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The Rate of Glucose Appearance Is Related to Postprandial Glucose and Insulin Responses in Adults: A Systematic Review and Meta-analysis of Stable Isotope Studies

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ABSTRACT

Background: It is often assumed that lower postprandial glucose (PPG) and insulin (PPI) responses are induced by slower glucose influx from the gut (e.g., by delayed carbohydrate digestion). However, changes in the rate of appearance of glucose in the peripheral circulation [rate of appearance of exogenous glucose (RaE)] may be accompanied by changes in endogenous glucose production (EGP) and the rate of disappearance of total glucose into tissues (RdT). The quantitative relationships between reductions in RaE and PPG/PPI levels are unclear.

Objectives: The objective was to perform a meta-analysis to quantify the effect of changes in RaE on changes in PPG and PPI levels (primary) and EGP and RdT (secondary).

Methods: We systematically searched the Scopus, Medline, and Cochrane library databases through 10 January 2019 for randomized, controlled, carbohydrate-rich interventions that aimed to reduce RaE in humans, measured using dual or triple stable isotope methods. The 2-h net incremental AUCs for all variables were extracted or calculated. Relationships between RaE and outcomes were quantified by weighted regression analyses.

Results: There were 12 articles, including 17 comparisons, that satisfied the inclusion criteria. The subjects were mainly men (60%), with age and BMI ranges of 18–40 y and 20.0–27.5 kg/m^2, respectively. A 10% reduction in RaE was associated with reductions in PPG levels, PPI levels, and the RdT of 7% (95% CI: 2%, 12%; $P = 0.010$), 8% (95% CI: 2%, 13%; $P = 0.012$), and 11% (95% CI: 4%, 17%; $P = 0.005$), respectively, but was not significantly associated with a change in EGP (13%; 95% CI: −7%, 33%; $P = 0.176$). All fluxes together explained 70% and 26% of the variances in PPG and PPI levels, respectively.

Conclusions: In adults, reducing glucose RaE by diet is associated with significant reductions in PPG levels, PPI levels, and the rate of glucose disposal. This trial was registered in the PROSPERO database with identifier CRD42018084824. *J Nutr* 2019;149:1896–1903.

Keywords: glucose fluxes, glucose kinetics, pasta, bread, rice, cereals, biscuits, carbohydrate digestion, weighted regression

Introduction

Repeated exposures to high postprandial glucose (PPG) and/or insulin (PPI) levels after a meal are detrimental for health (1). There is evidence that reducing the PPG level improves glycaemic control (2–6) and, as a consequence, reduces the progression from pre-diabetes to type 2 diabetes mellitus (2, 3, 5, 7). These effects have been shown in studies with the α-glucosidase inhibitor Acarbose (2, 7) and in meta-analyses and reviews of studies with low glycemic index/load diets (3–6).

It is often assumed that slowing the rate of digestion of carbohydrates, resulting in a slower influx of glucose from the gut (6, 8), directly leads to reduced PPG and PPI levels. However, the PPG response profile is the net result of the rate of appearance of exogenous glucose (originating from food) in the peripheral circulation (RaE), tissue uptake [rate of disappearance of total glucose (RdT)], and hepatic glucose production [endogenous glucose production (EGP) (9)]. It is important to keep in mind that the RaE does not provide information on how much glucose the liver extracts. Testing the relationship between the RaE and the PPG response requires the determination of glucose fluxes, because changes in the RaE may be accompanied (compensated or enhanced) by substantial changes in EGP and the RdT. Indeed, there is at least 1 example comparing pasta with bread (control) where the RaE was significantly lower but the PPG level was the same (9). Hence, the quantitative contribution of the RaE per se to PPG and PPI

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responses is not obvious. It is also not clear to what extent changes in the RaE are related to changes in the other flux parameters.

The only way to measure plasma glucose kinetics in humans is the dual or triple stable isotope technique. These methods are based on the assumption that the physiological behavior of a labeled tracer and unlabeled tracee are identical. In both methods, subjects consume a ^{13}C-labeled carbohydrate source while a ^{2}H-glucose tracer is infused (10). In the dual-tracer method, EGP is calculated from the other fluxes, while the triple-tracer method introduces a third tracer (6–^{3}H glucose) (11). The additional tracer and infusion procedures minimize non–steady state errors and improve the determination of EGP, but this method is more costly and technically more demanding (12). These study designs enable the determination of the different fluxes and, together with PPG and PPI levels, also allow for quantitatively modeling the relationships between the RaE and postprandial responses. Although there are a growing number of stable isotope studies measuring glucose fluxes, to our knowledge there is no previous systematic search and meta-analysis of all these data. The only related meta-analysis is limited to a subset of studies comparing glucose fluxes to in vitro digestibility of starch in breakfast products (13).

The primary objective of this study was, therefore, to perform a systematic review and a meta-analysis of randomized, controlled human intervention trials to quantify the effect of variations in the RaE on PPG and PPI responses. The secondary objective was to estimate the effect of a change in the RaE on the changes in EGP and RdT. An exploratory analysis also looked at the contribution of EGP and RdT to PPG levels and of the contribution of PPI responses to EGP and RdT.

Methods

Protocol and reporting

The protocol for this meta-analysis was registered a priori with the PROSPERO International Prospective Register of Systematic Reviews (CRD42018084824). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (14) and a checklist was completed.

Data sources and searches

We searched titles, abstracts, and keywords using the Cochrane Library, Scopus, and Medline databases (latter using the Ovid platform), with no time restriction. The date of the last search was 10 January 2019. The search strategy was designed for the Scopus database initially and was adapted for use with the Cochrane and Medline databases. The Scopus search strategy is presented in **Supplemental Table 1**. The search strategy was designed to identify randomized, controlled trials using dual and triple stable isotope studies that compared iso-carbohydrate–based food interventions (≥25 g available carbohydrates) and focused on exposures that may influence the rate of carbohydrate digestion or absorption (such as varying in composition or cooking time, or combined with drugs acting on RaE).

Study selection

We used the methods of the Cochrane Handbook for Systematic Reviews (http://community.cochrane.org/handbook) to identify studies meeting the inclusion criteria. These were based on the following 5 criteria: *1*) healthy humans (>1 year old) and subjects with obesity and (pre-)diabetes; *2*) iso-carbohydrate–rich interventions (≥25 g carbohydrates) varying in composition or cooking time, or combined with drugs known to act primarily on RaE; *3*) comparison to a control product with a similar amount of available carbohydrates (up to 10% deviation); *4*) randomized, controlled interventions using a dual or triple stable isotope method; and *5*) outcome data on RaE, PPG levels, and PPI levels in the ≥2 h post-meal period.

Article titles and abstracts were independently assessed by each member of a pair of co-authors (HMB/HPFP and MA/DJM) for inclusion or exclusion. Differences in the initial allocation were resolved by consensus. We then examined the full-text articles from all included abstracts. The inclusion or exclusion of full-text articles was assessed independently by each member of a co-author pair. Discrepancies between authors were resolved by consensus.

Data extraction

All data were extracted by HMB and checked by HPFP. Extracted data included: *1*) publication characteristics (author, year, title); *2*) meal test characteristics (time of fasting), mixed meal content [total energy and energy% from carbohydrates (total and available), dietary fibers (g), food sources, and food format (processing)]; *3*) study design characteristics (crossover or parallel design, dual or triple labeled studies, wash-out days, standardized pre-diet, duration, and times when blood taken); *4*) population (total number of participants, health status, baseline characteristics, ethnicity); *5*) exposure (RaE, AUC, means, and SDs); and *6*) outcomes (glucose, insulin, RdT, EGP, AUC, incremental AUC, all means and SDs). In addition, the components of the Jadad scale, used for quality assessment (15), were independently assessed by 2 authors (HMB and HPFP).

The quantitative outcome data extracted were the 2-hour net incremental AUCs [net incremental AUC (iAUC) mean and SD] values for RaE, PPG levels, PPI levels, RdT, and EGP. We chose the AUC over the first 2 h because, in healthy subjects, this is a standardized way of measuring PPG levels (e.g., in glucose tolerance tests or determining glycemic indices of foods) and it reflects the predominant portion of the postprandial response curve. No paper directly reported the 2-hour net iAUC values and, therefore, these data were extracted from response curves using the Microsoft Excel add-in tool "TM Image-to-data" (16). We contacted 3 authors to retrieve their data because response curves were unavailable or unclear: all provided the iAUCs or single timepoints (means and SDs) that allowed a net iAUC to be calculated. **Table 1** shows the source of the net iAUC data. Outcome data were extracted into a worksheet by 1 author (HMB) and double-checked by another author (HPFP). The net iAUC data were recalculated as needed into standard units [RaE, RdT, and EGP in mg/(kg · min), glucose in mmol/L, insulin in pmol/L].

Statistical methods

For the purposes of calculating change values, the intervention was defined as the treatment arm with the lowest RaE and the comparator treatment was designated the control. Weighted linear regression analyses were used to relate the change in RaE with the primary and secondary outcomes. The changes in RaE and all other outcomes were calculated as $\%\text{Change} = 100 \times [\text{iAUC}_{(\text{intervention})} - \text{iAUC}_{(\text{control})}]/\text{iAUC}_{(\text{control})}$. Regression analyses were weighted for the inverse $\text{SE}_{(\text{relative change})}^{2}$ of the outcome variable. Because the mean baseline values of intervention and control treatments were similar in the only trial using a parallel design, the formula for the SE of relative change for crossover designs was universally applied (for formula, see

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Supplemental Tables 1–6 and Supplemental Figures 1 and 2 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/jn/.
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Abbreviations used: EGP, endogenous glucose production; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; iAUC, incremental AUC; PPG, postprandial glucose response; PPI, postprandial insulin response; RaE, rate of appearance of exogenous glucose; RaT, rate of appearance of total glucose; RdT, rate of disappearance of total glucose.

TABLE 1 Characteristics of stable isotope studies and study arms included in the meta-analysis[1]

		Participants									
First author, year (reference)	T	Type	*n*	Age, y	BMI, kg/m^2	Control (available CHO), g	Control format	Intervention (available CHO), g	Treatment format	Outcome parameters and data provided	Jadad score
Boers et al., 2017 (17)	1	Healthy men	12	23.0 ± 0.6	22.6 ± 0.3	69.5	Flatbread	62.5	Flatbread + 2% guar gum	RaE[3], RdT[3], EGP[3], PPG[3], PPI[3]	10
	2							61.4	Flatbread + 4% guar gum		
Eelderink et al., 2012 (9)	1	Healthy men	10	21.0 ± 0.5	23.0 ± 0.6	50.0	Bread	50.0	Bread with purple wheat bran	RaE[2], RdT[3], PPG[2], PPI[4]	7
Eelderink et al., 2015 (18)	1	Healthy men	10	24.0 ± 0.6	22.0 ± 0.2	50.0	Bread	50.0	Pasta	RaE[2], RdT[3], EGP[3], PPG[2], PPI[2]	7
	2							50.0	Flatbread		
Eelderink et al., 2016 (19)	1	Healthy men	10	24.0 ± 0.6	22.0 ± 0.2	50.0	Bread	50.0	Kernel bread	RaE[2], RdT[3], EGP[3], PPG[2], PPI[2]	7
Eelderink et al., 2012 (20)	1	Healthy men	9	21.0 ± 0.5	23.0 ± 0.6	24.0 ± 0.6	Bread	50.0	Pasta	RaE[2], RdT[3], EGP[3], PPG[2], PPI[4]	7
Korach-Andre et al., 2004 (21)	1	Healthy men	8	22.4 ± 0.6	22.1 ± 0.6	273.0	Polished rice	270.0	Parboiled rice	RaE[2], EGP[2], PPG[2], PPI[2]	7
Nazare et al., 2010 (22)	1	Men and women	19 and 19	38.3 ± 1.5	27.3 ± 0.2	59.0	Flakes (extruded)	59.0	Plain biscuits	RaE[2], PPG[2], PPI[2]	9
Nazare et al., 2009 (23)	1	Healthy men	12	34.0 ± 2.0	27.5 ± 0.3	72.3	Polenta	72.3	Polenta with 5 g β-glucan	RaE[2], EGP[2], PPG[2], PPI[2]	9
Normand et al., 2001 (24)	1	Healthy women	9	24.0 ± 2.0	20.4 ± 0.7	75.0	Pasta	75.0	Pasta with 15 g fat	RaE[2], EGP[2], PPG[2], PPI[2]	8
	2							75.0	Pasta with 40 g fat		
Péronnet et al., 2015 (25)	1	Healthy women	16	Range 18–40	Range 20–25	51.5	Extruded cereals	51.6	Biscuit 1	RaE[3], RdT[2], EGP[2], PPG[3], PPI[3]	9
	2							51.6	Biscuit 2		
	3							51.8	Biscuit 3		
Priebe et al., 2008 (26)	1	Healthy men	4	23.0 ± 1.1	21.4 ± 1.3	Range 18–40	Bread	50.0	Glucose	RaE[3], RdT[2], EGP[2], PPG[3], PPI[3]	7
Wachters-Hagedoorn et al., 2006 (27)	1	Healthy men	7	23.4 ± 1.0	21.6 ± 1.1	50.0	Glucose	50.0	Uncooked cornstarch	RaE[2], PPG[2], PPI[2]	7

[1] Values are means ± SEMs unless otherwise indicated. CHO, carbohydrate; EGP, endogenous glucose production; PPG, postprandial glucose response; PPI, postprandial insulin response; RaE, rate of appearance of exogenous glucose; RdT, rate of disappearance of total glucose; T, treatment arm.
[2] Data are from figures with response curves in the published article.
[3] Data are from single timepoints directly provided by the authors.
[4] Incremental AUC provided directly by authors.

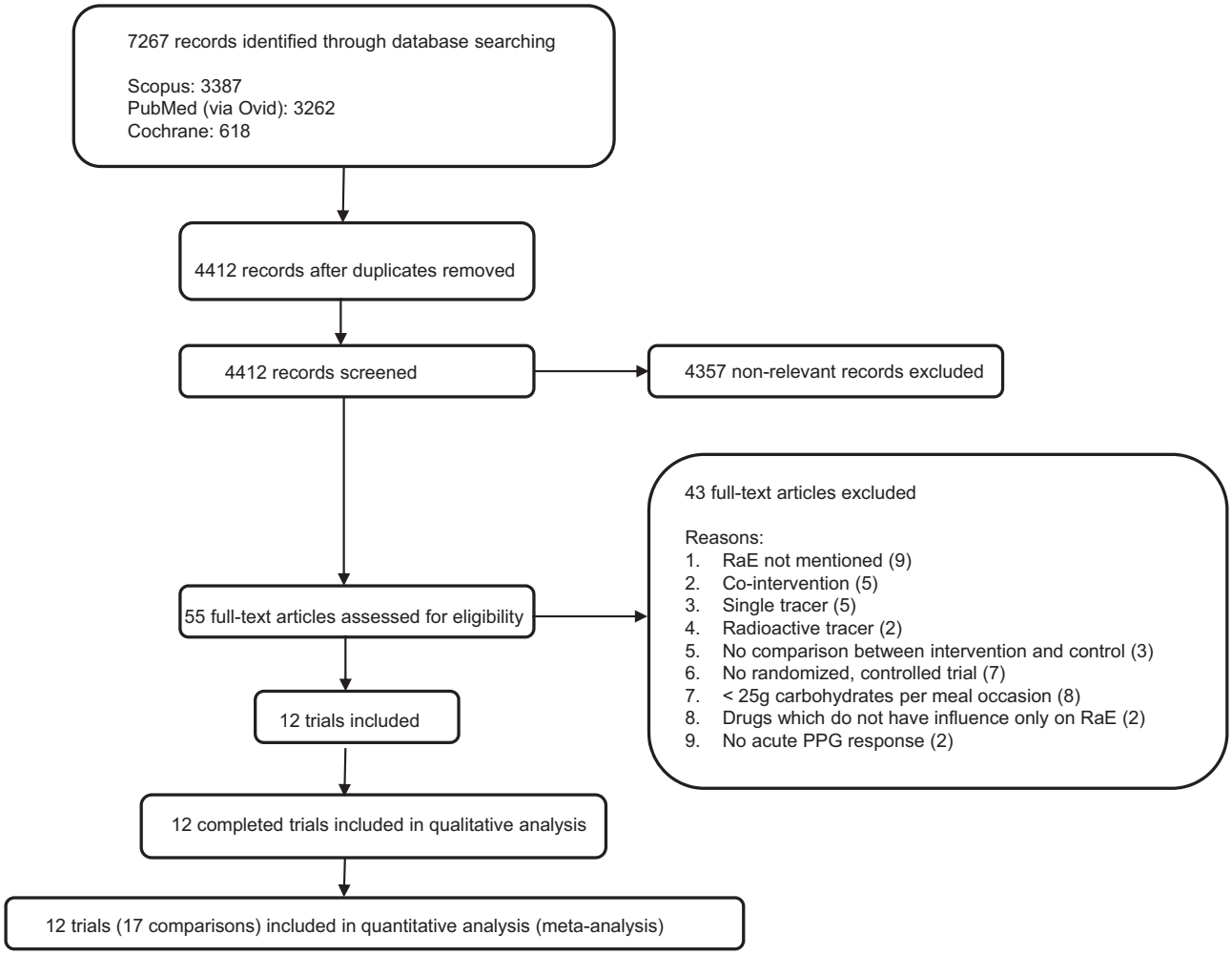

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) diagram of included studies. PPG, postprandial glucose response; RaE, rate of appearance of exogenous glucose.

Supplemental Table 2). To study whether the association of RaE with PPG and PPI levels was dependent on other fluxes, a multivariate regression model including all flux variables was used. The percentages of variance in PPG and PPI levels explained by different fluxes (alone and together) and amongst different fluxes in linear regression models were estimated by R^2. Funnel plots of PPG and PPI levels were created in Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) as a visual indicator of potential publication bias.

As a sensitivity analysis, we corrected for the inclusion of multiple treatments within studies by dividing the sample size of the shared control group by the number of treatments. This n was used in the weighting of studies (by $1/SE^2$) in the regression analyses. All analyses were performed in IBM SPSS Statistics version 21 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study selection

After the removal of duplicates, 4412 articles remained (**Figure 1**). After abstract and full-text screening, 17 comparisons from 12 articles met the inclusion criteria (Figure 1) and were used in the analysis. All comparisons contained information on RaE, PPG levels, and PPI levels, while the RdT was additionally reported in 11 comparisons and EGP was reported in 15 comparisons.

Study characteristics

All the comparisons meeting the inclusion criteria were used in the final analysis, and these are described in Table 1. All of the studies were performed among healthy subjects without (pre)diabetes, and all studies used a dual-tracer methodology. With the exception of 1 study using a parallel design (22), the studies used a crossover design. All studies used intrinsically labeled test products that varied in available carbohydrate content (50 g to 273 g) and the source of starch (rice, wheat, maize, etc.; see Table 1).

Effects of changes in rate of appearance of exogenous glucose

The relationships between the percentage change in RaE and the primary outcomes of PPG and PPI responses ($n = 17$) are shown in **Figure 2**A and B, respectively. The weighted regression analyses showed that a 10.0% reduction in the RaE (range across studies −1 to −50%) was associated with reductions in PPG and PPI levels of 6.8% (95% CI: 1.9%, 11.7%; $P = 0.010$) and 7.6% (95% CI: 1.9%, 13.3%; $P = 0.012$), respectively. The relationships between the RaE and the secondary outcomes of the RdT and EGP are shown in Figure 2C and D, respectively. These analyses showed that a 10.0% reduction in the RaE was associated with a reduction in the RdT of 10.6% (95% CI: 4.0%, 17.2%; $P = 0.005$). There was no statistically significant

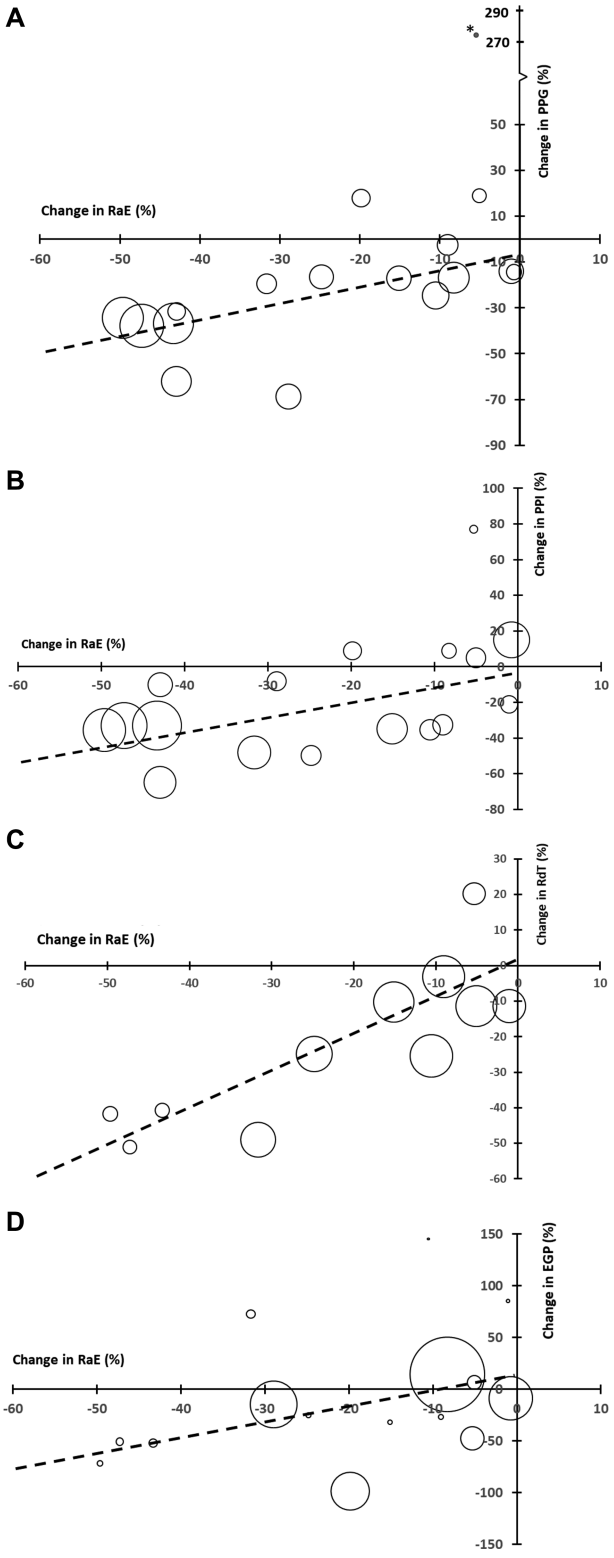

FIGURE 2 Weighted regression of change in RaE (%) versus change in (A) PPG (%; $n = 17$; $\beta = 0.68$; SE = 0.23), (B) PPI (%; $n = 17$; $\beta = 0.76$; SE = 0.27), (C) RdT (%; $n = 11$; $\beta = 1.06$; SE = 0.29), or (D) EGP (%; $n = 15$; $\beta = 1.31$; SE = 0.92), as measured in healthy adults. Bubble sizes reflect trial weight (inverse SE difference^2). *Bubble is 10 times greater than in reality. EGP, endogenous glucose production; PPG, postprandial glucose response; PPI, postprandial insulin response; RaE, rate of appearance of exogenous glucose; RdT, rate of disappearance of total glucose.

TABLE 2 Variance explained by glucose fluxes, as measured in healthy adults[1]

	Dependent variables			
Predictors	RdT	EGP	PPG	PPI
RaE	0.60	0.00	0.62	0.10
RdT		0.18	0.63	0.42[2]
EGP			0.16	0.24[2]
RaE, RdT, and EGP in 1 model			0.70	0.26

[1] Values are expressed as R^2, $n = 10$. EGP, endogenous glucose production; PPG, postprandial glucose response; PPI, postprandial insulin response; RaE, rate of appearance of exogenous glucose; RdT, rate of disappearance of total glucose.
[2] Analyzed with PPI as predictor.

association between the RaE and EGP (reduction in EGP per 10.0% reduction in RaE: 13.1%, 95% CI: −6.7%, 32.9%; $P = 0.176$). A 10.0% reduction in the PPI level was associated with a reduction in the RdT of 3.9% (95% CI: 0.4%, 7.4%; $P = 0.031$), but a change in the PPI level was not associated with postprandial changes in EGP (−3.2%, 95% CI: −14.9%, 8.6%; $P = 0.570$).

Among the studies with data on all flux parameters ($n = 10$), the variation of PPG levels explained by all fluxes together (R^2) was 70% (Table 2). In the multivariate regression model, which includes all glucose fluxes and controls for their effects on each other, none of the fluxes were significantly associated with PPG levels, but the RaE showed the largest effect estimate (a 10% change in the RaE was associated with a 12% change in the PPG level, 95% CI: −11%, 35%; $P = 0.256$). Compared to the univariate model, the association of the RdT with the PPG level was substantially lower, while EGP was also not associated with the PPG response.

The multivariate model including all fluxes explained 26% of the PPI response (Table 2 and Table 3). All data used for the analyses are shown in **Supplemental Tables 3–5.**

Quality assessment

The scores on the Jadad scale were uniformly high, ranging from 7–10 out of 11 points (Table 1 and **Supplemental Table 6**). In most cases, studies were described as randomized, while the information on double blinding was almost universally missing. Other factors which were often missing were justifications of the sample sizes and descriptions of the methods used to assess adverse effects.

Funnel plots

Funnel plots for the SE of PPG and PPI responses versus the mean difference of PPG and PPI responses (**Supplemental**

TABLE 3 Multivariate model for the association of glucose fluxes with postprandial glucose and postprandial insulin response, as measured in healthy adults[1]

	β (95% CI)	
Glucose fluxes	PPG, % change	PPI, % change
RaE	1.196 (−1.091, 3.483)	0.179 (−3.278, 3.637)
RdT	−0.275 (−2.164, 1.614)	0.295 (−2.457, 3.048)
EGP	−0.124 (−0.417, 0.168)	−0.072 (−0.562, 0.419)

[1] $n = 10$. EGP, endogenous glucose production; PPG, postprandial glucose response; PPI, postprandial insulin response; RaE, rate of appearance of exogenous glucose; RdT, rate of disappearance of total glucose.

Figures 1 and **2**, respectively) show a well-balanced distribution, with no indications of publication bias.

Sensitivity analysis

The sensitivity analysis correcting for multiple treatments within studies resulted in small changes in the quantitative associations between the RaE and PPG and PPI responses, which remained statistically significant. With this correction, a 10% reduction in the RaE reduced the PPG level by 8.7% (95% CI: 3.0%, 14.3%) and the PPI level by 9.1% (95% CI: 2.3%, 15.9%).

Discussion

Our systematic review and meta-analysis of stable isotope studies confirms that a change in the RaE from carbohydrate ingestion is significantly positively associated with changes in the PPG and PPI responses. Using data drawn from studies with carbohydrate-rich products that reduced RaEs via a range of different food compositions, each 10% reduction in the RaE reduced the PPG level by ~7% and the PPI level by ~8%. The RaE also had the strongest relationship with the PPG response, when other flux parameters are considered in the model. A reduction in the RaE was also significantly positively associated with a reduction in the RdT (a 10% reduction in the RaE reduced the RdT by ~11%), but had no statistically significant association with EGP.

All flux parameters considered together explained 70% of the variance in the PPG response, with the largest contributions coming from the RaE and RdT, which were also highly correlated with each other. In theory, all flux parameters together should explain 100% of the variance in the PPG response. However, in addition to measurement errors, the methodologies, assumptions, and computations of flux parameters from tracer studies are intricate and not completely standardized. Studies differed, for example, in the amount of ^{2}H-glucose tracer in the continuous infusion [ranging from 0.04 to 0.07 mg/(kg.min)] and, therefore, also in the bolus tracer amount (80 times the amount of infusion per minute). Importantly, though, in most of the included studies the total volume of distribution and the pool fraction used in the model to calculate the postprandial fluxes were comparable (ranging from 200 to 230 mL/kg and 0.75%, respectively). In addition, the calculation of the glucose kinetics was based on the same principles in all the included studies. The rate of appearance of total glucose (RaT; endogenous and exogenous) in plasma was estimated using the non-steady state equation of Steele et al. (28) as modified by De Bodo et al. (29). The RaE was calculated according to Tissot et al. (30) and the EGP was calculated by subtracting the RaE from the RaT (30).

The variations between studies in the contributions of different fluxes to postprandial responses may also come from the different types of interventions. There are many metabolic factors which influence PPG responses, such as insulin and the incretins [glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1)], and these may be differently affected by interventions (19, 18, 20, 27). Changes in the rate of digestion, which modifies the RaE, also change the overall delivery and rate of uptake of nutrients, influencing the incretins, insulin, glucose disposal, and endogenous liver production, which all have an influence on the PPG response.

There are many dietary approaches for reducing the RaE. Reductions of 10% or more in the RaE should be realistically achievable by different food compositions, as reductions of up to 50% were observed in the trials included here. This raises the question of whether the reductions in the RaE achievable by diet can result in clinically important changes in PPG responses. The target range for a clinically important change in the PPG level is suggested to be about 15–20% (31). Several examples here generated reductions in the RaE (~20–25%) that would achieve this. However, it should be noted that reducing the RaE is not the only way to reduce the PPG level.

Among the included comparisons, 3 comparisons used fibers and 14 used other food formats. In some cases, the same ingredients were used but were differently processed, leading, for example, to a difference in compactness (bread versus pasta; 18, 20). In other cases, extruded breakfast cereals were compared to baked cereals (such as biscuits; 22, 25). Other comparisons were glucose versus starch in the format of wheat bread (26) or versus raw cornstarch (27). With rice, different processing methods (parboiled versus boiled) were also used (21).

The observed reductions in the RaE by dietary fibers in these studies (% change −11 to −1%) were small (9, 17, 23) compared to the changes induced by the food format or food processing (% change −50 to −1%). However, it should be noted that these dietary interventions were all high-carbohydrate meals and that the levels of reductions that can be achieved via other food formats (e.g., high in proteins and/or fats) are unknown. Furthermore, while the aggregated data show that the RaE has a substantial effect on PPG and PPI responses, this was not observed in all underlying individual studies. For example Eelderink et al. (20) showed a lower RaE for pasta versus wheat bread, but no significant differences in PPG levels due to offsetting reductions in the RdT. In addition, Nazare et al. (23) and Normand et al. (24) reported reductions in RaEs that had no significant effects on PPI responses.

The finding that the changes in RaEs are not only related to changes in PPG levels but also to the RdT is a frequently neglected point. A meta-analysis of studies ($n = 3$) using cereal foods varying in slowly digestible starch content (13) found that a high amount of slowly digestible starch was associated with lower RaEs and RdTs. It can be generally hypothesized that a low RaE and, thus, lower plasma glucose concentrations could lead to decreased direct glucose stimulation of β-cells to secrete insulin, thereby leading to a lower glucose clearance (20). In line with this, we also observed positive associations between the RaE and insulin and between insulin and glucose disposal. We found no significant association between the RaE and EGP, which could be due to the fact that EGP has a small contribution in the postprandial state, compared to the RaE and RdT.

To better understand the possible underlying mechanisms, it may be helpful to consider studies where data have also been reported on the gut hormones GIP ($n = 10$) and GLP-1 ($n = 6$). These incretins affect glucose-dependent insulin production and hepatic glucose production (via glucagon) and could, therefore, indirectly influence glucose kinetics (32, 33). GLP-1 can also delay gastric emptying, which also influences the PPG response (34, 35). A few studies in this systematic review showed a strong correlation between GIP and the RaE (18, 20, 27, 25). Interestingly, in most of these studies there was a comparison between products with a difference in structure [e.g., flatbread versus normal bread (18), biscuits versus flakes (25), or pasta versus bread (20)] that may lead to a slower digestion rate and, therefore, a slower delivery of glucose to GIP-producing

K-cells in the duodenum and jejunum. For GLP-1, there is much less information available. In 1 study, the GLP-1 response was much lower after kernel bread than after the control bread, although the glucose kinetics of these breads were the same (19). After the consumption of uncooked corn starch, there was an increased late postprandial GLP-1 response, as compared to glucose (27). It may be concluded that a slower RaE leads to a cascade of metabolic effects, including lower GIP and insulin responses, which are likely to be beneficial for health in the long term.

A key benefit of aggregating the data identified from a systematic search of the literature is that this allowed for a robust, quantitative approach to the research question. A strength of this systematic review is that it includes a reasonably large set of studies sharing the use of the dual-label isotope technique and outcome measurements but not sharing all the same procedures, and scoring relatively highly for quality (Jadad score $\geq$7). There was no indication of a publication bias according to funnel plots, and the data seemed robust in a sensitivity analysis accounting for multiple comparisons from 1 study. A limitation of the stable isotope technique is that the net entry of glucose into plasma is measured, without being able to measure the fractional extraction of glucose across the liver (first-pass metabolism). The studies did not directly measure the entry of the digestion products of the carbohydrates into the portal vein. However, the carbohydrate source in all study products was starch or glucose. There are some studies in which small amounts of fructose and/or galactose were present in the test meals. Overall, the contribution of first pass metabolism in the liver would likely be minimal and, moreover, would be comparable between study arms and across studies (36).

Another limitation is that, in most studies, the RaE was reduced by a modification in starch type: in only a few studies was it reduced by the addition of fibers and in only 1 study by the addition of fat. Therefore, the results may not be representative for other types of food formats or processing; for meals with high fat and/or protein contents; or for other types of carbohydrates and fibers. Nevertheless, the amount of available carbohydrates differed widely between studies, which could be seen as an advantage in terms of generalizability. A limitation of the evidence base is that it consists only of studies using the dual-label method, whereas the triple-label method may provide more reliable estimates, of EGP in particular (11). It is known from the literature that the dual-tracer method may generate unreliable, negative estimates of EGP [seen here in 3 of the 12 studies (17, 21, 25)]. In our analyses, the net iAUC was used; therefore, the part of the AUC of EGP above baseline was subtracted from the iAUC. Since the area above baseline was relatively small and, moreover, comparable between treatments, this would have had little effect on the results. Lastly, data on the relationships between the RaE and the PPG/PPI responses were only available in healthy persons, mainly males, so we do not know whether these quantitative estimates are also valid for individuals with (pre-)diabetes or may differ in relation to sex. Thus, future research may benefit from use of the triple-tracer method for estimating EGP and from comparing glucose fluxes using a wider range of food compositions and subject populations.

In conclusion, reducing the RaE by diet is associated with significant reductions in PPG and PPI levels, and the rate of glucose disposal. Reducing the RaE may be a good target for dietary interventions because of a cascade of associated metabolic effects that may be beneficial for health. A better understanding and focus on dietary approaches to obtain a slower RaE would be of value.

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