "Glycemic load" OR glycemia) | Interventional Studies | Diabetes Mellitus, Type 2
Method S2. Information extracted from included studies

1) General information
Author, Year of publication, Title, Journal (title, volume, pages), Language, Country, Publication status, Country, Protocol, Funding

2) Trial design
Type of randomization (crossover or parallel), Blindness, Date of study initiation

3) Participants
Inclusion criteria, Exclusion criteria, Definition of type 2 diabetes, Total sample size, Age, Sex, Body mass index, Diabetes history, HbA1c levels.

4) Intervention
Number in the intervention group, Number in the control group, Type of intervention (e.g. eat vegetable salad first, then rice 10 minutes later), Type of control (e.g. eat rice first, then vegetable salad 10 minutes later), Other rules for diet (e.g. participants were seated for two hours during the test and were not allowed to exercise), Follow-up duration

5) Outcomes
Methods of assessment, Number of missing participants, Type of analysis (e.g. intention to treat, per-protocol), Pre-test and post-test means or change values and standard deviations or standard errors for all groups for all outcomes specified above
Table S1. PRISMA 2009 checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td>TITLE</td>
<td></td>
<td>Title</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<tr>
<td>ABSTRACT</td>
<td></td>
<td>Structured summary</td>
<td>2</td>
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<td></td>
<td>2</td>
<td>Provide a structured summary including, where applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td></td>
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<tr>
<td>INTRODUCTION</td>
<td></td>
<td>Rationale</td>
<td>4</td>
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<td></td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<td>4</td>
<td>Objectives</td>
<td>4</td>
</tr>
<tr>
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<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and the study design (PICOS).</td>
<td></td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td>Protocol and registration</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it may be accessed (e.g., Web address), and, where available, provide registration information including the registration number.</td>
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<td></td>
<td>6</td>
<td>Eligibility criteria</td>
<td>4-5</td>
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<tr>
<td></td>
<td></td>
<td>Specify study characteristics (e.g., PICOS, length of the follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td></td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>5</td>
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<tr>
<td>Search</td>
<td>8</td>
<td>Present the full electronic search strategy for at least one database, including any limits used, such that it may be repeated.</td>
<td>Method S1</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in a systematic review, and, where applicable, included in the meta-analysis).</td>
<td>5-6</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>6</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS and funding sources) and any assumptions and simplifications made.</td>
<td>Method S2</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing the risk of bias of individual studies (including the specification of whether this was performed at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>6</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio and difference in means).</td>
<td>6</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining the results of studies, if performed, including measures of consistency (e.g., I^2) for each meta-analysis.</td>
<td>7</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of the risk of bias that may affect cumulative evidence (e.g., publication bias and selective reporting within studies).</td>
<td>7</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe the methods of additional analyses (e.g., sensitivity or subgroup analyses and meta-regression), if performed, indicating which were pre-specified.</td>
<td>7</td>
</tr>
</tbody>
</table>

**RESULTS**

| Study selection | 17 | Give the numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8, |

8
<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>18</th>
<th>Regarding each study, present characteristics for which data were extracted (e.g., study size, PICOS, and the follow-up period) and provide citations.</th>
<th>Table 1, Table S2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on the risk of bias of each study and, where available, any outcome level assessment (see item 12).</td>
<td>Figure 2, Figure S3-5</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>Regarding all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>Table 2, Figure 3, Figure S2</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis performed, including confidence intervals and measures of consistency.</td>
<td>Table 2, Figure 3, Figure S2</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of the risk of bias across studies (see Item 15).</td>
<td>Figure 2, Figure S3-5</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if performed (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>Figure S2</td>
</tr>
</tbody>
</table>

**DISCUSSION**

<p>| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13 |
| Limitations | 25 | Discuss limitations at the study and outcome levels (e.g., the risk of bias), and at the review-level (e.g., incomplete retrieval of identified research, reporting bias). | 15 |</p>
<table>
<thead>
<tr>
<th>Conclusions</th>
<th>26</th>
<th>Provide a general interpretation of results in the context of other evidence, and implications for future research.</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNDING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>16</td>
</tr>
</tbody>
</table>


For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).
<table>
<thead>
<tr>
<th>Source</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Control</th>
<th>Other rules for both groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bae et al. (2018)</td>
<td>Patients aged 18–80 years with BMI of 18.5–35.0 kg/m², an estimated glomerular filtration rate of ≥30 mL/min/1.73 m², and aspartate aminotransferase and alanine aminotransferase levels of no more than 2.5-fold the upper limit of the normal range.</td>
<td>Participants diagnosed with type 1 diabetes mellitus or diabetic ketoacidosis; undergoing insulin therapy; with a history of allergies to flour, nuts, legumes, and milk; and a history of gastrointestinal surgery (except for hemorrhoidectomy, hernia repair surgery, and appendectomy); and women who were pregnant or lactating.</td>
<td>Started to eat a protein-enriched, dietary fiber-fortified bar (PFB) -30 min (08.30 hours) before the test meal breakfast at 0 min (09.00 hours) and consumed PFB at the end of the test meal.</td>
<td>Started to eat the test meal breakfast at 0 min (09.00 hours) and consumed PFB at the end of the test meal.</td>
<td>Visited the hospital at 08.30 hours after an overnight (10 h) fast on 2 separate days 1 week apart and underwent the mixed meal tolerance test. Participants stopped taking metformin or dipeptidyl peptidase-4 inhibitor 1 week before the first visit. A PFB was provided with 150 mL of water. Participants were instructed to eat the test meals and PFB, both within 15 min.</td>
</tr>
<tr>
<td>Imai et al. (2010)</td>
<td>Outpatients diagnosed with type 2 diabetes and being treated with diet alone exceeded 6.9% in the past 6 months, patients with a hepatic disorder, renal disorder, neurological disorder, or cardiovascular disease, smokers who smoke more than 40 cigarettes a day or drink more than 50 grams of alcohol equivalent per day.</td>
<td>Patients whose average HbA1c exceeded 6.9% in the past 6 months, patients with a hepatic disorder, renal disorder, neurological disorder, or cardiovascular disease, smokers who smoke more than 40 cigarettes a day or drink more than 50 grams of alcohol equivalent per day.</td>
<td>Eat vegetable salad first, then rice 10 minutes later.</td>
<td>Eat vice versa.</td>
<td>After 12 hours of fasting, participants came to the center at 8:45. They chewed 20 times per mouthful and took 15 minutes to consume the test meal. Participants were seated for two hours during the test and were not allowed to exercise.</td>
</tr>
<tr>
<td>Source</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
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</tr>
<tr>
<td>Imai et al. (2011)</td>
<td>Outpatients diagnosed with type 2 diabetes, aged between 20 and 90 years.</td>
<td>Patients with chronic liver disease or a clinical history and/or signs of cardiovascular disease, cerebrovascular disease, or peripheral arterial disease, heavy smoking (more than 40 cigarettes a day), and drinking (more than 50 g alcohol a day), patients with psychiatric disease.</td>
<td>Received instructions on a simple meal plan that involved eating vegetables before carbohydrates without taking energy intake into account.</td>
<td>Received instructions on a traditional exchange-based meal plan that used the food exchange system to focus on energy intake.</td>
<td>Detailed written instructions for the completion of food diaries were provided and participants were encouraged to contact the dietitian if they had any questions regarding this procedure. Physical activity involving moderate exercise, such as walking 30 to 40 min each day, was recommended.</td>
</tr>
<tr>
<td>Imai et al. (2012)</td>
<td>Outpatients diagnosed with type 2 diabetes</td>
<td>-</td>
<td>Ate the first dish of vegetables for 5 min, then the main dish, and consumed rice or bread with a 10-min interval between vegetables and carbohydrates in each test meal.</td>
<td>Eat vice versa.</td>
<td>Participants consumed each test meal at a fixed time on the 2nd and 3rd day.</td>
</tr>
<tr>
<td>Imai et al. (2013)</td>
<td>Outpatients diagnosed with type 2 diabetes, aged between 20 and 80 years.</td>
<td>Patients with type I diabetes, serious comorbidities, psychiatric disorders, and taking steroids or other drugs that affect blood glucose levels.</td>
<td>Ate the first dish of vegetables for 5 min, then the main dish, followed by rice or bread with a 10-min interval between vegetables and carbohydrates in each test meal.</td>
<td>Eat vice versa.</td>
<td>Participants consumed each test meal at a fixed time on the 2nd and 3rd day.</td>
</tr>
<tr>
<td>Source</td>
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<td>Intervention</td>
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</tr>
<tr>
<td>Imai et al. (2014)</td>
<td>Outpatients diagnosed with type 2 diabetes, HbA1c less than 9%</td>
<td>Patients with liver disease, any life-threatening disease, severe complications of diabetes, nephropathy, history of cerebral or myocardial infarction, treatment with steroidal anti-inflammatory drugs, and drug or alcohol abuse.</td>
<td>Ate the first dish of vegetables for 5 min, then the main dish for 5 min, followed by rice or bread for 5 min of the test meal.</td>
<td>Eat vice versa.</td>
<td>At 12:00 on the 1st day, each participant wore a continuous glucose monitoring system (CGMS) at the clinic, consumed the test meals at 7:00, 12:00, and 19:00 at home on the 2nd and 3rd days, and the CGMS was removed at the clinic at noon on the 4th day.</td>
</tr>
<tr>
<td>Kuwata et al. (2016)</td>
<td>Individuals with untreated type 2 diabetes aged 30–75 years, HbA1c 9.0% or less, and BMI 35 kg/m² or less</td>
<td>Participants with type 1 diabetes, gastrointestinal tract disease including gastroparesis, a history of gastrointestinal surgery, cardiac disease, pulmonary disease, pancreatic disease, liver disease, renal disease, alcohol or drug abuse, glucose-lowering medication, diabetogenic medication, or malignancy, or pregnancy, and individuals allergic to mackerel.</td>
<td>First ingested 920 kJ of boiled mackerel and, 15 min later, 1,004 kJ of steamed rice.</td>
<td>Eat vice versa.</td>
<td>Participants were subjected to meal sequence tests in the morning after an overnight fast on two separate days.</td>
</tr>
<tr>
<td>Source</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
<td>Control</td>
<td>Other rules for both groups</td>
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<tr>
<td>Shukla et al. (2017)</td>
<td>Male and female participants aged 35-65, BMI 25–40 kg/m², and metformin-treated type 2 diabetes of less than 10 years duration with HbA1c less than or equal to 8%.</td>
<td>Patients taking corticosteroids, antidiabetic medication other than metformin, and patients with chronic renal or hepatic disease or a previous history of bariatric surgery diets caribbean</td>
<td>Protein (skinless grilled chicken breast) and vegetables (lettuce, tomatoes, and cucumber with Italian vinaigrette) first over 10 min, a 10 min rest interval, and then carbohydrates (ciabatta bread and orange juice) over 10 min.</td>
<td>Eat vice versa.</td>
<td>All participants consumed isocaloric meals of the same composition on three separate days, 1 week apart, after a 12-hour overnight fast. Participants were instructed to maintain their usual level of physical activity and diet throughout the study period, particularly on the day prior to each test session.</td>
</tr>
<tr>
<td>Shukla et al. (2018)</td>
<td>Male and female participants aged 35-65, BMI 25–40 kg/m², and metformin-treated type 2 diabetes of less than 10 years duration with HbA1c less than or equal to 8%.</td>
<td>Patients taking corticosteroids, antidiabetic medication other than metformin, and patients with chronic renal or hepatic disease or a previous history of bariatric surgery diets caribbean</td>
<td>Protein (skinless grilled chicken breast) and vegetables (lettuce, tomatoes, and cucumber with Italian vinaigrette) first over 10 min, a 10 min rest interval, and then carbohydrates (ciabatta bread and orange juice) over 10 min.</td>
<td>Eat vice versa.</td>
<td>All participants consumed isocaloric meals of the same composition on three separate days, 1 week apart, after a 12-hour overnight fast. Participants were instructed to maintain their usual level of physical activity and diet throughout the study period, particularly on the day prior to each test session.</td>
</tr>
<tr>
<td>Shukla et al. (2019)</td>
<td>Male and female participants aged 30-65, BMI 25–40 kg/m², and with prediabetes (HbA1c 5.7-6.4%)</td>
<td>Patients taking corticosteroids, antidiabetic medication, and those with chronic renal or hepatic disease or a previous history of bariatric surgery and pertinent food allergies</td>
<td>Protein (skinless grilled chicken breast) and vegetables (lettuce, tomatoes, bell peppers, and red cabbage with balsamic vinegar and olive oil) first over 10 minutes, a 10-minute rest</td>
<td>Eat vice versa.</td>
<td>All participants consumed isocaloric meals with exactly the same composition, on three separate days, 1 week apart, after a 12-hour overnight fast. Participants were counselled to maintain their usual level of physical activity and diet throughout the study period, particularly on the day prior to each study visit.</td>
</tr>
<tr>
<td>Source</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
<td>Control</td>
<td>Other rules for both groups</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Trico et al. (2016)</td>
<td>Patients aged 40-80 years, BMI: &lt;35 kg/m², HbA1c of 48-58 mmol/mol, duration of diabetes &lt;5 years, stable antidiabetic therapy with metformin only (&gt;6 months).</td>
<td>Serious disability, dietary or pharmacological therapy for obesity, women with gestational diabetes, breastfeeding women, a history of cancer, heart failure, or other systemic diseases of a severity that compromises patient compliance and changes their life expectancy, uncontrolled hypothyroidism, a history of alcohol abuse, liver disease, chronic kidney disease, participation in another clinical study in the four weeks preceding enrollment, endocrinological diseases, previous gastrointestinal interventions.</td>
<td>Received indications on the macronutrient composition of foods and were strongly recommended to fix the sequence of macronutrient ingestion at each main meal (lunch and dinner) in order to eat high carbohydrate-containing foods (e.g., bread, pasta, and potatoes) preferably after the ingestion of high-protein and high-fat foods (e.g., meat, cheese, and fish).</td>
<td>Were asked to follow a standard balanced mild-hypocaloric diet.</td>
<td>Received a dietary plan with the food composition of three typical meals (breakfast, lunch, and dinner) and a table of possible substitutions with variable equicaloric amounts of different foods. Meals and variants were pondered to yield a caloric deficit of ~ 200 kcal per day with respect to the total daily caloric need, to produce an expected weight loss of ~ 1 kilogram a month. All participants were asked to report their overall compliance to the caloric content and to the sequence of nutrients of the prescribed diet by checking on an ad hoc designed form at each meal.</td>
</tr>
<tr>
<td>Source</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Intervention</td>
<td>Control</td>
<td>Other rules for both groups</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------------</td>
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<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Yabe et al. (2019)</td>
<td>Male and female participants aged 40–60 years and no history of diabetes, fasting plasma glucose levels ≤126 mg/dL, HbA1c ≥5.6%(=prediabetes), and BMI 18–30 kg/m²</td>
<td>Individuals with renal impairment, hepatic impairment, heart failure, a history of cerebrocardiovascular disease, or gastrointestinal surgery as well as those receiving glucose-lowering, blood pressure-lowering, or lipid-lowering drugs. Subjects diagnosed with diabetes in their health check-up within 3 months.</td>
<td>Received dietary instructions including meal sequencing</td>
<td>Received conventional dietary instructions (received dietary instructions with a focus on energy expenditure).</td>
<td>They received health guidance education on weeks 1–2. Individuals received a 6-month personalized lifestyle modification program, in which they were asked to adjust energy intake to balance the total energy expenditure and were encouraged to walk.</td>
</tr>
</tbody>
</table>

*Studies included in the qualitative synthesis.*
Figure S1. Funnel plot for HbA1c (Random effect model)
A. HbA1c (NGSP) (%) from 2 months to 2 years (rice only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yabe 2018</td>
<td>7.2</td>
<td>1</td>
<td>7</td>
<td>7.1</td>
<td>1</td>
<td>7</td>
<td>0.1</td>
<td>-0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.09, 0.06)</td>
<td>(0.04, 0.03)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>25</td>
<td>19</td>
<td>44</td>
<td>19</td>
<td></td>
<td></td>
<td>-0.13</td>
<td>(0.04, 0.03)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Chi^2 = 0.39$, $df = 1$ ($P = 0.53$), $I^2 = 0$
Test for overall effect: $Z = 0.79$ ($P = 0.43$)

B. HbA1c (NGSP) (%) from 2 months to 2 years (fixed effect model)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yabe 2018</td>
<td>6.4</td>
<td>0.6</td>
<td>8</td>
<td>8.6</td>
<td>0.3</td>
<td>9</td>
<td>-0.27</td>
<td>-0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.08, 0.03)</td>
<td>(0.04, 0.02)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>95</td>
<td>52</td>
<td>147</td>
<td>52</td>
<td></td>
<td></td>
<td>-0.27</td>
<td>(0.04, 0.02)</td>
</tr>
</tbody>
</table>

Heterogeneity: $Chi^2 = 1.55$, $df = 2$ ($P = 0.49$), $I^2 = 0$
Test for overall effect: $Z = 1.59$ ($P = 0.05$)

C. HbA1c (NGSP) (%) from 2 months to 2 years (Exclusion of studies using imputed statistics)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yabe 2018</td>
<td>6.4</td>
<td>0.6</td>
<td>8</td>
<td>8.6</td>
<td>0.3</td>
<td>9</td>
<td>-0.27</td>
<td>-0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.08, 0.03)</td>
<td>(0.04, 0.02)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>26</td>
<td>20</td>
<td>46</td>
<td>20</td>
<td></td>
<td></td>
<td>-0.27</td>
<td>(0.04, 0.02)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Chi^2 = 0.12$, $df = 1$ ($P = 0.73$), $I^2 = 0$
Test for overall effect: $Z = 0.30$ ($P = 0.73$)

D. Plasma glucose (mg/dL) 120 min after lunch

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yabe 2018</td>
<td>165.8</td>
<td>90.2</td>
<td>9</td>
<td>122.1</td>
<td>60.8</td>
<td>10</td>
<td>-43.7</td>
<td>-43.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(22.7, 141.3)</td>
<td>(22.7, 141.3)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>19</td>
<td>36</td>
<td>19</td>
<td></td>
<td></td>
<td>-43.7</td>
<td>(22.7, 141.3)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Chi^2 = 0.84$, $df = 1$ ($P = 0.36$), $I^2 = 0$
Test for overall effect: $Z = 1.28$ ($P = 0.20$)

E. Plasma glucose (mg/dL) 120 min after dinner

<table>
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<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
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<th>Total</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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<tbody>
<tr>
<td>Yabe 2018</td>
<td>179.6</td>
<td>52.2</td>
<td>9</td>
<td>213.2</td>
<td>67</td>
<td>10</td>
<td>-33.6</td>
<td>-33.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(87.34, 2014)</td>
<td>(87.34, 2014)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17</td>
<td>19</td>
<td>36</td>
<td>19</td>
<td></td>
<td></td>
<td>-33.6</td>
<td>(87.34, 2014)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $Chi^2 = 0.24$, $df = 1$ ($P = 0.63$), $I^2 = 0$
Test for overall effect: $Z = 1.21$ ($P = 0.23$)
F. Plasma glucose (mg/dL) 120 min after meals (short-term only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imai 2010</td>
<td></td>
<td>180.6</td>
<td>59.8</td>
<td>15</td>
<td>179.5</td>
<td>71.0</td>
<td>15</td>
<td>11.3%</td>
<td>15.11</td>
<td>32.11</td>
<td>62.31</td>
<td>2.18 [54.78, 19.16]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shulka 2019</td>
<td></td>
<td>112.7</td>
<td>25.4</td>
<td>15</td>
<td>97.1</td>
<td>24.9</td>
<td>15</td>
<td>40.4%</td>
<td>15.80</td>
<td>12.08</td>
<td>33.28</td>
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<td></td>
<td></td>
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<tr>
<td>Total (95% CI)</td>
<td></td>
<td>180.6</td>
<td>59.8</td>
<td>15</td>
<td>179.5</td>
<td>71.0</td>
<td>15</td>
<td>11.3%</td>
<td>15.11</td>
<td>32.11</td>
<td>62.31</td>
<td>2.18 [54.78, 19.16]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: T^2 = 60.07, df = 4, I^2 = 60%, P = 0.00%

Test for overall effect: Z = 2.20 (P = 0.03)

G. Plasma glucose (mg/dL) 120 min after meals (rice only) (=vegetable only)

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Imai 2010</td>
<td></td>
<td>180.6</td>
<td>59.8</td>
<td>15</td>
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<td></td>
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</tr>
<tr>
<td>Shulka 2019</td>
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<td>112.7</td>
<td>25.4</td>
<td>15</td>
<td>97.1</td>
<td>24.9</td>
<td>15</td>
<td>40.4%</td>
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<td></td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>180.6</td>
<td>59.8</td>
<td>15</td>
<td>179.5</td>
<td>71.0</td>
<td>15</td>
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<td>32.11</td>
<td>62.31</td>
<td>2.18 [54.78, 19.16]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: T^2 = 60.07, df = 4, I^2 = 60%, P = 0.00%

Test for overall effect: Z = 2.20 (P = 0.03)

H. Plasma glucose (mg/dL) 120 min after meals (except for rice)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
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<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<tbody>
<tr>
<td>Imai 2010</td>
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<tr>
<td>Shulka 2019</td>
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<td>12.08</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
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<td>59.8</td>
<td>15</td>
<td>179.5</td>
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<td>2.18 [54.78, 19.16]</td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: T^2 = 60.07, df = 4, I^2 = 60%, P = 0.00%

Test for overall effect: Z = 2.20 (P = 0.03)

I. Plasma insulin (μIU/mL) 120 min after meals (short-term only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Experimental</th>
<th>Mean</th>
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<tr>
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<td>97.1</td>
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<td>15</td>
<td>40.4%</td>
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<td>Total (95% CI)</td>
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<td>179.5</td>
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<td>62.31</td>
<td>2.18 [54.78, 19.16]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: T^2 = 60.07, df = 4, I^2 = 60%, P = 0.00%

Test for overall effect: Z = 2.20 (P = 0.03)

J. Plasma insulin (μIU/mL) 120 min after meals (rice only)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Experimental</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
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<tr>
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<td>179.5</td>
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<td>15</td>
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<td>24.9</td>
<td>15</td>
<td>40.4%</td>
<td>15.80</td>
<td>12.08</td>
<td>33.28</td>
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<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
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<td>59.8</td>
<td>15</td>
<td>179.5</td>
<td>71.0</td>
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<td>11.3%</td>
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<td>2.18 [54.78, 19.16]</td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: T^2 = 60.07, df = 4, I^2 = 60%, P = 0.00%

Test for overall effect: Z = 2.20 (P = 0.03)
K. Plasma insulin (μIU/mL) 120 min after meals (except for rice)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>Experimental SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Total Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio 2018</td>
<td>32.9</td>
<td>7.9</td>
<td>7</td>
<td>78</td>
<td>38.4</td>
<td>9</td>
<td>-37.16 [-42.16, -31.22]</td>
<td></td>
</tr>
<tr>
<td>Shida 2017</td>
<td>29.2</td>
<td>3.9</td>
<td>16</td>
<td>86.5</td>
<td>34.3</td>
<td>18</td>
<td>45.5%</td>
<td>-7.30 [-31.03, 17.03]</td>
</tr>
<tr>
<td>Shida 2019</td>
<td>90.7</td>
<td>43.9</td>
<td>15</td>
<td>94.5</td>
<td>121.1</td>
<td>15</td>
<td>11.7%</td>
<td>5.20 [-60.00, 76.39]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>38</td>
<td>39</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td>-100 [-50, 0]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 176.02; CI^2 = 3.29, df = 2 (P = 0.19); I^2 = 93%$  
Test for overall effect: $Z = 1.52$ (P = 0.13)

Figure S2. Forest plot of comparisons

IV, inverse variance; HbA1c, Hemoglobin A1c; NGSP, national glycohemoglobin standardization program.

NGSP (%) = 1.02*JDS (%) + 0.25.
Figure S3. (A) Risk of bias graph for plasma glucose (B) Risk of bias summary for plasma glucose.
Figure S4. (A) Risk of bias graph for plasma insulin (B) Risk of bias summary for plasma insulin.
Figure S5. (A) Risk of bias graph for plasma incretin (B) Risk of bias summary for plasma incretin.