REVIEW

Effect of Isomaltulose on Glycemic and Insulinemic Responses: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Evidence regarding the effect of isomaltulose on glycemic and insulinemic responses is still conflicting, which limits isomaltulose's application in glycemic management. The purpose of this study was to comprehensively evaluate its effectiveness and evidence quality. We systematically searched PubMed, Embase, and the Cochrane Library for randomized controlled trials (RCTs) prior to October 2021. RCTs were eligible for inclusion if they enrolled adults to oral intake of isomaltulose or other carbohydrates dissolved in water after an overnight fast and compared their 2-h postprandial glucose and insulin concentrations. The DerSimonian-Laird method was used to pool the means of the circulating glucose and insulin concentrations. Both random-effects and fixed-effects models were used to calculate the weighted mean difference in postprandial glucose and insulin concentrations in different groups. Subgroup, sensitivity, and meta-regression analyses were also conducted. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of evidence. Finally, 11 RCTs ($n = 175$ participants) were included. The trials were conducted in 4 countries (Japan, Brazil, Germany, and the Netherlands), and all of the enrolled participants were >18 y of age with various health statuses (healthy, type 2 diabetes, impaired glucose tolerance, and hypertension). Moderate evidence suggested that oral isomaltulose caused an attenuated glycemic response compared with sucrose at 30 min. Low evidence suggested that oral isomaltulose caused an attenuated but more prolonged glycemic response than sucrose and an attenuated insulinemic response. Low-to-moderate levels of evidence suggest there may be more benefit of isomaltulose for people with type 2 diabetes, impaired glucose tolerance, or hypertension; older people; overweight or obese people; and Asian people. The study was registered on PROSPERO (International Prospective Register of Systematic Reviews) as CRD42021290396 (available at https://www.crd.york.ac.uk/prospero/). *Adv Nutr* 2022;13:1901–1913.

Statement of Significance: Replacement of sucrose or other high–glycemic index carbohydrates with isomaltulose would lead to an attenuated and more prolonged glycemic response and an attenuated insulinemic response, thus functioning in the prevention and management of diabetes.

Keywords: isomaltulose, palatinose, diabetes, glycemic and insulinemic response, systematic review and meta-analysis

Introduction

Diabetes mellitus severely impairs quality of life, has several life-threatening complications, and is a worldwide public health concern. The International Diabetes Federation estimated that 463 million people had diabetes and that 4.2 million deaths were attributable to diabetes globally in 2019 (1). Nearly 10% of global health expenditure is spent on diabetes (US $760 billion) (2). Carbohydrate-restricted diets have been widely recommended to prevent and manage diabetes (3, 4). Recent studies have focused on the quality, rather than the quantity, of carbohydrate in such diets, and the results have suggested that the former has more bearing on the development and progression of diabetes (5). In addition, previous studies have shown that the total carbohydrate intake of an individual and the proportion of carbohydrate in a diet are not significantly associated with diabetes risk. Instead, a high glycemic index (GI) is associated with a higher risk of type 2 diabetes. In a meta-analysis of 3 large cohorts, the participants in the highest quintile of energy-adjusted GI had a 33% higher risk (95% CI: 26%, 41%) of type 2 diabetes than those in the lowest quintile (6).

The GI of a carbohydrate represents its effect on postprandial blood glucose concentrations compared with glucose or white bread. The higher the GI value, the faster the carbohydrate is digested and absorbed, and the greater the effect on postprandial blood glucose concentrations (7). Several low-GI carbohydrates have been proposed as substitutes for high-GI carbohydrates in diets to reduce the glycemic response. However, large disparities exist among different low-GI carbohydrates. For instance, some people are intolerant to lactose (GI = 46), such that its ingestion can cause symptoms such as abdominal pain, diarrhea, nausea, flatulence, and/or bloating (8). Fructose (GI = 20) is one of the sweetest carbohydrates, and sweetness generally promotes feeding behavior, inducing overeating, obesity, and other metabolic disorders. Thus, a high dietary content of fructose is associated with hepatic insulin resistance, nonalcoholic fatty liver disease, greater circulating uric acid concentration, and cancer (9, 10). In contrast, isomaltulose (6-O-α-D-glucopyranosyl-D-fructose; GI = 32) is a naturally occurring low-GI isomer of sucrose (GI = 65) that is found in honey, pollen, and sugarcane. It is ~50% as sweet as sucrose but generates 4 kcal/g energy, as does sucrose. It is only absorbed in the small intestine, following hydrolysis into glucose and fructose, which occurs at 32% of the rate for sucrose (11). Few gastrointestinal symptoms or side effects have been reported following isomaltulose consumption. Because of these characteristics, studies have been performed to determine whether it could be used to prevent and/or manage diabetes. In some of these studies, the effects of the long-term replacement of high-GI carbohydrates in beverages and foods with isomaltulose on glycemic metabolism were investigated (12, 13). However, it is not possible to quantitatively evaluate the real effect of isomaltulose because the other ingredients of the meals, such as dietary fiber and fat, may affect the absorption of the carbohydrates. A few population-based experimental studies have examined the effect of consuming isomaltulose alone and compared with that of sucrose. However, the observed time points and conclusions (the differential effects following isomaltulose and sucrose digestion in circulating glucose and insulin concentrations of various time points) were inconsistent between studies.

We aimed to evaluate the utility of isomaltulose for diabetes prevention by evaluating the effects of isomaltulose ingestion on glucose and insulin concentrations after digestion, especially in participants with differing characteristics. To this end, we conducted a systematic review and meta-analysis, and assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol of the study was registered with PROSPERO (registration no. CRD42021290396)

Inclusion and exclusion criteria

Studies of isomaltulose loading were eligible for inclusion if they enrolled adults (age ≥18 y), compared the glycemic and insulinemic responses of participants who ingested isomaltulose or a high-GI carbohydrate dissolved in water after an overnight fast, reported circulating glucose and insulin concentrations within 2 h of carbohydrate ingestion, and were designed as randomized controlled trials (RCTs), including both crossover and parallel trials. Studies were excluded if they were performed in animals; were published in the form of reports, replies, or conference abstracts; if they were observational studies; if they included participants with different characteristics of glycemic metabolism compared with those of normal or diabetes population, including hyperthyroidism, Cushing's syndrome, and recent surgery; and if the intervention involved mixing isomaltulose with other foods or beverages.

Two researchers (JX and JL) independently conducted searches of online databases (PubMed, Embase, and the Cochrane Library) for studies published prior to October 2021, with no restriction on language. To maximize the number of relevant articles identified, the search was supplemented by reviewing the reference lists of the identified reports of trials and systematic reviews. After the removal of duplicates, the 2 researchers screened the titles, abstracts, and full texts of the eligible studies. Any disagreements were resolved with discussion in a group meeting.

Data-collection process

Data were extracted for the following parameters describing the participants: ethnicity; number; health status; mean age; mean BMI; the circulating glucose and insulin concentrations 0, 30, 60, 90, 120, and 180 min after carbohydrate ingestion; the intervention and control measures being used; and the study design. When the data of interest were only shown in plots, WebPlotDigitizer (version 4.4; https://automeris.io/WebPlotDigitizer) was used to obtain the numerical data.

Risk-of-bias assessment

Two researchers independently used the Revised Cochrane Collaboration Risk of Bias 2 tool for crossover trials (14) to assess the risk of bias for each trial. The tool consists of 5 domains that concern aspects of the study design,

Supported by grants from National Nature Science Foundation of China (grant nos. 82173514, 81973036, and 81302419), Capital's Funds for Health Improvement and Research (CFH202041033).
Author disclosures: The authors report no conflicts of interest. The supporting source had no involvement or restrictions regarding publication.
Supplemental Figures 1–8 and Supplemental Tables 1–9 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: GI, glycemic index; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; iAUC, incremental AUC; IGT, impaired glucose tolerance; RCT, randomized controlled trial; WMD, weighted mean difference.

conduct, and reporting that correspond to biases arising from the randomization process, period and carryover effects, deviation from the intended intervention, missing outcome data, the measurement of the outcomes, and the selection of the reported results. Within each domain, a series of questions are used to elicit information regarding the features of the study and an algorithm is used to assess the risk of bias, which is categorized as low risk, "some concerns," or high risk. Any disagreements were resolved with discussion.

Data synthesis

The DerSimonian-Laird method was used to pool the means and SDs of the circulating glucose and insulin concentrations of all the participants. Weighted mean differences (WMDs) and their 95% CIs at time points following carbohydrate ingestion were calculated to evaluate the differences in circulating glucose and insulin concentrations after the ingestion of isomaltulose or sucrose. $P < 0.05$ was considered to represent statistical significance. The I^2 statistic was used to assess the heterogeneity of studies, which was categorized as 25%, 50%, or 75%, representing low, moderate, and considerable heterogeneity, respectively. If the I^2 index was <50%, a fixed-effects model was used; otherwise, a random-effects model was used. The possibility of publication bias was assessed qualitatively using funnel plots and quantitatively using Egger's and Begg's tests. If the results of the Egger's or Begg's tests were statistically significant, a trim-and-fill method was used to adjust the data for the influence of publication bias.

Subgroup analyses were performed to assess the effect of isomaltulose in different types of participants, according to their health status (healthy or unhealthy), age (≤50 and >50 y), BMI (normal-weight or overweight/obesity), and ethnicity (Asian or European). Participants who had been diagnosed with conditions, including type 2 diabetes, impaired glucose tolerance (IGT), and hypertension, were assigned to the Unhealthy group; otherwise, they were assigned to the Healthy group (those with normal glucose tolerance). Participants with a mean BMI (in kg/m^2) >23 if Asian and >25 if European were placed in the Overweight/Obesity group; otherwise, they were assigned to Normal-Weight group.

Sensitivity analyses were performed by excluding 1 or several similar studies at a time to test the robustness of the findings. Meta-regression was conducted to analyze the heterogeneity and investigate the relation between the effects of isomaltulose and the characteristics of the participants (BMI and age). Stata version 14.0 (StataCorp, LLC) was used for the statistical analysis.

GRADE assessment

The GRADE method was used to assess the quality of evidence and generate a profile that ranked the evidence as high, moderate, low, or very low certainty. Two authors (JX and JL) independently conducted a GRADE evaluation of each result. The initial rating of RCTs was high by default, but this was downgraded according to the following prespecified criteria: risk of bias, assessed using the Cochrane Risk of Bias Tool; inconsistency (I^2 ≥50% that could not be explained by subgroup analyses), indirectness of the intervention, participants, or outcomes that limited the generalizability of the results; imprecision (the sample size for an outcome was below the optimal size); and publication bias (visually asymmetric funnel plots and P for Egger's or Begg's test <0.05).

Results

Selected studies and risk of bias

A total of 882 records were identified from PubMed, Embase, and the Cochrane Library, 278 of which were excluded due to duplication, leaving 604 records. After review of the title, abstract, and full text of each, 6 studies were found to fulfill the eligibility criteria. An additional 4 studies were identified through manual searches of the reference lists of the selected studies and relevant systematic reviews. The results of 2 eligible trials were published together by Kawai et al. (15). Therefore, 10 eligible studies that involved a total of 11 RCTs and 175 participants were included. **Figure 1** is a flow diagram that describes the process of study inclusion and **Supplemental Figure 1** provides the details of the risk-of-bias assessment. The overall risks of bias for the included studies were categorized as "some concerns" with respect to the lack of information regarding the study design and conduct (the randomization process, analyses of period and carryover effects, and the assignment and compliance with the intervention), but "low risk" with respect to missing outcome data, the measurement of the outcomes, and the selection of the reported results.

Characteristics of the studies and participants

Table 1 presents the characteristics of the eligible studies and their participants. The trials were conducted in 4 countries (Japan, Brazil, Germany, and the Netherlands) and all of the enrolled participants were >18 y of age. The participants had various health statuses (healthy, type 2 diabetes, IGT, and hypertension) and their mean BMIs (in kg/m^2) ranged from 19.5 to 32.1. All the participants ingested isomaltulose or sucrose dissolved in water within a period of several minutes in the morning after an overnight fast, and then the same process was repeated after a washout period (all the trials had a crossover design). In all but 3 of the trials, 50 g isomaltulose was administered orally to the participants in the intervention arm. In the studies of van Can et al. (16, 17), 75 g carbohydrate was ingested, and in the study of Yamori et al. (18), the intervention group ingested 45 g isomaltulose plus 5 g sucrose. All of the participants consumed the same mass of sucrose as that of isomaltulose in the control arms of the trials.

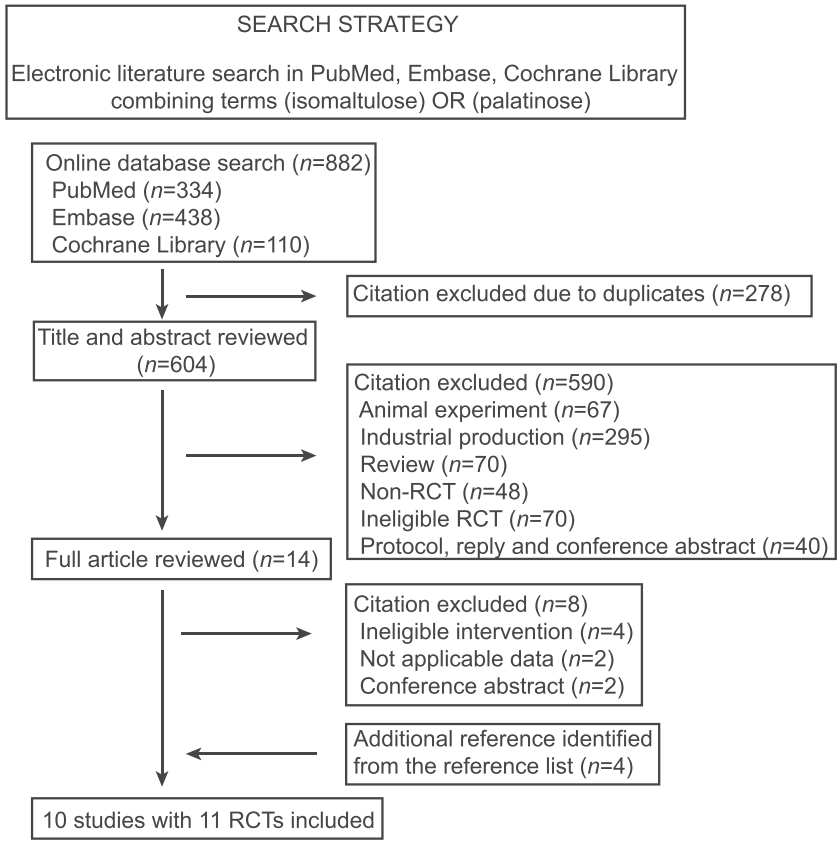

FIGURE 1 Flowchart of study identification and selection. RCT, randomized controlled trial.

Effects of the oral administration of isomaltulose on glycemia and insulinemia

The pooled means (± SD) of the baseline circulating glucose concentrations for the isomaltulose and sucrose arms were 5.55 ± 2.90 mmol/L and 5.56 ± 2.83 mmol/L, respectively ($P = 0.974$). The pooled means of the baseline circulating insulin concentration for the isomaltulose and sucrose arms were 63.7 ± 102 pmol/L and 68.2 ± 99.1 pmol/L, respectively ($P = 0.673$). As shown in **Figure 2**A and C, although the circulating concentrations of these 2 carbohydrates demonstrated roughly similar profiles, there were some obvious differences. Isomaltulose ingestion was associated with slower increases in the circulating glucose and insulin concentrations and slower decreases after the peak than sucrose ingestion. The peak concentrations of glucose ($P = 0.0016$) and insulin ($P = 0.0017$) following isomaltulose ingestion were much less than those following sucrose ingestion (**Supplemental Table 1**).

As shown in Figure 2B and D and **Supplemental Figure 2**, significant negative WMDs at 30 min (WMD: −1.83 mmol/L; 95% CI: −1.99, −1.66 mmol/L; $P < 0.001$; $I^2 = 0.0\%$) and 60 min (WMD: −0.98 mmol/L; 95% CI: −1.53, −0.44 mmol/L; $P < 0.001$; $I^2 = 78.9\%$) indicate an attenuated glycemic response of oral isomaltulose compared with sucrose. The WMDs were significant and opposite at 120 min (WMD: 0.46 mmol/L; 95% CI: 0.00, 0.91 mmol/L; $P = 0.049$; $I^2 = 94.9\%$) and 180 min (WMD: 0.46 mmol/L; 95% CI: 0.04, 0.87 mmol/L; $P = 0.031$; $I^2 = 97.1\%$), indicating a prolongation of the glycemic response to oral isomaltulose. In addition, isomaltulose ingestion was associated with a significantly attenuated insulinemic response at 30 min (WMD: −149.71 pmol/L; 95% CI: −200.09, −99.33 pmol/L; $P < 0.001$; $I^2 = 96.7\%$), 60 min (WMD: −68.49 pmol/L; 95% CI: −99.83, −37.14 pmol/L; $P < 0.001$; $I^2 = 88.3\%$), and 90 min (WMD: −30.55 pmol/L; 95% CI: −60.67, −0.44 pmol/L; $P = 0.047$; $I^2 = 86.3\%$) compared with that to sucrose (**Supplemental Figure 3**). The circulating insulin concentrations at 120 min (WMD: 7.19 pmol/L; 95% CI: −19.12, −33.5 pmol/L; $P = 0.592$; $I^2 = 90.9\%$) and 180 min (WMD: −7.78 pmol/L; 95% CI: −26.06, −10.51 pmol/L; $P = 0.404$; $I^2 = 70.2\%$) did not significantly differ. Funnel plots of WMDs were visibly asymmetric and the results of Egger's and Begg's tests were statistically significant at some time points, indicating the existence of publication bias. All the results described above that may have been subject to publication bias (P for Egger's or Begg's test <0.05) were adjusted using the trim-and-fill method (**Supplemental Figure 4** and **Supplemental Table 2**).

TABLE 1 Characteristics of included studies in this systematic review and meta-analysis[1]

Study (reference)	Ethnicity	Participants, *n* (% male)	Characteristics of participants	Intervention method	Outcome	Methods of biochemical analysis	Intervention	Control	Study type	Washout period	Mean BMI, kg/m^2	Mean age, y
Kawai et al. (37)	Japanese	8 (50%)	Health, 95.6% of subjects were at ideal body weight	Ingesting sugars dissolved in 150 mL water over 2–3 min after an overnight fast	Plasma glucose and insulin concentration	Blood glucose concentrations (glucose oxidase method; glucose analyzer 2, Beckman), blood insulin concentrations (radioimmunoassay)	Isomaltulose (50 g)	Sucrose (50 g)	Crossover study	2 d	Unknown[2]	23.0
Kawai et al. (15)	Japanese	10 (50%)	Health	Ingesting sugars dissolved in 150 mL water within 2–3 min after an overnight fast	Plasma glucose and insulin concentration	Blood glucose concentrations (glucose oxidase method; glucose analyzer 2, Beckman), blood insulin concentrations (radioimmunoassay)	Isomaltulose (50 g)	Sucrose (50 g)	Crossover study	2 d	19.5	23.1
Kawai et al. (15)	Japanese	10 (90%)	T2D, 60% of the subjects received dietary therapy and 40% received sulfonylureas	Ingesting sugars dissolved in 150 mL water within 2–3 min after an overnight fast	Plasma glucose and insulin concentration	Blood glucose concentrations (glucose oxidase method, glucose analyzer 2; Beckman), blood insulin concentrations (radioimmunoassay)	Isomaltulose (50 g)	Sucrose (50 g)	Crossover study	2 d	22.7	55.2
Yamori et al. (18)	Japanese	9 (100%)	Health, Japanese immigrants living in Brazil	Oral administration	Blood glucose and insulin concentration	Unknown	Isomaltulose (45 g) + sucrose (5 g)	Sucrose (50 g)	Crossover study	Unknown	Unknown	Unknown
van Can et al. (16)	Dutch	10 (80%)	Health, overweight	Ingesting sugars dissolved in 400 mL water within 15 min after an overnight fast	Plasma glucose and insulin concentration	Blood glucose concentrations (ABX Diagnostics Enzymatic Method; Montpellier, France), blood insulin concentrations (Human Insulin RIA Kit; LINCO Research Inc., St Charles, MO, USA)	Isomaltulose (75 g)	Sucrose (75 g)	Single-blind randomized crossover study	1 wk	27.7	31

(*Continued*)

TABLE 1 (*Continued*)

Study (reference)	Ethnicity	Participants, *n* (% male)	Characteristics of participants	Intervention method	Outcome	Methods of biochemical analysis	Intervention	Control	Study type	Washout period	Mean BMI, kg/m^2	Mean age, y
Holub et al. (19)	German	10 (10%)	Health	Ingesting sugars dissolved in 500 mL water within 5 min after fasting and refrained from smoking for 8 h	Blood glucose and plasma insulin concentration	Blood glucose concentrations (glucose oxidase method; Hitado, Delecke-Moähnesee, Germany), blood insulin concentrations (electrochemiluminescence immunoassay; Elecsysw 1010/2010/MODULAR ANALYTICS E170, Roche Diagnostics GmbH, Mannheim, Germany)	Isomaltulose (50 g)	Sucrose (50 g)	Double-blind randomized crossover study	Unknown	23.3	30.9
van Can et al. (17)	Dutch	10 (60%)	IGT, overweight, 2 women were postmenopausal	Ingesting sugars dissolved in 400 mL water within 15 min after an overnight fast	Plasma glucose and insulin concentration	Blood glucose concentrations (ABX Diagnostics Enzymatic Method; Roche Diagnostica), blood insulin concentrations (Human Insulin RIA Kit; Linco Research)	Isomaltulose (75 g)	Sucrose (75 g)	Single-blind randomized crossover study	1 wk	30.8	56
Maeda et al. (21)	Japanese	10 (100%)	Health, BMI ≤23, normal blood pressure, no underlying disease and no medication	Ingesting sugars dissolved in 300 mL water within a few minutes after an overnight fast	Plasma glucose and insulin concentration	Unknown	Isomaltulose (50 g)	Sucrose (50 g)	Double-blind, placebo-controlled crossover study	≤2 wk	21.1	46.4

(*Continued*)

TABLE 1 (*Continued*)

Study (reference)	Ethnicity	Participants, *n* (% male)	Characteristics of participants	Intervention method	Outcome	Methods of biochemical analysis	Intervention	Control	Study type	Washout period	Mean BMI, kg/m^2	Mean age, y
Keyhani-Nejad et al. (22)	German	10 (80%)	T2D, overweight	Ingesting sugars dissolved in 300 mL water after an overnight fast	Blood glucose and serum insulin concentration	Blood glucose concentrations (unknown); blood insulin concentrations (ELISA kits; Mercodia, Uppsala, Sweden)	Isomaltulose (50 g)	Sucrose (50 g)	Randomized within-subject crossover study	≥1 wk	32.1	61
Keyhani-Nejad et al. (23)	German	10 (50%)	IGT	Ingesting sugars dissolved in 300 mL water within 5 min after fasting for 10 h	Blood glucose and serum insulin concentration	Blood glucose concentrations [Glucose Analyzer (EKF Diagnostics; Cardiff, UK); blood insulin concentrations (ELISA kits; Mercodia, Upsalla, Sweden)]	Isomaltulose (50 g)	Sucrose (50 g)	Randomized single-blind within-subject crossover study	≥1 wk	29.9	61.6
de Groot et al. (38)	Dutch	78 (65%)	Obese subjects with mild hypertension whose body weights were stable and physical activity was low to moderate	Ingesting sugars dissolved in 500 mL water within 10 min after an overnight fast at least 10 h	Serum glucose and insulin concentration	Blood glucose concentrations (the hexokinase method; (3L82, ARCHITECT c system, Abbott Laboratories, Abbott Park, IL 60064, USA); blood insulin concentrations (chemiluminescent microparticle immunoassay; (8K41, ARCHITECT c system, Abbott Laboratories, USA)	Isomaltulose (50 g)	Sucrose (50 g)	Double-blind controlled crossover study	2–6 wk	28.9	46.6

[1] IGT, impaired glucose tolerance; T2D, type 2 diabetes.
[2] In the subgroup analysis, participants in this study were assigned to the normal-weight group because 95.6% of subjects were at an ideal body weight.

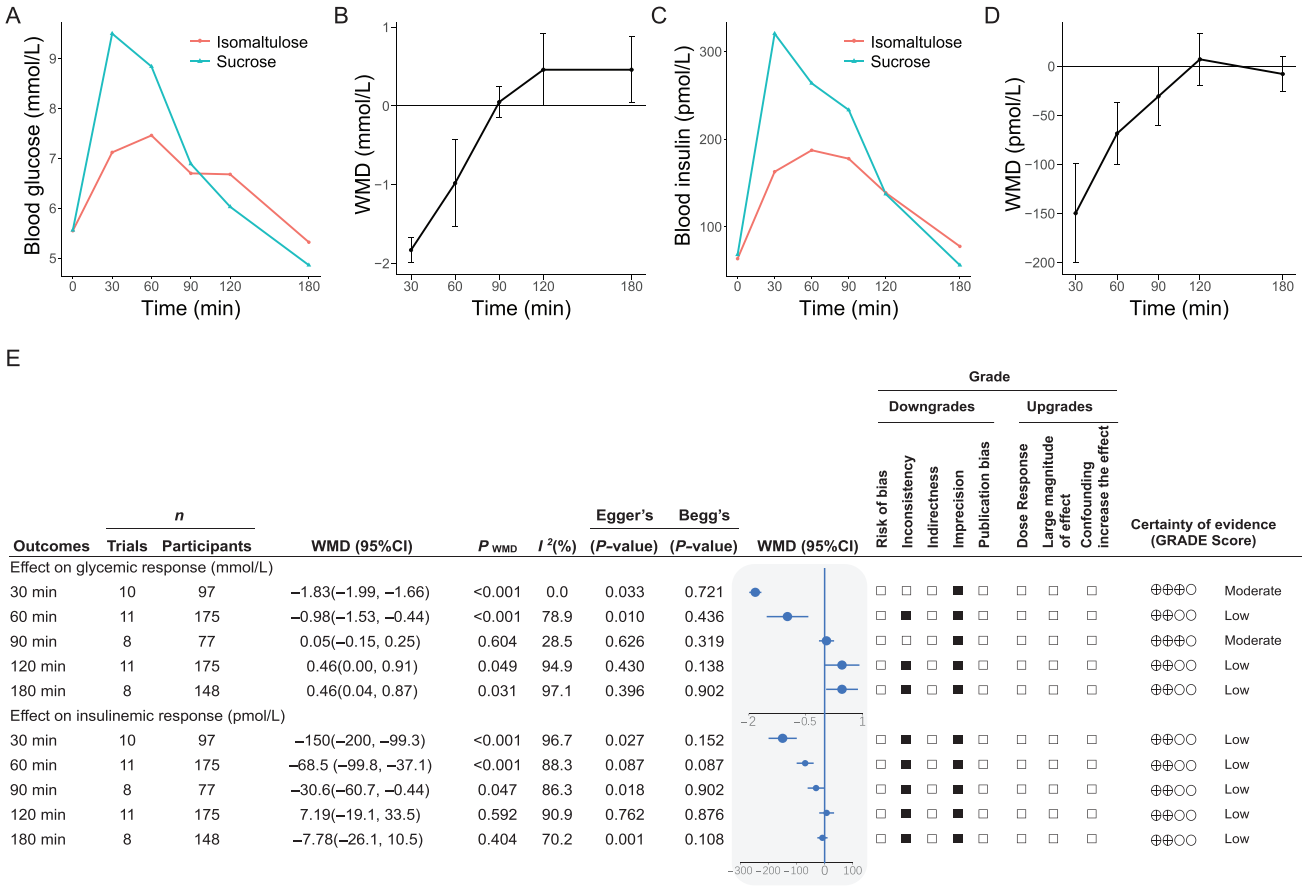

FIGURE 2 Changes in blood glucose (A) and insulin (C) concentrations after ingestion, WMD in postprandial blood glucose (B) and insulin (D) concentrations between the 2 groups, and a summary plot of the GRADE assessment (E). Values are means in panel A and C. Panel B and D show the WMDs and corresponding 95% CIs (vertical lines around every point). GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; WMD, weighted mean difference.

Effects of oral isomaltulose in the various populations

Healthy vs. unhealthy.

Figure 3 presents comparisons of the glycemic and insulinemic responses to isomaltulose and sucrose in the various populations. Irrespective of whether isomaltulose or sucrose was ingested, the circulating glucose concentrations of unhealthy participants were greater than those of healthy participants (P values for isomaltulose: 0 min, $P = 0.0052$; 30 min, $P = 0.0159$; 60 min, $P = 0.0304$; 120 min, $P = 0.0129$; and 180 min, $P = 0.0105$; P values for sucrose: 0 min, $P = 0.0086$; 30 min, $P = 0.0164$; 120 min, $P = 0.0003$; and 180 min, $P = 0.0047$) (**Supplemental Table 3**). No significant differences were identified in the insulin concentrations between healthy and unhealthy participants (Figure 3B), but the peak insulin concentrations were at 90 min following isomaltulose and sucrose ingestion in unhealthy participants, which were 30 min and 60 min later than those in healthy participants.

Figure 4 shows the differences (WMDs) in circulating glucose and insulin concentrations between the isomaltulose and sucrose arms at the various time points for the subgroups. As shown in Figure 4A, there were statistically significant negative WMDs of circulating glucose at 30 min (WMD: −2.20 mmol/L; 95% CI: −2.76, −1.64 mmol/L; $P < 0.001$; $I^2 = 0.0\%$) and 60 min (WMD: −1.45 mmol/L; 95% CI: −2.36, −0.53 mmol/L; $P = 0.002$; $I^2 = 63.6\%$) in unhealthy people, and at 30 min (WMD: −1.79 mmol/L; 95% CI: −1.96, −1.61 mmol/L; $P < 0.001$; $I^2 = 0.0\%$) in healthy people. In addition, there were larger fluctuations in the WMDs in circulating glucose and smaller fluctuations in the WMDs in insulin concentration in the unhealthy participants than in the healthy participants, although these were not statistically significant (**Supplemental Tables 4** and **5**).

≤50 y vs. >50 y of age.

As shown in Figure 3C, the circulating glucose concentrations of the older participants (>50 y) were greater than those of the younger participants (following isomaltulose ingestion: 0 min, $P = 0.0028$; 30 min, $P = 0.0095$; 60 min, $P = 0.0023$; 120 min, $P = 0.0008$; and 180 min, $P < 0.0001$; following sucrose ingestion: 0 min, $P = 0.0007$; 30 min,

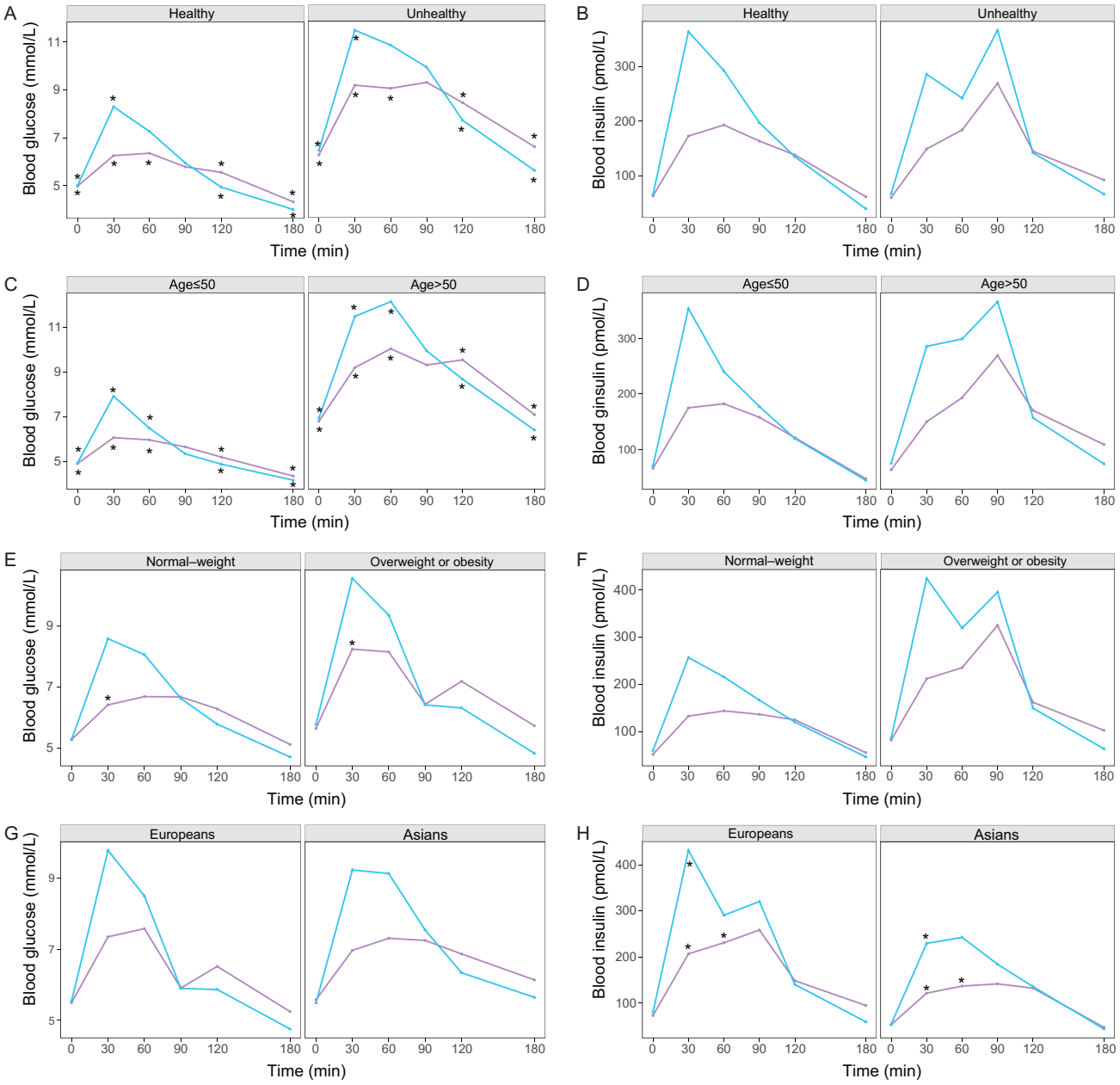

FIGURE 3 Subgroup analyses of the changes in blood glucose and insulin concentrations after ingestion. Comparisons of the changes in blood glucose and insulin concentrations to each carbohydrate are shown for participants with differing health status (A and B), age category (C and D), BMI category (E and F), and ethnicity (G and H). The numbers of included studies of 0, 30, 60, 90, 120, and 180 min for the healthy group are 6, 6, 6, 6, 6, and 3; for the unhealthy group are 5, 4, 5, 2, 5, and 5; for the age ≤50-y group are 6, 5, 6, 5, 6, and 4; for the age >50-y group are 4, 4, 4, 2, 4, and 4; for the normal-weight group are 5, 5, 5, 5, 5, and 3; for the overweight or obesity group are 5, 4, 5, 2, 5, and 5; for the Asian group are 5, 5, 5, 5, 5, and 2; and for the European group are 6, 5, 6, 3, 6, and 6. Values are means. *Significant difference between the subgroups.

$P = 0.0057$; 60 min, $P = 0.0009$; 120 min, $P = 0.0023$; and 180 min, $P = 0.0061$; Supplemental Table 3). There was no difference in insulin concentration between the younger and older participants (Figure 3D).

As shown in Figure 4B, there were significant negative WMDs in the circulating glucose concentrations at 30 min (WMD: −2.20 mmol/L; 95% CI: −2.76, −1.64 mmol/L; $P < 0.001$; $I^2 = 0.0\%$) and 60 min (WMD: −1.80 mmol/L; 95% CI: −2.54, −1.06 mmol/L; $P < 0.001$; $I^2 = 0.0\%$) in the older subgroup, and at 30 min (WMD: −1.76 mmol/L; 95% CI: −1.94, −1.58 mmol/L; $P < 0.001$; $I^2 = 0.0\%$) in the younger subgroup. Strikingly, there was a significant prolongation of the glycemic response difference between the isomaltulose and sucrose arms (WMD: 0.82 mmol/L; 95%

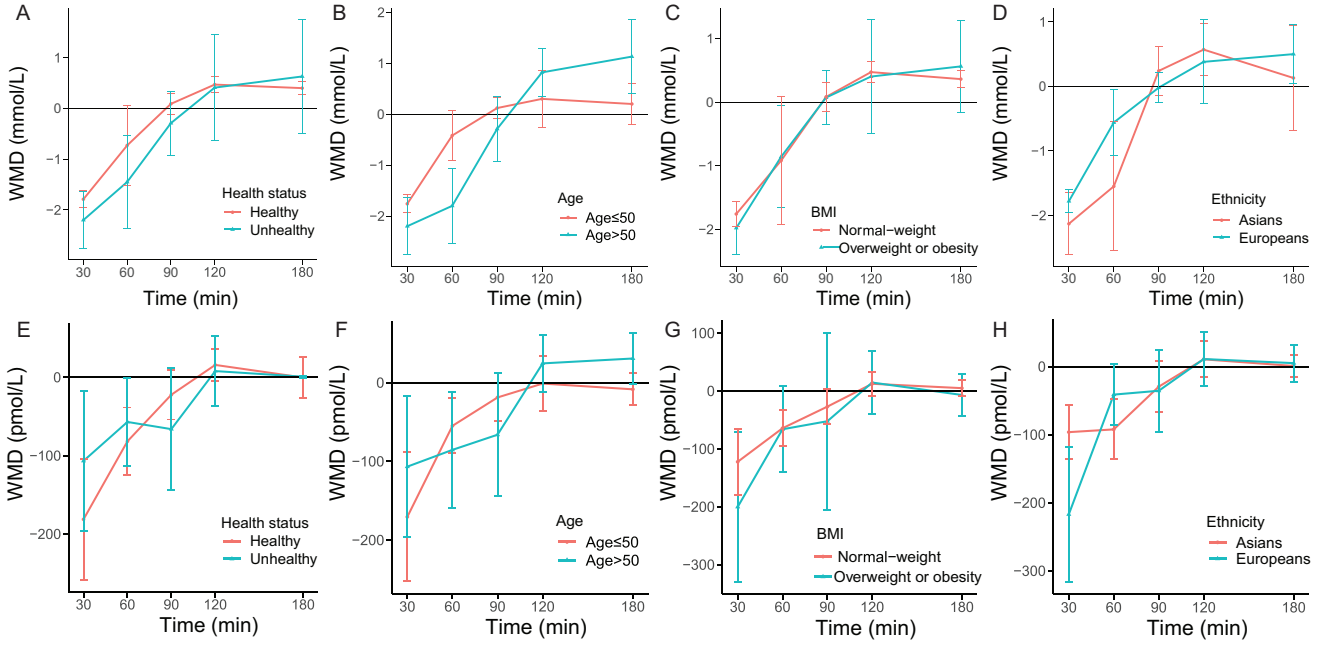

FIGURE 4 Subgroup analyses of the weighted mean difference in postprandial blood glucose and insulin concentrations between the isomaltulose and sucrose arms. Comparisons of the WMDs of these two carbohydrates in people with differing health status (A and E), age category (B and F), BMI category (C and G), and ethnicity (D and H). Each panel shows the WDMs and corresponding 95% CIs (vertical lines around every point). The numbers of included studies of 0, 30, 60, 90, 120, and 180 min for the healthy group are 6, 6, 6, 6, 6, and 3; for the unhealthy group are 5, 4, 5, 2, 5, and 5; for the age ≤50-y group are 6, 5, 6, 5, 6, and 4; for the age >50-y group are 4, 4, 4, 2, 4, and 4; for the normal-weight group are 5, 5, 5, 5, 5, and 3; for the overweight or obesity group are 5, 4, 5, 2, 5, and 5; for the Asian group are 5, 5, 5, 5, 5, and 2; and for the European group are 6, 5, 6, 3, 6, and 6. *Significant difference between the subgroups. WMD, weighted mean difference.

CI: 0.35, 1.29 mmol/L; $P = 0.001$; $I^2 = 0.0\%$ at 120 min and WMD: 1.13 mmol/L; 95% CI: 0.41, 1.85 mmol/L; $P = 0.002$; $I^2 = 27.3\%$ at 180 min) only in the older subgroup. There were larger fluctuations in the WMDs of circulating glucose concentration in the older subgroup (WMDs in circulating glucose concentration, older vs. younger subgroups: 30 min, −2.2 vs. −1.76 mmol/L, $P = 0.137$; 60 min, −1.8 vs. −0.42 mmol/L, $P = 0.002$; 90 min, −0.29 vs. 0.12 mmol/L, $P = 0.227$; 120 min, 0.82 vs. 0.3 mmol/L, $P = 0.168$; 180 min, 1.13 vs. 0.2 mmol/L, $P = 0.028$) (Supplemental Tables 4 and 5).

Overweight/Obesity vs. Normal-Weight subgroups.

As shown in Figure 3E and F, the Overweight/Obesity subgroup had a greater circulating glucose concentration than the Normal-Weight group at 30 min ($P = 0.0159$, Supplemental Table 3). Greater circulating insulin concentrations were maintained for a longer period (from 30 to 90 min) following sucrose and isomaltulose ingestion in the Overweight/Obesity subgroup. As shown in Figure 4C, there were significant negative WMDs of circulating glucose concentration at 30 min and 60 min in the Overweight/Obesity subgroup and at 30 min in the Normal-Weight subgroup. There were larger fluctuations in the WMDs in circulating glucose and insulin concentrations between the isomaltulose and sucrose arms in the Overweight/Obesity subgroup, although this was not statistically significant (Supplemental Tables 4 and 5).

Asian vs. European participants.

As shown in Figure 3H, Asian participants had lower circulating insulin concentrations than European participants, regardless of whether they ingested isomaltulose or sucrose (Supplemental Table 3). There were significant differences in insulin concentration 30 min following sucrose ingestion ($P = 0.0216$) and 30 min ($P = 0.0257$) and 60 min ($P = 0.005$) following isomaltulose ingestion between Asian and European participants. As shown in Figure 4D and H, the fluctuation in the WMD in circulating insulin concentration between the isomaltulose and sucrose arms at 30 min in Asians was not as large as that in the European participants (Asian vs. European participants: −96.39 vs. −217.21 pmol/L, $P = 0.027$; Supplemental Table 5).

Sensitivity analysis and meta-regression

Sensitivity analyses showed that the results were robust (**Supplemental Figure 5**), except for the effect of isomaltulose on circulating glucose concentration at 30 min, which was influenced by the study by Holub et al. (19). However, after excluding this, the effect of isomaltulose on circulating glucose concentration was not abolished or inverted (WMDs for the data after the exclusion of the study vs. the original

data: 30 min, −2.04 vs. −1.83 mmol/L, respectively). As shown in **Supplemental Figure 6**, meta-regression analyses showed that, with increasing age, the effect of isomaltulose on reducing glycemic response at 60 min was significantly stronger ($\beta = -0.06$; 95% CI: −0.10, −0.02; $P = 0.012$) (**Supplemental Table 6**).

GRADE assessment

Figure 2E shows the result of GRADE assessments of the overall certainty of evidence for the effect of isomaltulose on circulating glucose and insulin concentrations. The evidence for the effect of isomaltulose on circulating glucose at 30 and 90 min was graded as moderate, but the evidence for its effects on circulating glucose at 60, 120, and 180 min, and circulating insulin at 30, 60, 90, 120, and 180 min, was graded as low because of inconsistency and imprecision (**Supplemental Table 7**). We also assessed the certainty of evidence provided by the subgroup analyses of the effects of isomaltulose. As shown in **Supplemental Figures 7** and **8**, all of these were graded as moderate or low (**Supplemental Tables 8** and **9**).

Discussion

The epidemic of diabetes and the serious associated health and economic burdens necessitate the identification of effective preventive measures. The key finding of this study is that isomaltulose represents an ideal substitute for high-GI carbohydrates in diets because of the attenuated but longer glycemic responses and attenuated insulinemic responses induced. Individuals with impaired glycemia and insulinemia, including those with type 2 diabetes, IGT, or hypertension, older people, those who have overweight or obesity, and Asians, are likely to benefit more from the use of isomaltulose.

The postprandial increase in circulating glucose concentration is limited by the secretion of insulin, which is induced directly by glucose in B cells and via the incretin effect (20). Isomaltulose is a low-GI carbohydrate that is hydrolyzed in the gut at ∼32% of the rate of sucrose (11), which implies that isomaltulose is more slowly digested and absorbed through the gut than sucrose, resulting in more prolonged provision of glucose for metabolism. Therefore, the postingestion circulating glucose concentration would increase more slowly but maintain the glycemia for a longer period of time, and there is less stimulation of the B cell. Furthermore, isomaltulose consumption leads to less secretion of gastric inhibitory polypeptide (GIP), as well as the secretion of glucagon-like peptide-1 (GLP-1) at 30 min after digestion, both of which play an important role in postprandial insulin secretion (21). Thus, together with the reduced stimulation to B cells by postprandial circulating glucose concentrations, reductions in the secretion of GIP and GLP-1 (within 30 min after digestion) also result in less postprandial insulin secretion. Previous studies of this topic differed with respect to the characteristics of the participants, the interventions and measurements used, and the time points studied, which may explain the inconsistent results generated. By synthesizing the data obtained in these studies, we provide evidence that isomaltulose is associated with a significantly attenuated but more prolonged glycemic response and an attenuated insulinemic response compared with sucrose.

The results of subgroup analyses found that the effect of isomaltulose on the glycemic response seems to be more prominent in unhealthy participants. However, the effect of isomaltulose on circulating insulin concentration was opposite (Figure 4E), which may be explained by the difference in the rate of gut hydrolysis of sucrose and isomaltulose and the difference in the incretin effect in healthy and unhealthy individuals. First, isomaltose hydrolyzes much more slowly, causing it to bypass the K cells in the upper intestine (which secrete GIP) and reach the more distal L-cells, which produce GLP-1 (22). It implies that isomaltulose would be associated with more GLP-1 secretion (22, 23). In healthy individuals, GIP accounts for approximately two-thirds of the incretin effect (24); however, in patients with type 2 diabetes, the endocrine pancreas remains responsive to GLP-1 but is not responsive to GIP (25). Therefore, in individuals with type 2 diabetes, isomaltulose ingestion is associated with greater production of GLP-1 than sucrose ingestion. In addition, studies have shown that isomaltulose stimulates more GLP-1 than sucrose after 60 min, as evidenced by the significantly greater AUCs of GLP-1 than that of sucrose between 60 and 90 min (21). It thereby reduces the difference in insulinemia following sucrose and isomaltulose ingestion in unhealthy individuals. In addition, previous studies have shown that essential hypertension is an insulin-resistant state (26); therefore, the replacement of high-GI carbohydrate with isomaltulose may also be beneficial for patients with hypertension.

The mechanisms underlying the alterations in B-cell function with age have been elucidated, and include impairments in Ca^{2+} signaling (27) in human islets and epigenetic changes that affect gene expression (28). In addition, circulating glucose is primarily disposed of into muscle, but aging is associated with an increase in visceral fat and a decrease in muscle mass, which result in insulin resistance and hyperglycemia (29). Such aging-related changes reflect a poorer ability of older people to metabolize circulating glucose. Wolever et al. (30) found that the glycemic load in older individuals (>40 y) was significantly greater than that in younger individuals (<40 y). The mean AUCs for 4 foods (glucose, white bread, chocolate-chip cookies, and fruit leather) was 128 mmol · min/L in the younger participants, which was less than the 165 mmol · min/L for the older participants ($P < 0.05$). Consistent with this, there were significantly greater circulating glucose concentrations in the older participants in the present study, regardless of whether sucrose or isomaltulose was ingested. According to the meta-regression, increasing age is associated with an increasing difference in the glycemic responses to isomaltulose and sucrose, with a statistically significant result 60 min after ingestion (β: −0.06, $P = 0.012$). Therefore, considering that most of the older population has impaired glucose tolerance,

we believe that isomaltulose would be more beneficial with respect to glycemia and insulinemia in older individuals.

Obesity-derived insulin resistance is considered to substantially increase the risk of type 2 diabetes. Individuals with overweight or obesity require greater insulin secretion to maintain glucose homeostasis, even if they have the same diet as normal-weight individuals. Recently, Hoddy et al. (31) suggested that both metabolically healthy obesity and metabolically unhealthy obesity are associated with impaired insulin sensitivity and peripheral insulin resistance, independent of metabolic status. Similarly, in the present study, the participants who had overweight or obesity had greater circulating insulin and glucose concentrations. Significant differences between the WMDs of these 2 subgroups were not identified. Underestimation of the difference can be attributed to the uneven distribution of other characteristics—for example, the participants in the Overweight/Obesity subgroup were all European.

People from East, South, and Southeast Asia develop diabetes at younger ages and progress from prediabetes to diabetes more quickly than Whites of comparable BMI (32). Jainandunsing et al. (33) found that, in South Asians, a rapid deterioration in B-cell function occurs under insulin-resistant conditions, and this may explain the earlier onset of type 2 diabetes in nonobese individuals from this region than in Whites. Venn et al. (34) assessed the glycemic responses to glucose and cereal in White and Asian people and found that the mean differences in incremental AUC (iAUC), representing glycemia and insulinemia, were 29% and 63% greater, respectively, in the latter group. Dickinson et al. (35) also found that Whites had a significant less iAUC than South or East Asian, Chinese, or Indian people after the consumption of 75 g white bread. In the present study, we found significantly greater circulating insulin concentration after the ingestion of isomaltulose or sucrose in European people. Considering the limited capacity for insulin secretion in East Asian people, even a small decrease in insulin secretion may lead to a rapid decrease in the threshold of insulin resistance, which may explain the higher risk of type 2 diabetes in this group, compared with Whites (36). Thus, the use of isomaltulose in place of sucrose in the diet may be more beneficial for Asian people.

Our findings also need to be interpreted in the light of several limitations. First, due to the limited number of studies that have yield iAUCs for postingestion circulating glucose and insulin concentrations, we could only analyze the glucose and insulin concentrations at certain time points. Second, due to the complexity and inconsistency of mixed meals and beverages containing isomaltulose in previous trials, we only included trials in which the intervention was the ingestion of carbohydrates dissolved in water. Although this approach was capable of demonstrating an independent effect of isomaltulose in RCTs, people usually ingest isomaltulose in meals in the real world. Third, the subgroup analyses were usually based on a single parameter classification, and the influence of residual confounders that resulted from the unbalanced distributions of other important characteristics cannot be entirely excluded. Fourth, although differences (WMDs) in the effect of isomaltulose compared with sucrose on glycemia and insulinemia were identified in various subgroups in the present study, only a few were statistically significant. However, notably, in the included studies, most participants ingested 50 g isomaltulose or sucrose, which is less than the quantity that people typically consume daily in the real world, and especially during the epidemic of obesity. This implies that, as a larger amount of sucrose is replaced with isomaltulose, the effect would become more pronounced and the differences in its effects between specific populations would become more marked.

In conclusion, the present study shows that the replacement of sucrose or other high-GI carbohydrates with isomaltulose should be associated with an attenuated and more prolonged glycemic response and an attenuated insulinemic response. Patients with type 2 diabetes, IGT, or hypertension, older people, overweight and obese people, and Asian people may particularly benefit from the use of isomaltulose. More RCTs performed using standard mixed meals containing isomaltulose and further systematic reviews are required in order to provide higher-grade evidence to guide its use.

Acknowledgments

The authors' responsibilities were as follows—MW: conceived the idea for the review; MW and FW: designed, supervised, and coordinated the study; QQ and HN: gave crucial intellectual input; JX, JL, YY, and ZH: searched the literature, extracted data, and assessed risk of bias; JX, JL, and YG: coded the statistical analysis, figures, and supplementary materials in collaboration with ZL; JX, JL, FW, and MW: interpreted the data; FW and JX: drafted the manuscript; MW, HN, and QQ: obtained funding; MW: attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted; FW and MW: are the guarantors of this manuscript; and all authors: read and approved the final manuscript.

Data Availability

Data described in the manuscript and analytic code will be made available upon request.

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract 2019;157:107843.
2. International Diabetes Federation. IDF Diabetes Atlas. [Internet]. [Accessed 2021 Oct 1]. Available from: https://www.diabetesatlas.org/en/.
3. Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2018;139:239–52.
4. Brouns F. Overweight and diabetes prevention: is a low-carbohydrate-high-fat diet recommendable? Eur J Nutr 2018;57(4):1301–12.

5. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet North Am Ed 2014;383(9933):1999–2007.
6. Bhupathiraju SN, Tobias DK, Malik VS, Pan A, Hruby A, Manson JE, et al. Glycemic index, glycemic load, and risk of type 2 diabetes: results from 3 large US cohorts and an updated meta-analysis. Am J Clin Nutr 2014;100(1):218–32.
7. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34(3):362–6.
8. Heyman MB; Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. Pediatrics 2006;118(3):1279–86.
9. Ter Horst KW, Serlie MJ. Fructose consumption, lipogenesis, and non-alcoholic fatty liver disease. Nutrients 2017;9(9):981.
10. Taylor SR, Ramsamooj S, Liang RJ, Katti A, Pozovskiy R, Vasan N, et al. Dietary fructose improves intestinal cell survival and nutrient absorption. Nature 2021;597(7875):263–7.
11. Tian Y, Deng Y, Zhang W, Mu W. Sucrose isomers as alternative sweeteners: properties, production, and applications. Appl Microbiol Biotechnol 2019;103(21–22):8677–87.
12. Okuno M, Kim MK, Mizu M, Mori M, Mori H, Yamori Y. Palatinose-blended sugar compared with sucrose: different effects on insulin sensitivity after 12 weeks supplementation in sedentary adults. Int J Food Sci Nutr 2010;61(6):643–51.
13. Brunner S, Holub I, Theis S, Gostner A, Melcher R, Wolf P, et al. Metabolic effects of replacing sucrose by isomaltulose in subjects with type 2 diabetes: a randomized double-blind trial. Diabetes Care 2012;35(6):1249–51.
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions version 6.2. Updated February 2021 [Internet]. Cochrane Collaboration; 2021. Available from: www.training.cochrane.org/handbook.
15. Kawai K, Yoshikawa H, Murayama Y, Okuda Y, Yamashita K. Usefulness of palatinose as a caloric sweetener for diabetic patients. Horm Metab Res 1989;21(06):338–40.
16. van Can JG, Ijzerman TH, van Loon LJ, Brouns F, Blaak EE. Reduced glycaemic and insulinaemic responses following isomaltulose ingestion: implications for postprandial substrate use. Br J Nutr 2009;102(10):1408–13.
17. van Can JG, van Loon LJ, Brouns F, Blaak EE. Reduced glycaemic and insulinaemic responses following trehalose and isomaltulose ingestion: implications for postprandial substrate use in impaired glucose-tolerant subjects. Br J Nutr 2012;108(7):1210–7.
18. Yamori Y, Mori M, Mori H, Kashimura J, Sakuma T, Ishikawa PM, et al. Japanese perspective on reduction in lifestyle disease risk in immigrant Japanese Brazilians: a double-blind, placebo-controlled intervention study on palatinose. Clin Exp Pharmacol Physiol 2007;34(s1):S5–S7.
19. Holub I, Gostner A, Theis S, Nosek L, Kudlich T, Melcher R, et al. Novel findings on the metabolic effects of the low glycaemic carbohydrate isomaltulose (palatinose). Br J Nutr 2010;103(12):1730–7.
20. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev 2005;26(2):19–39.
21. Maeda A, Miyagawa J, Miuchi M, Nagai E, Konishi K, Matsuo T, et al. Effects of the naturally-occurring disaccharides, palatinose and sucrose, on incretin secretion in healthy non-obese subjects. J Diabetes Investig 2013;4(3):281–6.
22. Keyhani-Nejad F, Kemper M, Schueler R, Pivovarova O, Rudovich N, Pfeiffer AF. Effects of palatinose and sucrose intake on glucose metabolism and incretin secretion in subjects with type 2 diabetes. Diabetes Care 2016;39(3):e38–e39.
23. Keyhani-Nejad F, Barbosa Yanez RL, Kemper M, Schueler R, Pivovarova-Ramich O, Rudovich N, et al. Endogenously released GIP reduces and GLP-1 increases hepatic insulin extraction. Peptides 2020;125:170231.
24. Nauck MA, Bartels E, Orskov C, Ebert R, Creutzfeldt W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. J Clin Endocrinol Metab 1993;76(4):912–7.
25. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol 2016;4(6):525–36.
26. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317(6):350–7.
27. Westacott MJ, Farnsworth NL, St Clair JR, Poffenberger G, Heintz A, Ludin NW, et al. Age-dependent decline in the coordinated [Ca(2+)] and insulin secretory dynamics in human pancreatic islets. Diabetes 2017;66(9):2436–45.
28. Bacos K, Gillberg L, Volkov P, Olsson AH, Hansen T, Pedersen O, et al. Blood-based biomarkers of age-associated epigenetic changes in human islets associate with insulin secretion and diabetes. Nat Commun 2016;7:1, 11089.
29. van den Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endocrine systems with ageing. Lancet Diabetes Endocrinol 2018;6(8):647–58.
30. Wolever TM, Jenkins AL, Vuksan V, Campbell J. The glycaemic index values of foods containing fructose are affected by metabolic differences between subjects. Eur J Clin Nutr 2009;63(9):1106–14.
31. Hoddy KK, Axelrod CL, Mey JT, Hari A, Beyl RA, Blair JB, et al. Insulin resistance persists despite a metabolically healthy obesity phenotype. Obesity (Silver Spring) 2022;30:39–44.
32. Caleyachetty R, Barber TM, Mohammed NI, Cappuccio FP, Hardy R, Mathur R, et al. Ethnicity-specific BMI cutoffs for obesity based on type 2 diabetes risk in England: a population-based cohort study. Lancet Diabetes Endocrinol 2021;9(7):419–26.
33. Jainandunsing S, Ozcan B, Rietveld T, van Miert JN, Isaacs AJ, Langendonk JG, et al. Failing beta-cell adaptation in South Asian families with a high risk of type 2 diabetes. Acta Diabetol 2015;52(1):11–9.
34. Venn BS, Williams SM, Mann JI. Comparison of postprandial glycaemia in Asians and Caucasians. Diabet Med 2010;27(10):1205–8.
35. Dickinson S, Colagiuri S, Faramus E, Petocz P, Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. J Nutr 2002;132(9):2574–9.
36. do Vale Moreira NC, Ceriello A, Basit A, Balde N, Mohan V, Gupta R, et al. Race/ethnicity and challenges for optimal insulin therapy. Diabetes Res Clin Pract 2021;175:108823.
37. Kawai K, Okuda Y, Yamashita K. Changes in blood glucose and insulin after an oral palatinose administration in normal subjects. Endocrinol Jpn 1985;32(6):933–6.
38. de Groot E, Schweitzer L, Theis S. Efficacy of isomaltulose compared to sucrose in modulating endothelial function in overweight adults. Nutrients 2020;12(1):141.