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The Effect of Rye-Based Foods on Postprandial Plasma Insulin Concentration: The Rye Factor

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Consumption of whole grain has been associated with lower incidence of type-2 diabetes, cardiovascular disease and their risk factors including improved glycemic control. In comparison with other whole grain products, rye bread has been shown to induce lower insulin response in the postprandial phase, without affecting the glucose response. This phenomenon has been referred to as the “rye factor” and is being explored in this review where we summarize the findings from meal and extended meal studies including rye-based foods. Overall, results from intervention studies showed that rye-based foods vs. (wheat) control foods had positive effect on both insulin and glucose responses in the postprandial phase, rather than on insulin alone. Mechanistic studies have shown that the rye factor phenomenon might be due to slowing of the glucose uptake in the intestine. However, this has also been shown for wheat-based bread and is likely an effect of structural properties of the investigated foods rather than the rye *per se*. More carefully controlled studies where standardized structural properties of different cereals are linked to the postprandial response are needed to further elucidate the underlying mechanisms and determinants for the effect of specific cereals and product traits on postprandial glycemic control.

Keywords: rye, cereals, structure, insulin, glucose, diabetes, rye factor

INTRODUCTION

The link between cereal consumption, health and disease has been widely studied and whole grain intake has been consistently associated with lower risk of developing or dying from several major non-communicable diseases such as cardiovascular disease, type-2 diabetes, colorectal cancer, and their main risk factors (1–5). On the contrary, refined grains have been associated with increased or no difference in risk of similar conditions (6, 7). Moreover, there is a general consensus that food grain structure is of importance primarily for blood glucose response, but also risk factors such as cholesterol and low-grade inflammation (8–11), where coarser whole grain cereals have been shown to have positive health benefits, while cereals of more refined character have been shown to have a negative impact on health parameters (3, 12, 13). Authorities in several countries recommend consumption of whole grains instead of refined grains (14, 15). However, some studies have indicated that the effect of cereal consumption may vary among different types of cereals, which could be attributed to variations in content of dietary fiber, bioactive components or other features (16–21). For example, some studies have indicated that glycemic control is improved when the

whole grain intake is dominated by rye (6, 19, 22). Rye has the highest dietary fiber content among the cereals and it typically reaches 20% of dry matter and beyond, whereas wheat, oat and barley have approximately 10–15%, although the fiber content differ somewhat depending on variety and cultivation (18, 23). Furthermore, the dietary fiber content of commercially available cereal products may also differ widely, depending on formulation and processing (24, 25). Nonetheless, rye has higher total dietary fiber content than other cereals (18). Besides total fiber content, the composition of the dietary fiber also varies among the cereal types. Oat and barley are dominated by soluble beta-glucan, whereas the main fiber type in rye and wheat is arabinoxylan (18). Due to the overall higher content of dietary fiber, rye has approximately 50% more arabinoxylan than wheat and a larger proportion of the arabinoxylans in rye are soluble (18, 26). Soluble arabinoxylans in rye increase viscosity and are less sensitive to degradation compared with beta-glucans and may therefore exert beneficial effects on glycemic profiles and cholesterol when consumed in a wide range of products (27–29). Although observational studies have linked insoluble fiber and main sources thereof such as whole grain wheat products with reduced risk of developing type-2 diabetes and improved glycemic control, it is well established from short-term intervention studies that soluble fiber have beneficial effects on glycemic control whereas the effects on glycemia attributed to insoluble fiber are more uncertain (30, 31). An acute meal study involving 19 women showed that a meal rich in soluble fiber reduced postprandial insulin compared to a meal containing a matched amount of insoluble fiber, however, more studies directly comparing soluble and insoluble fiber in dietary intervention settings would be needed to draw strong conclusions (32).

Acute or extended meal studies investigating the effect of rye-based meals on postprandial glycemic response have repeatedly shown a pattern of reduced insulin following rye-based meals, despite similar glucose response. This phenomenon has been described and discussed as the “rye factor,” both within academia and in the industry (33), and it has been speculated whether this reduction in postprandial insulin may in part explain the mechanism behind the inverse association between rye intake and type-2 diabetes incidence (33, 34). High insulin levels have been shown to have a negative influence on the endothelial function, potentially through impaired vasodilation, which may play a role in the development of cardiovascular disease (35–37). However, not all studies investigating the postprandial response of rye-based products have supported the rye factor phenomenon and the prevalence of this phenomenon across studies and the underlying mechanisms and determinants remain unclear.

The purpose of this review was to gather studies that have investigated the acute effect of rye products on postprandial insulin and glucose and evaluate the occurrence of the rye factor phenomenon. Furthermore, we aimed to evaluate characteristics of investigated products to identify features that could help us to improve the understanding of the mechanisms behind the rye factor phenomenon. Lastly, we intended to evaluate the effect of habitual consumption of rye products on postprandial glucose and insulin response.

METHOD

A search was conducted in PubMed, Scopus, and Web of Science to identify studies investigating postprandial glucose and postprandial insulin response following at least one rye product and a non-rye control product. Reference lists of known and identified articles were inspected to identify additional relevant studies. In addition to studies investigating acute postprandial effects, studies investigating effects of regular rye consumption on insulin, glucose and other known risk markers for diabetes was included. Studies on extracts or isolated fiber fractions, as well as studies including insulin dependent diabetics, were excluded. Data on identified studies were extracted into tables. If studies included several different test products, only products directly compared to the rye product(s; i.e., statistical test result reported) were included in the tables. Products with added extracts or isolated fiber fractions were not considered, as were products designed to test the effect of adding acids to a test product. Only outcomes related to glucose and insulin metabolism were considered.

Additionally, a dataset was made containing detailed information on the pairwise testing of a rye product to a non-rye product in the Postprandial phase. As several of the included studies included more than one pair of products, the same study could appear several times in this table. Similarly, a test product could appear several times, if compared to more than one other product in the original study. Since the studies evaluated the Effect on glucose and insulin in various ways, focus was put on the area under the curve (AUC) for a time period of 3–4.5 h or 2 h for studies of shorter duration and the peak values, as these measures were available for the majority of the studies. As neither AUC nor peak were reported in all studies, it was decided to use both methods in the evaluation. It was evaluated whether the rye products resulted in lower/same/higher response than the wheat product in at least one of the mentioned evaluation methods (AUC or peak). In case rye product showed higher/lower response in one the methods and no effect in the other method it was classified as lower/higher according to the method that showed effect. None of the included studies reported conflicting results (i.e., one method showing higher and the other showing lower) for any pairwise comparisons. The tested pairs were categorized as follows: “no effect” (no effect on glucose or insulin) “glucose reduction” (lower glucose, no effect on insulin), “insulin reduction” (lower insulin, no effect on glucose, i.e., rye factor phenomenon), “reducing both” (lower glucose and lower insulin), and “increase” (higher glucose and/or insulin).

RESULTS AND DISCUSSION

Postprandial Effects

In total, 24 studies investigating the effects of rye products in the postprandial or extended postprandial phase were found (**Supplementary Table 1**). Most of the studies followed a design with a breakfast meal containing a rye product or control product served after an overnight fast. Venous or capillary blood was collected at regular intervals (every 7.5–30 min) from right before

the breakfast was served and for the following 3–4.5 h. Three studies covered a shorter period of only 2 h (38–40), while two studies extended over 6 and 7.8 h and included a standardized lunch in addition to the breakfast meal (41, 42). Most of the studies consisted of more than one rye product and/or more than one non-rye product (control), and thereby consisted of more than one pairwise comparison between a rye product and a control product.

From the 24 studies included in **Supplementary Table 1**, 72 pairwise comparisons could be extracted, and a descriptive summary of the pairs is presented in **Table 1** and **Figure 1**. Almost all the control products were wheat based, while a few studies included barley and oat products. Most of the tested products were soft breads and the remaining could be categorized as crisp bread, cold cereal (defined as breakfast type cereals, typically eaten cold with milk, or yogurt) and porridge. The majority of the pairwise comparisons were made between the same kind of product (e.g., soft rye bread vs. soft wheat bread). However, when evaluating the processing of the cereals used in the products, most of the control products were refined endosperm-based products, whereas most of the rye products were coarser products made with whole grain rye flour or rye kernels. A large proportion of the control breads were yeast fermented breads, whereas the rye breads were a mixture of yeast and sourdough fermented breads, as well as a few unfermented breads. It should be noted that not all studies clearly report the method of fermentation of the investigated products (**Table 1**). Only 21 out of 72 pairwise comparisons were done between products of similar processing (e.g., endosperm wheat flour product vs. endosperm rye flour product), whereas most studies compared effects between endosperm wheat products and whole grain rye products. While rye generally has a higher dietary fiber content than other cereals (18, 43), the difference in processing has also contributed to the difference in fiber content between the rye products and the control products in the pairwise comparisons (**Figure 1**). The difference in available carbohydrate was low since most of the studies were standardized with regard to available carbohydrate content of the test meals. The serving size of rye products was often higher than the control product to obtain the same amount of available carbohydrate. The rye content of the rye products tested in the different studies are generally high (50–100% of cereal ingredients), except for the four bran based products, which were wheat based breads with 35% added rye bran (39, 44). Due to the higher fiber content of bran, compared to other cereal fractions, these bran-based rye breads have fiber content in similar range as the other rye-based breads (12–19 g/portion), despite the lower rye content.

The Effect of Dietary Fiber on Postprandial Responses

Generally, it should be noted that the majority of the pairs (64%) fall into categories showing a positive effect of rye in the postprandial phase (lower glucose and/or insulin response), whereas 32% show no effect and only 4% show a negative effect in the form of higher insulin or glucose following consumption of a rye product, compared to a control product (**Table 1**). Interestingly, the bran-based rye products fall in the latter

categories showing no or negative effect of rye. Lappi et al. found a rye factor effect when comparing a whole grain rye bread to a refined wheat bread, but also when comparing the whole grain rye bread to two different rye bran breads, indicating no beneficial effect of bran based rye breads on postprandial glucose and insulin despite a dietary fiber content similar to that of the whole grain rye bread (44). This suggests that the positive effect of rye cannot be purely attributed to the high fiber content of rye products. Furthermore, most of the endosperm rye products, which have a lower dietary fiber content than other types of rye products, fall into categories supporting a positive effect of rye, further highlighting that the fiber content might not alone explain the effect. However, it should be noted that endosperm rye flour still has a higher fiber content than endosperm wheat flour, and a beneficial role of a higher dietary fiber content cannot be ruled out.

The Effect of Processing and Fermentation on Postprandial Responses

Although a relatively wide range of products were found in each category, we found some indications of systematic differences in the product processing and fermentation across the different categories (**Table 1**). The rye factor phenomenon effect was seemingly more consistent when the rye food type or processing was compared with a similar control food or processing, whereas the other effect categories had more comparisons of products of different type or processing. This could indicate that using products that differ in several factors, e.g., different processing in addition to different cereal sources, might make it difficult to disentangle the effect of rye *per se*, due to confounding by differences in structural properties or through difference in volume (45). Additionally, there seems to be a difference between the categories when looking at the fermentation method used to produce the tested breads. The rye factor phenomenon is most evident among comparisons between a sourdough fermented rye bread and a yeast fermented control product indicating that sourdough fermentation might be partly responsible for the rye factor. However, some studies using unfermented rye crisp breads (46, 47), as well studies investigating rye based porridges (39, 42), also found evidence of the rye factor phenomenon indicating that the rye factor is not restricted to sourdough fermented rye breads. Most of the pairs falling into categories of reduction in both insulin and glucose, as well as no effect on either, consist of a yeast fermented rye bread compared to a yeast fermented control bread.

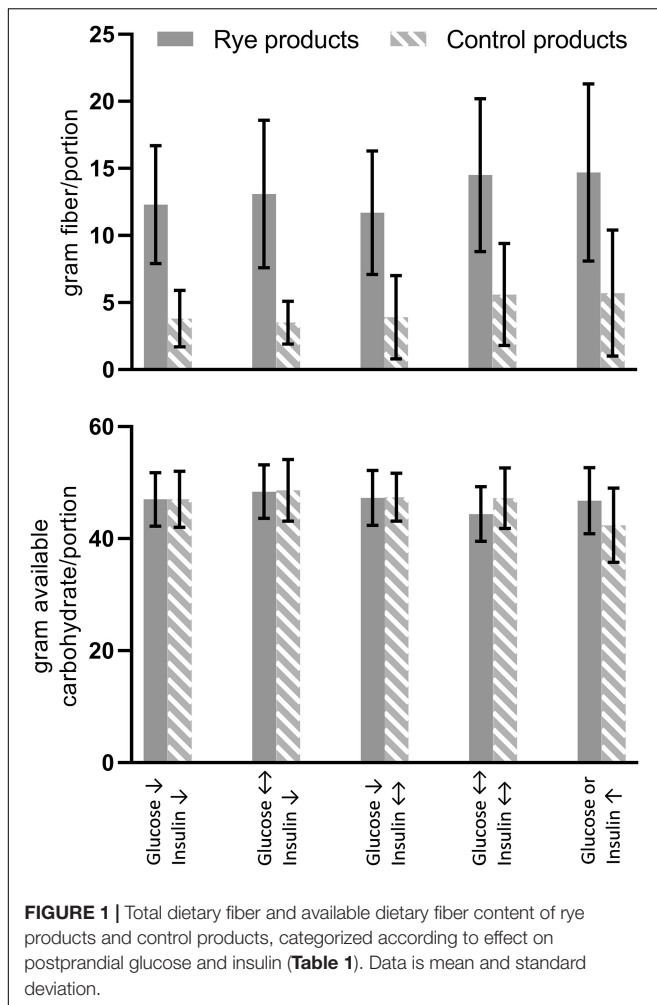
Second Meal Effects

The second meal effect is a phenomenon where the effect of one meal extends into the following meal, e.g., an evening meal affecting our response to the following breakfast meal (48). The second meal effect is typically investigated by giving participants a test breakfast meal followed by a standardized lunch meal (morning design) or a test meal in the evening followed by a standardized breakfast meal (evening design) and monitoring the postprandial response to the standardized meal (48). A few studies have investigated the second meal effect of rye-based foods on glucose and insulin responses. Three studies using

TABLE 1 | Pairs of rye-control comparisons extracted from the studies presented in **Supplementary Table 1**, grouped according to effect on postprandial insulin and glucose.

	Glucose ↓ Insulin ↓ [n: 18 (25%)]	Glucose ↔ Insulin ↓ (“Rye factor”) [n: 23 (32%)]	Glucose ↓ Insulin ↔ [n: 5 (7%)]	Glucose ↔ Insulin ↔ [n: 23 (32%)]	Glucose or Insulin ↑ [n: 3 (4%)]
Rye products					
Product type	Soft bread: 16 Crisp bread: 0 Cold cereal: 0 Porridge: 2	Soft bread: 19 Crisp bread: 2 Cold cereal: 0 Porridge: 2	Soft bread: 4 Crisp bread: 0 Cold cereal: 0 Porridge: 1	Soft bread: 17 Crisp bread: 2 Cold cereal: 1 Porridge: 3	Soft bread: 2 Crisp bread: 0 Cold cereal: 0 Porridge: 1
Method of fermentation (soft bread and crisp bread only)	Yeast: 14 Sourdough: 1 Unfermented: 0 Not reported: 1	Yeast: 6 Sourdough: 9 Unfermented: 2 Not reported: 4	Yeast: 1 Sourdough: 1 Unfermented: 0 Not reported: 2	Yeast: 16 Sourdough: 2 Unfermented: 0 Not reported: 1	Yeast: 2 Sourdough: 0 Unfermented: 0 Not reported: 0
Cereal form [‡]	Bran: 0 Flakes: 0 Kernels: 7 ES flour: 3 WG flour: 8	Bran: 0 Flakes: 0 Kernels: 4 ES flour: 7 WG flour: 12	Bran: 0 Flakes: 0 Kernels: 0 ES flour: 1 WG flour: 4	Bran: 3 Flakes: 2 Kernels: 6 ES flour: 1 WG flour: 11	Bran: 1 Flakes: 1 Kernels: 1 ES flour: 0 WG flour: 0
Rye content (% w/w of cereal ingredients) [†]	81.7 ± 9.7 (75) n = 16	96.4 ± 10.3 (100) n = 17	82.0 ± 15.7 (75) n = 3	82.3 ± 24.5 (100) n = 20	67.5 ± 46.0 (67.5) n = 2
Control products					
Product type	Soft bread: 16 Crisp bread: 0 Porridge: 2	Soft bread: 19 Crisp bread: 2 Porridge: 2	Soft bread: 5 Crisp bread: 0 Porridge: 0	Soft bread: 17 Crisp bread: 2 Porridge: 4	Soft bread: 2 Crisp bread: 0 Porridge: 1
Method of fermentation (soft bread and crisp bread only)	Yeast: 16 Sourdough: 0 Unfermented: 0 Not reported: 0	Yeast: 12 Sourdough: 1 Unfermented: 0 Not reported: 8	Yeast: 1 Sourdough: 0 Unfermented: 0 Not reported: 3	Yeast: 16 Sourdough: 1 Unfermented: 0 Not reported: 2	Yeast: 0 Sourdough: 1 Unfermented: 0 Not reported: 1
Cereal form [‡]	Kernels: 2 ES flour: 14 WG flour: 2	Kernels: 1 ES flour: 20 WG flour: 2	Kernels: 0 ES flour: 4 WG flour: 1	Kernels: 5 ES flour: 14 WG flour: 4	Kernels: 1 ES flour: 2 WG flour: 0
Cereal source [‡]	16 wheat, 1 oat, 1 barley	21 wheat, 1 oat, 1 barley	5 wheat	18 wheat, 5 barley	2 wheat, 1 barley
Rye vs. control products					
Same product type within pair [n (%)]	14 (78%)	23 (100%)	4 (80%)	19 (83%)	1 (33%)
(SB = soft bread CB = crisp bread CC = cold cereal P = porridge)	(SB-SB: 14 SB- <i>P</i> _{rye} : 2 P-SB _{rye} : 2)	(SB-SB: 19 CB-CB: 2 P-P: 2)	(SB-SB: 4 SB- <i>P</i> _{rye} : 1)	(SB-SB: 15 SB-CC _{rye} : 1 SB- <i>P</i> _{rye} : 1 CB-CB: 2 P-SB _{rye} : 2 P-P: 2)	(SB-SB: 1 SB- <i>P</i> _{rye} : 1 P-SB _{rye} : 1)
Same cereal form within pair [n (%)]	6 (33%)	8 (35%)	2 (40%)	4 (17%)	1 (33%)
(B = bran F = flakes K = kernels EF = endosperm flour WF = whole grain flour)	(K-K: 2 EF-K _{rye} : 4 EF-EF: 3 EF-WF _{rye} : 7 WF-K _{rye} : 1 WF-WF: 1)	(K-K: 1 EF-K _{rye} : 3 EF-EF: 6 EF-WF _{rye} : 11 WF-RF _{rye} : 2 WF-WF: 1)	(RF-RF: 1 RF-WF _{rye} : 3 WF-WF: 1)	(K-K: 3 K-EF _{rye} : 1 K-WF _{rye} : 1 EF-B _{rye} : 3 EF-F _{rye} : 2 EF-WF _{rye} : 3 WF-K _{rye} : 3 WF-WF: 1)	(K-K: 1 EF-B _{rye} : 1 EF-F _{rye} : 1)
Same method of fermentation [‡]	12 of 13 (92%)	5 of 13 (39%)	1 of 1 (100%)	13 of 16 (81%)	0 of 1 (0%)
(Y = yeast SD = sourdough UF = unfermented)	(Y-Y: 12 Y-SD _{rye} : 1)	(Y-Y: 5 Y-SD _{rye} : 5 SD-Y _{rye} : 1 Y-UF _{rye} : 2)	(Y-Y: 1)	(Y-Y: 13 Y-SD _{rye} : 2 SD-Y _{rye} : 1)	(SD-Y _{rye} : 1)
Population (n: healthy/MetS/NIDD)	16/1/1	16/6/1	3/0/2	22/3/1	3/0/0

[‡]In case a bread was composed of a mixture of rye ingredients (e.g., a rye bread with whole grain rye flour rye and rye bran) the product was categorized according to the main ingredient (weight basis). [†]Rye content was not reported by all studies therefore n is as stated by the data and data is mean ± SD (median). [‡]According to the main cereal ingredient (w/w%). [‡]Only bread-bread (soft bread or crisp bread) comparisons where fermentation method was reported for both products are included. Abbreviations: MetS, metabolic syndrome; NIDD, non-insulin dependent diabetics; WG, whole grain; and ES, endosperm.



an evening design to test the second meal effect of rye based vs. wheat based control products, were identified (Table 2). The participants in these studies consumed an evening meal containing a rye product or a wheat product and the next morning the postprandial response of a standardized breakfast meal was evaluated. Additionally, two of the studies included in Supplementary Table 1 also included an evaluation of the second meal effect (41, 42). In these studies, participants consumed a breakfast meal containing a rye product or a wheat based control product, followed by a standardized lunch 4 h later, with glucose and insulin responses being monitored throughout the day (41, 42). The two studies using the breakfast design found no difference in postprandial insulin or glucose following the standardized lunch, whereas two (49, 50) of the three studies (49–51) using an evening design found lower postprandial insulin and glucose from the breakfast the day after consumption of the rye-based evening meal, compared to the wheat based evening meals. One of the studies using an evening design investigated the effect of having participants consume the rye or wheat products for three consecutive evenings before the breakfast test meal, as opposed to only consuming the rye or wheat products on the evening before the standardized breakfast test (49). However, this

did not affect the results and the breakfast meal induced similar reduction in glucose and insulin response following the rye based evening meal, compared to the wheat based evening meal, independent on whether the evening meals had been consumed one or three evenings leading up to the breakfast meal (49).

These studies indicate that an evening meal containing rye may have a beneficial effect on glycemic control at the following breakfast meal, but none of these studies showed a postprandial response in line with the rye factor phenomenon.

Effects of Habitual Rye Consumption on Glycemic Control

While many studies investigating the acute postprandial effect of rye consumption have been conducted and in general show positive effects on postprandial glucose and insulin responses, only a few randomized intervention studies have investigated the effect of habitual rye consumption on postprandial glycemic control. Five studies investigating the effect of habitual rye consumption on markers of glycemic control were identified and are shown in Table 3. These studies consist of four randomized cross-over studies with a duration of 4–8 weeks (27, 52–54), as well as a 12-week randomized parallel study (55). The studies all included an intervention arm based on rye products, whereas the products included in the control arm(s) vary between the studies, but typically contained wheat products. The result from these studies show mixed results, with some studies showing a positive effect of rye consumption (52, 55), whereas others show no or negative effect (27, 54). Lappi et al. found a positive effect of whole grain rye bread on postprandial insulin response after 4 weeks of intervention, compared to 4 weeks intervention with refined wheat bread, whereas no such effect was found after 4 weeks of intervention with refined wheat bread with added rye bran (52). No difference in glucose response was found between either of the arms, indicating a pattern in agreement with the rye factor phenomenon. The lack of a positive effect of the rye bran-based intervention arm is in line with observations from postprandial studies, where similar types of rye bran bread did not lower postprandial insulin or glucose response and could indicate that the fiber content is not the sole explanation of the positive effects of rye consumption. However, McIntosh et al compared high fiber rye products to low fiber wheat products, as well as to high fiber wheat products, in a three armed 4-week intervention study, and found a positive effect of both high fiber rye and high fiber wheat, compared to refined wheat, but no difference between the two high fiber arms (53). On a similar note, Eriksen et al. found no difference in an oral glucose tolerance test after 4 and 8 weeks of consumption of whole grain rye products or whole grain wheat products matched for fiber content, indicating no difference between the sources of cereals under conditions where the fiber content of the two intervention diets were matched (27). On the other hand, Laaksonen et al. found reductions in insulinogenic index and insulin disposition index in an oral glucose tolerance test following a 12-week intervention with rye products and pasta, compared to 12-week intervention with oat, wheat and potato based products with a similar fiber content (55). However, there were no differences in fasting insulin and

TABLE 2 | Second meal effect studies.

Design*	Subjects [‡]	Intervention products*	Study procedure	Outcomes (data analysis)*	Results Mean ± SEM, unless otherwise stated
Sandberg et al. (50)	Cross-over, randomized, two test meals 38 (30 f/8 m), age 63.9 ± 5.5 year, BMI 24.2 ± 2.5 kg/m ² , fasting glucose 5.7 ± 0.4 mmol/l, no known metabolic disease, non-smoking.	Rye bread with added resistant starch (RBRS):43% rye kernels, 43% whole grain rye flour, 14% Hi-Maze flour (60% resistant starch type 2, 40% digestible starch). White wheat bread (WWB): 100% refined wheat flour. Composition rye bread/wheat bread (g/portion): portion size 239/171, starch 89/76 (available starch 75/75), insoluble DF 21/4, soluble DF 6/1.	Subjects consumed one portion of test bread per day for three days before visiting the clinic. On day 1 and 2 bread was divided over the day, on day 3 the portion was consumed at 9 pm. At the clinic subjects consumed 114 g WWB 50 g available starch with 2 dl water after an overnight fast (from 9 pm). Blood was taken at 0, 15, 30, 45, 60, 90, 120, and 180 min.	Glucose (capillary blood), insulin (venous blood). iAUC _{0–30} , iAUC _{0–120} , incremental peak, Composite Insulin Sensitivity Index (ISI _{composite}), HOMA-IR.	Glucose: iAUC _{0–30} lower following RBRS, compared to WWB (–14%, $p < 0.05$). Insulin: Incremental peak lower following RBRS, compared to WWB (–15%, $p < 0.01$). ISI _{composite} higher following RBRS, compared to WWB (+11%, $p < 0.05$).
Sandberg et al. (51)	Cross-over, randomized, three test meals 21 (10 m/11 f), age 25.3 ± 3.9 year, BMI 22.7 ± 2.3 kg/m ² , no known metabolic disease, non-smoking.	Whole grain rye flour bread (RFB): 100% whole grain rye flour. Whole grain rye flour and rye kernel bread (RKB): 50% whole grain rye flour, 50% rye kernels White wheat bread (WWB; reference): 100% refined wheat flour. Composition of RFB/RKB/WWB (g/portion): portion size 187/184/122, starch 53/57/52 (available starch 50/50/50, RS 3/7/1), insoluble NSP 11/13/2, soluble NSP 4/4/1, total DF 18/23/4.	Subjects consumed test breads at 9 pm the night before visiting the clinic. At the clinic subjects consumed one portion WWB with 2 dl water after an overnight fast (from 9 pm). Capillary blood taken at 0, 15, 30, 60, 90, 120, 150, and 180.	Glucose (all timepoints), insulin (all timepoints except 15 min) iAUC _{0–120} , incremental peak.	No difference
Sandberg et al. (49)	Cross-over, randomized, four test meals (2 × 2 factorial design) 19 (9 m/10 f), age 21.9 ± 1.87 year, BMI 25.6 ± 3.5 kg/m ² , no known metabolic disorders, non-smoking.	White wheat bread (WWB; reference): 85% rye kernels and 15% white wheat flour (of cereal dry matter). 121.4 g bread/portion. Rye kernel bread (RKB): 100% white wheat flour. Composition WWB/RKB [g/portion (142.5 g)]: starch 51.3/53.9 (available starch 50/50, resistant starch 1.3/4.9), insoluble NSP 1.5/9.0, soluble NSP 1.1/2.8, DF 3.9/15.6.	Subjects consumed one portion of test bread with water at 9:30 pm either: the day before visiting the clinic (WWB-1D or RKB-1D) or for three consecutive days before visiting the clinic (WWB-3D or RKB-3D). At the clinical visit the subjects consumed 121.4 g WWB with 2 dl water after an overnight fast (from 9:30 pm). Venous blood drawn at 0, 15, 30, 45, 60, 90, 120, and 180 min.	Glucose (all timepoints), insulin (all timepoints except 15 min) iAUC _{0–120} , incremental peak, Matsuda index (insulin sensitivity).	No effect of length of priming (1 or 3 days) were found in any of the outcomes. <u>Glucose</u> : iAUC _{0–120} and incremental peak was lower following a RKB evening meal than a WWB evening meal (23 and 16%, respectively, $p < 0.01$). <u>Insulin</u> : iAUC _{0–120} was lower following a RKB evening meal than a WWB evening meal (13%, $p < 0.05$).

[‡]Data is mean ± sd or (range). *Only test meals and outcomes of interest for investigating the rye factor (insulin, glucose) is included in the table. Abbreviations: BMI, body mass index; DF, dietary fiber; f, female; HOMA-IR, homeostatic model assessment for insulin resistance; iAUC, incremental area under the curve; m, male; and NSP, non-starch polysaccharides.

glucose, as well as $AUC_{0-120 \text{ min}}$ of glucose and insulin in the oral glucose tolerance test (55). Furthermore, it should be noted that the products included in the intervention arms included pasta and potatoes in addition to several different breads, making it hard to pin the results exclusively to the rye products (55).

In summary, there is no consistent evidence supporting a positive effect of habitual rye consumption on postprandial glycemic control, despite the predominantly positive effect found in acute meal studies. However, it should be mentioned that most of these studies evaluate the effect of the intervention on oral glucose tolerance, which may not be directly comparable to a meal tolerance test such as the ones typically used in the acute meal studies. Furthermore, the relatively large variations in study duration, outcomes assessed, and intervention products used makes it difficult to draw firm conclusions and further studies are needed to understand the potential link between the positive effects from acute meal studies and the long-term associations with improvements in glycemic control and reduced risk of type-2 diabetes.

Potential Mechanisms Behind the Rye Factor

Several mechanisms behind the rye factor phenomenon have been suggested and discussed (33). One suggested mechanism is related to structural differences in the cereal products resulting in slower glucose uptake in the gastrointestinal tract following consumption of a rye-based cereal product, compared to a non-rye control product (54, 56). If glucose uptake is slower, less insulin would be needed to maintain a similar concentration of glucose in the blood and therefore the insulin secretion is lower following consumption of the rye-based product, while the glucose response is similar to the control product. This hypothesis was tested by Östman et al. who studied the glucose kinetics using a dual tracer technique, as well as glucose and insulin response, to a rye bread and a wheat bread in a dual isotope labeling study (57). They found that the rye factor phenomenon was related to slower uptake of glucose in the intestine but not to altered disappearance or clearance of glucose in the blood stream.

Furthermore, high fiber cereals have been shown to increase the fecal energy excretion, through binding of nutrients from the food and reduce the absorption (58). Therefore, it could be theorized, that even though the studies match the rye and control products in terms of available carbohydrate, a larger amount of the available carbohydrate will be bound to the dietary fiber matrix in the fiber-rich rye products, compared to the control products which typically has a lower fiber content, and therefore the amount of carbohydrate available for absorption in the intestine will in reality be lower for rye foods, despite similar content. This could then lead to a slower and/or reduced intestinal absorption of glucose and subsequent reduced insulin secretion.

Different fermentation methods affect the structure of bread, which could in turn be thought to influence the metabolic response to bread consumption (59, 60). Two studies have tested the effects of unfermented rye crisp bread and sourdough or

yeast fermented rye crisp bread on postprandial glucose and insulin response. They found lower postprandial insulin response following consumption of the unfermented crisp bread and the authors suggest that this could be due to structural differences in the unfermented breads, compared to the fermented breads (46, 47). A recent study showed that increasing the sourdough content in rye bread affected the structure of the bread and that bread with higher sourdough content resembled refined wheat bread more than a bread with lower sourdough content (61). One could hypothesize that this would lead to higher postprandial glucose and insulin response, but this remains to be tested *in vivo*. Additional studies investigating the effect of different fermentation methods on structural properties of bread is needed in order to fully understand the effect of fermentation on structure and potentially link it to the physiological response *in vivo*.

Branched chain amino acids (BCAA) have been shown to induce insulin secretion (62) and it has been speculated whether the amino acid composition and content of cereal products may influence the postprandial response (46). Generally, the content of amino acids, including BCAA, seem to be higher in the bran fraction of the cereal, compared to whole grain flour and sifted flour (63), which could potentially contribute to the lack of a positive effect of bran based rye breads on postprandial insulin and glucose. However, the amino acid content is also highly affected by baking and fermentation, as well as cultivation, why more research is needed in order to understand the potential effect of cereal amino acids on postprandial response (63).

Rye contains several different bioactive compounds that have been suggested to have positive effects on various health outcomes, such as glycemic control and insulin sensitivity (33). Lignans and alkylresorcinols have been shown in *in vitro* and animal studies to improve insulin sensitivity (64, 65). An association between alkylresorcinols and insulin sensitivity has been confirmed in human studies (29, 66), but since alkylresorcinols may just be a marker of whole grain rye and wheat intake, it is difficult to distinguish between the effect of the alkylresorcinols and other components of whole grain products that could influence insulin sensitivity (67). Human studies on lignans and health has primarily been focused on cancer, due to the potential mild estrogenic effects of certain lignan metabolites (68). The few studies that have investigated the potential link between lignan intake and outcomes related to glycemic control and type-2 diabetes have found conflicting results (69) and as with alkylresorcinols it is difficult to distinguish between the effect of lignans and the effect of other potentially beneficial components of rye. Furthermore, it should be noted that lignans are found in relatively high amounts in other foods, such as flaxseeds, and the associations found in observational studies is not necessarily reflecting an association with lignans from rye (70).

If the mechanism behind the rye factor is mainly related to fiber content and structure, a rye factor phenomenon could likely be obtained with other cereals than rye. Eelderink et al. used a similar methodology as Östman et al. to examine the postprandial response to two wheat based breads with similar ingredients, but different structure (a standard sliced loaf bread and a flat bread;

TABLE 3 | Studies investigating the effect on habitual consumption of rye products on glycemic control.

Design*	Subjects [†]	Intervention products*	Study procedure/clinical examinations*	Outcomes (data analysis)*	Results Mean ± SEM, unless otherwise stated	
Eriksen et al. (27)	Cross-over, randomized, two intervention period (8 + 8 weeks, separated by 8-week wash-out).	49 men, age 49–74, BMI 26–41 kg/m ² , signs of metabolic syndrome.	Rye period: breakfast cereals, crisp bread and pasta based on whole grain rye. Wheat period: breakfast cereals, crisp bread and pasta based on whole grain wheat with added wheat bran to match the fiber content of rye products. Products were aimed to constitute 30% of daily energy intake.	OGTT (75 g) in the beginning, middle and end of each intervention period (week 0, 4, and 8). Intravenous blood was drawn at 0, 30, 60, and 120 min.	Glucose, insulin. AUC _{0–120} glucose and insulin.	No effect.
Lappi et al. (52)	Cross-over, randomized, 4 weeks run-in period and two intervention periods (4 + 4 weeks). No wash out period.	21 males and females, age 38–65 year, BMI 19–30 kg/m ² , fasting glucose 4.9–6.3 mmol/l.	Refined wheat bread (WW; run-in period): two commercial breads with 100% white wheat flour, 20–35 g/slice. Whole grain rye (WGR; intervention period): sourdough fermented whole grain rye bread, 25–30 g/slice. Wheat bread with bioprocessed rye bran (WWBRB; intervention period): white wheat bread with 35% (dry matter) bioprocessed rye bran, 25–30 g/slice. Subjects were instructed to consume 6–10 slices bread/day. Reported intake per day of WW/WWBRB/WGR: 169/195/205 g bread, 5/20/21 g DF from bread.	3-h meal test at the end of run-in period and end of each intervention period. Meal (80 g WW bread, 20 g cheese, 40 g cucumber, 3 dl juice. 550 kcal, 3.7 g DF) was consumed after an overnight fast. Venous blood samples were collected at 0, 30, 60, 120, and 180 min.	Glucose, insulin Fasting values, iAUC _{0–120} , first-phase insulin secretion (0–30 min), insulin disposition index.	<u>Glucose</u> : No difference <u>Insulin</u> : WGR lower at 120 min, compared to WW ($p = 0.023$). Disposition index higher after WGR, compared to WW ($3,614 \pm 2,883$ vs. $2,500 \pm 1,336$, $p = 0.033$).
Laaksonen et al. (55)	Parallel, 4-week run-in (habitual diet), hereafter randomized to one of two 12-week intervention arms.	72 (36 m/36 f), metabolic syndrome, age 40–70 year, BMI 26–40 kg/m ² . 65% had impaired fasting glucose, 42% had impaired glucose tolerance.	Oat-wheat-potato (OWP) group: wheat bran bread, graham crisp, graham toast and oat bread (60% whole meal oat). Rye-pasta (RP) group: two whole meal rye breads, whole meal rye crisp bread, endosperm rye bread. Subjects were instructed to replace habitual bread with test breads. Furthermore, subjects in RP was instructed to consume ≥ 3 portions (min 210 g/week) dark pasta per week. Subjects in OWP were instructed to eat similar amount of potatoes. Reported intake OWP/RP: 247/244 g bread/day, potato products 4.4/2.9 times/week, pasta 0.7/2.9 times/week, energy 7.9/8.3 MJ/day, DF 21/26 g/day.	OGTT at baseline and after 12 weeks. Glucose solution (75 g glucose) consumed after an overnight fast. Blood drawn at 0, 15, 30, 45, 60, 90, and 120 min.	Glucose, insulin Fasting values, QUICKI, insulinogenic index (IGI), insulin disposition index (DI), AUC	IGI and DI increased more in the RP group, than in the OWP group (approx. 30% vs. 5%, $p = 0.026–0.030$)

(Continued)

TABLE 3 | (Continued)

	Design*	Subjects [‡]	Intervention products*	Study procedure/clinical examinations*	Outcomes (data analysis)*	Results Mean \pm SEM, unless otherwise stated
McIntosh et al. (53)	Cross-over, randomized, three intervention periods (4 + 4 + 4 weeks).	28 males, age 40–65 year, no gastrointestinal disorders, BMI 30 ± 0.9 kg/m ² .	<u>Intervention product per day (for 4 weeks):</u> Low fiber diet: 140 g refined wheat bread, 40 g refined wheat crisp bread, 50 g low fiber rice cereal (19 g DF/day). High fiber wheat diet: 140 g whole meal bread, 40 g whole meal wheat crisp bread, 50 g whole wheat breakfast cereal (32 g DF/day). High fiber rye diet: 140 g whole grain rye bread, 40 g rye crisp bread, 50 whole-rye breakfast cereal (32 g DF/day).	1-h meal tolerance test at the end of each 4-week period. Subjects consumed one portion of breakfast cereal according to randomization (50 g available CHO) with 1 dl milk after an overnight fast. Venous blood drawn at 0 and 60 min.	Glucose, insulin. Fasting and postprandial. Fasting values, $\Delta_{0-60 \text{ min}}$	Glucose: $\Delta_{0-60 \text{ min}}$ lower after high fiber diets, compared to low fiber diet (1.35 ± 0.3 , 0.95 ± 0.2 , 2.42 ± 0.4 , $p < 0.0005$)*. Insulin: $\Delta_{0-60 \text{ min}}$ lower after high fiber diets, compared to low fiber diet (19.6 ± 2.1 , 20.8 ± 2.8 , 48.9 ± 6.5 , $p < 0.0001$)*. *high fiber rye, high fiber wheat, low fiber.
Juntunen et al. (54)	Cross-over, randomized, two intervention periods (8 + 8 weeks). Intervention was preceded by 2-3-week run-in period and separated by an 8-week wash-out period (both habitual diet).	20 postmenopausal women, healthy, age 59 ± 6.0 year, BMI 27.5 ± 2.9 kg/m ² .	Subjects were instructed to replace habitual bread with intervention breads during the 8-week intervention periods. Subjects were instructed to consume at least 4–5 portions of bread per day (20–28 g/174–249 kcal per portion). Rye period: subjects could choose from four different rye breads with similar nutrient composition ($\approx 19\%$ DF) Wheat period: Subjects could choose from seven different wheat breads produced from refined wheat flour ($\approx 2.8\%$ DF)	Frequently sampled intravenous glucose tolerance test (FSIGTT) was conducted at baseline and after each intervention period. Glucose dose of 330 mg/kg body was infused, and intravenous samples taken at 0, 2, 4, 6, 8, 10, 12, 14, 16, 19, 22, 24, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 min.	Glucose, insulin. Fasting values. Repeated measures, glucose effectiveness and insulin sensitivity. Acute insulin response (AIR) calculated as AUC_{0-10} .	The increase in AIR (compared to baseline) was higher in the rye period ($9.9 \pm 24.2\%$) than in the wheat period ($2.8 \pm 36.3\%$).

[‡]Data is mean \pm sd or (range). *Only test meals and outcomes of interest for investigating the rye factor (insulin, glucose) is included in the table.

57, 71). While glucose response was similar between the breads, insulin response was lower for the flat bread, compared to the loaf bread, and glucose kinetics revealed a slower uptake of glucose in the intestine from the flat bread, which likely explains the lower insulin response. In a similar study, comparing two different loaf type wheat breads with different structure and fiber content, Eelderink et al. found similar, but less pronounced results (72). Goletzke et al. found that a whole meal spelt bread had similar effects as two rye based breads, compared to a low fiber soft wheat pretzel (38). Liljeberg et al. found lowering of insulin, without affecting glucose, when comparing barley kernel based breads and a rye kernel based bread with a wheat kernel based bread (73). Together, these findings suggest that the rye factor phenomenon is not restricted to rye-based products. However, rye and barley have higher contents of soluble fiber than wheat, which will likely affect the structure and digestion of the cereal products and may explain the similarities in the physiological response. Bran has more insoluble fiber, and less soluble fiber, than endosperm and whole grain flour which may explain the lack of a beneficial effect

of bran-based rye breads on postprandial insulin and glucose (39, 44).

In summary, limited evidence for the underlying mechanism behind the rye factor exist, but it appears that structural properties, such as particle size, viscosity, and fiber matrix, are likely the major determinants for the postprandial response to consumption of cereal products.

Limitations and Future Perspectives

Amongst the studies included in this review there is a large variation in the methodology used to evaluate the postprandial response to the tested products. Some studies report the results of repeated measures models, some report AUC or iAUC over time periods varying between 2 and 5 h and some used other measures, such as peak values, glycemic index and insulin disposition index. This makes it impossible to directly compare the effect size between different studies and give an overall estimate on the magnitude of the effect across studies. While postprandial glucose response has been shown to correlate with glycated

hemoglobin, which is a stronger predictor of diabetes risk, little is known about the long term implications of postprandial insulin response (74). Some studies have indicated an association between postprandial insulin response and risk of metabolic disease (75, 76), however, more evidence is needed in order to evaluate the implications of reductions in postprandial insulin response on long term disease risk.

Our understanding of the mechanism of action behind the effect of different cereals on postprandial glucose and insulin response remains suggestive, as only few studies include more mechanistic outcome measures such as measures of glucose kinetics using tracer techniques. Studies by Eelderink et al. and Östman et al. shed some light on a potential underlying mechanism by incorporating tracer-techniques, but more studies are needed to draw general conclusions (57, 71, 72).

The degree of characterization and the reporting of compositional information on products vary between studies and makes it hard to make comparisons across studies. Generally, more detailed characterization beyond nutritional values, is needed to further elucidate the effects of rye products on glycemic control as well as the underlying mechanisms. Furthermore, many studies compare rye products with a relatively high fiber content to wheat-based products with a relatively low fiber content, which makes it difficult to distinguish between the effect of fiber content and other factors, such as cereal source. However, it is important to keep in mind that the different cereals have a different fiber content and composition, even in their native form (18), why there will be differences in the fiber content, even when comparing a 100% whole grain rye product to a 100% whole grain wheat product – which underlines that fiber content and composition may explain part of the rye factor phenomenon. Moreover, one should consider the effect of different processing techniques, e.g., a milled whole grain rye flour compared with rolled whole grain rye flakes which may have very similar fiber content and composition, but at the same time express vastly different structural properties, which may in turn affect the physiological response (77).

Method of fermentation has been shown to influence the structure of bread, which could in turn influence the physiological response to consumption of the breads. However, this is often clouded by the fact that sourdough fermented rye breads are often compared to yeast fermented wheat breads, making it difficult to disentangle the effect of cereal source from the method of fermentation. From an applicational point of view it is sensible to test a yeast fermented wheat bread with a sourdough fermented rye bread, as this is the typical types of bread available on the market and consumed by consumers. However, from a mechanistic point of view studies investigating

different combinations of cereal sources and methods of fermentation are needed in order to understand the underlying mechanisms and determinates for postprandial response.

CONCLUSION

In conclusion, rye-based products have consistently been shown to lower insulin response in the postprandial phase, either alone or in combination with reductions in glucose response, compared to wheat-based products. Recent mechanistic studies using tracer-techniques have suggested that this may be attributed to slower glucose uptake in the intestine, which in turn may be linked to structural properties of rye products, rather than fiber content *per se*. However, the rye factor phenomenon might not be a unique property of rye-based cereal products, as similar effects have been observed from other types of cereal products with similar fiber content and structural properties. Some studies indicate a role of sourdough fermentation, potentially through its effect on structure, but due to lack of studies properly designed to address this research question, effects of fermentation from other factors cannot be disentangled. There is a need for carefully controlled studies investigating the postprandial effects of products based on different cereals, as well as the structural properties standardized across cereal species to understand the link between structural properties and postprandial response.

AUTHOR CONTRIBUTIONS

RL conceived the idea for the review. KI and KJ conducted the literature search and extracted the data. KI analyzed the data and wrote the article under supervision of RL. All authors read the manuscript, provided valuable inputs, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2022.868938/full#supplementary-material>

REFERENCES

- Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: a meta-analysis. *Nutr Metab Cardiovasc Dis.* (2008) 18:283–90. doi: 10.1016/j.numecd.2006.12.008
- Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr.* (2012) 142:1304–13. doi: 10.3945/jn.111.155325
- Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ.* (2016) 353:i2716. doi: 10.1136/bmj.i2716

4. Zong G, Gao A, Hu FB, Sun Q. Whole grain intake and mortality from all causes, cardiovascular disease, and cancer. *Circulation*. (2016) 133:2370–80. doi: 10.1161/CIRCULATIONAHA.115.021101
5. Haas P, Machado MJ, Anton AA, Silva ASS, de Francisco A. Effectiveness of whole grain consumption in the prevention of colorectal cancer: meta-analysis of cohort studies. *Int J Food Sci Nutr*. (2009) 60:1–13. doi: 10.1080/09637480802183380
6. Aune D, Norat T, Romundstad PP, Vatten LJ. Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Eur J Epidemiol*. (2013) 28:845–58. doi: 10.1007/s10654-013-9852-5
7. McKeown NM, Troy LM, Jacques PF, Hoffmann U, O'Donnell CJ, Fox CS. Whole- and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults: the Framingham heart study. *Am J Clin Nutr*. (2010) 92:1165–71. doi: 10.3945/ajcn.2009.29106
8. Slavin J. Why whole grains are protective: biological mechanisms. *Proc Nutr Soc*. (2003) 62:129–34. doi: 10.1079/PNS2002221
9. Hollænder PLB, Ross AB, Kristensen M. Whole-grain and blood lipid changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. (2015) 102:556–72. doi: 10.3945/ajcn.115.109165
10. Xu Y, Wan Q, Feng J, Du L, Li K, Zhou Y. Whole grain diet reduces systemic inflammation: a meta-analysis of 9 randomized trials. *Medicine (Baltimore)*. (2018) 97:e12995. doi: 10.1097/MD.00000000000012995
11. Roager HM, Vogt JK, Kristensen M, Hansen LBS, Ibrügger S, Mærkedahl RB, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. *Gut*. (2019) 68:83–93. doi: 10.1136/gutjnl-2017-314786
12. Masters RC, Liese AD, Haffner SM, Wagenknecht LE, Hanley AJ. Whole and refined grain intakes are related to inflammatory protein concentrations in human plasma. *J Nutr*. (2010) 140:587–94. doi: 10.3945/jn.109.116640
13. Zhang B, Zhao Q, Guo W, Bao W, Wang X. Association of whole grain intake with all-cause, cardiovascular, and cancer mortality: a systematic review and dose-response meta-analysis from prospective cohort studies. *Eur J Clin Nutr*. (2018) 72:57–65. doi: 10.1038/ejcn.2017.149
14. Ross AB, van der Kamp JW, King R, Lê KA, Mejborn H, Seal CJ, et al. Perspective: a definition for whole-grain food products – recommendations from the healthgrain forum. *Adv Nutr*. (2017) 8:525–31. doi: 10.3945/an.116.014001
15. Seal CJ, Nugent AP, Tee ES, Thielecke F. Whole-grain dietary recommendations: the need for a unified global approach. *Br J Nutr*. (2016) 115:2031–8. doi: 10.1017/S0007114516001161
16. Suhr J, Vuholm S, Iversen KN, Landberg R, Kristensen M. Wholegrain rye, but not wholegrain wheat, lowers body weight and fat mass compared with refined wheat: a 6-week randomized study. *Eur J Clin Nutr*. (2017) 71:959–67. doi: 10.1038/ejcn.2017.12
17. Johnsen NF, Frederiksen K, Christensen J, Skeie G, Lund E, Landberg R, et al. Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort. *Br J Nutr*. (2015) 114:608–23. doi: 10.1017/S0007114515001701
18. Frølich W, Åman P, Tetens I. Whole grain foods and health - a Scandinavian perspective. *Food Nutr Res*. (2013) 57. doi: 10.3402/fnr.v57i0.18503
19. Biskup I, Kyro C, Marklund M, Olsen A, van Dam RM, Tjønneland A, et al. Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and risk of type 2 diabetes in Scandinavian men and women. *Am J Clin Nutr*. (2016) 104:88–96. doi: 10.3945/ajcn.116.133496
20. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre? *Nutr Res Rev*. (2010) 23:65–134. doi: 10.1017/S0954422410000041
21. Kyro C, Tjønneland A, Overvad K, Olsen A, Landberg R. Higher whole-grain intake is associated with lower risk of type 2 diabetes among middle-aged men and women: the danish diet, cancer, and health cohort. *J Nutr*. (2018) 148:1434–44. doi: 10.1093/jn/nxy112
22. De Munter JSL, Hu FB, Spiegelman D, Franz M, Van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. *PLoS Med*. (2007) 4:e261. doi: 10.1371/journal.pmed.0040261
23. Kamal-Eldin A, Lærke HN, Knudsen K-EB, Lampi A-M, Piironen V, Adlercreutz H, et al. Physical, microscopic and chemical characterisation of industrial rye and wheat brans from the Nordic countries. *Food Nutr Res*. (2009) 53:1912. doi: 10.3402/fnr.v53i0.1912
24. Slavin JL, Jacobs D, Marquart L. Grain processing and nutrition. *Crit Rev Food Sci Nutr*. (2000) 40:309–26. doi: 10.1080/10408690091189176
25. Ciudad-Mulero M, Fernández-Ruiz V, Matallana-González MC, Morales P. Dietary fiber sources and human benefits: the case study of cereal and pseudocereals. *Adv Food Nutr Res*. (2019) 90:83–134. doi: 10.1016/bs.afnr.2019.02.002
26. Buksa K, Praznik W, Loeppert R, Nowotna A. Characterization of water and alkali extractable arabinoxylan from wheat and rye under standardized conditions. *J Food Sci Technol*. (2016) 53:1389–98. doi: 10.1007/s13197-015-2135-2
27. Eriksen AK, Brunius C, Mazidi M, Hellström PM, Risérus U, Iversen KN, et al. Effects of whole-grain wheat, rye, and lignan supplementation on cardiometabolic risk factors in men with metabolic syndrome: a randomized crossover trial. *Am J Clin Nutr*. (2020) 1:846–76. doi: 10.1093/ajcn/nqaa026
28. Magnúsdóttir OK, Landberg R, Gunnarsdóttir I, Cloetens L, Åkesson B, Rosqvist F, et al. Whole grain rye intake, reflected by a biomarker, is associated with favorable blood lipid outcomes in subjects with the metabolic syndrome – a randomized study. *PLoS One*. (2014) 9:e110827. doi: 10.1371/journal.pone.0110827
29. Magnúsdóttir OK, Landberg R, Gunnarsdóttir I, Cloetens L, Åkesson B, Landin-Olsson M, et al. Plasma alkylresorcinols C17:0/C21:0 ratio, a biomarker of relative whole-grain rye intake, is associated to insulin sensitivity: a randomized study. *Eur J Clin Nutr*. (2014) 68:453–8. doi: 10.1038/ejcn.2014.12
30. Xie Y, Gou L, Peng M, Zheng J, Chen L. Effects of soluble fiber supplementation on glycemic control in adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr*. (2021) 40:1800–10. doi: 10.1016/j.clnu.2020.10.032
31. Hartley L, May MD, Loveman E, Colquitt JL, Rees K. Dietary fibre for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. (2016) 2016:CD011472. doi: 10.1002/14651858.CD011472.pub2
32. Burton-Freeman B, Liyanage D, Rahman S, Edirisinghe I. Ratios of soluble and insoluble dietary fibers on satiety and energy intake in overweight pre- and postmenopausal women. *Nutr Heal Aging*. (2017) 4:157–68. doi: 10.3233/NHA-160018
33. Jonsson K, Andersson R, Bach Knudsen KE, Hallmans G, Hanhineva K, Katina K, et al. Rye and health – where do we stand and where do we go? *Trends Food Sci Technol*. (2018) 79:78–87. doi: 10.1016/j.tifs.2018.06.018
34. Moazzami AA, Bondia-Pons I, Hanhineva K, Juntunen K, Antl N, Poutanen K, et al. Metabolomics reveals the metabolic shifts following an intervention with rye bread in postmenopausal women- a randomized control trial. *Nutr J*. (2012) 11:88. doi: 10.1186/1475-2891-11-88
35. Dimina L, Mariotti F. The postprandial appearance of features of cardiometabolic risk: acute induction and prevention by nutrients and other dietary substances. *Nutrients*. (2019) 11:1963. doi: 10.3390/nu11091963
36. Campia U, Sullivan G, Bryant MB, Waclawiw MA, Quon MJ, Panza JA. Insulin impairs endothelium-dependent vasodilation independent of insulin sensitivity or lipid profile. *Am J Physiol Circ Physiol*. (2004) 286:H76–82. doi: 10.1152/ajpheart.00539.2003
37. Mahmoud AM, Szczurek MR, Blackburn BK, Mey JT, Chen Z, Robinson AT, et al. Hyperinsulinemia augments endothelin-1 protein expression and impairs vasodilation of human skeletal muscle arterioles. *Physiol Rep*. (2016) 4:e12895. doi: 10.14814/phy2.12895
38. Goletzke J, Atkinson FS, Ek KL, Bell K, Brand-Miller JC, Buyken AE. Glycaemic and insulin index of four common German breads. *Eur J Clin Nutr*. (2016) 70:808–11. doi: 10.1038/ejcn.2016.9
39. Rosén LA, Silva LOB, Andersson UK, Holm C, Östman EM, Björck IM. Endosperm and whole grain rye breads are characterized by low post-prandial insulin response and a beneficial blood glucose profile. *Nutr J*. (2009) 8:42. doi: 10.1186/1475-2891-8-42
40. Heinonen L, Korpela R, Mantere S. The effect of different types of Finnish bread on postprandial glucose response in diabetic patients. *Hum Nutr Appl Nutr*. (1985) 39:108–13.

41. Lee I, Shi L, Webb D-L, Hellström PM, Risérus U, Landberg R. Effects of whole-grain rye porridge with added inulin and wheat gluten on appetite, gut fermentation and postprandial glucose metabolism: a randomised, cross-over, breakfast study. *Br J Nutr.* (2017) 116:2139–49. doi: 10.1017/S0007114516004153
42. Hartvigsen ML, Lærke HN, Overgaard A, Holst JJ, Bach Knudsen KE, Hermansen K. Postprandial effects of test meals including concentrated arabinoxylan and whole grain rye in subjects with the metabolic syndrome: a randomised study. *Eur J Clin Nutr.* (2014) 68:567–74. doi: 10.1038/ejcn.2014.25
43. Ward JL, Poutanen K, Gebruers K, Piironen V, Lampi A-M, Nyström L, et al. The HEALTHGRAIN cereal diversity screen: concept, results, and prospects. *J Agric Food Chem.* (2008) 56:9699–709. doi: 10.1021/jf8009574
44. Lappi J, Aura A-M, Katina K, Nordlund E, Kolehmainen M, Mykkänen H, et al. Comparison of postprandial phenolic acid excretions and glucose responses after ingestion of breads with bioprocessed or native rye bran. *Food Funct.* (2013) 4:972. doi: 10.1039/c3fo60078e
45. Burton P, Lightowler HJ. Influence of bread volume on glycaemic response and satiety. *Br J Nutr.* (2006) 96:877–82. doi: 10.1017/BJN20061900
46. Johansson DP, Lee I, Risérus U, Langton M, Landberg R. Effects of unfermented and fermented whole grain rye crisp breads served as part of a standardized breakfast, on appetite and postprandial glucose and insulin responses: a randomized cross-over trial. *PLoS One.* (2015) 10:e0122241. doi: 10.1371/journal.pone.0122241
47. Zamaratskaia G, Johansson DP, Junqueira MA, Deissler L, Langton M, Hellström PM, et al. Impact of sourdough fermentation on appetite and postprandial metabolic responses – a randomised cross-over trial with whole grain rye crispbread. *Br J Nutr.* (2017) 118:686–97. doi: 10.1017/S000711451700263X
48. Fletcher JA. The second meal effect and its influence on glycemia. *J Nutr Disord Ther.* (2012) 02:1–5. doi: 10.4172/2161-0509.1000108
49. Sandberg JC, Björck IME, Nilsson AC. Rye-based evening meals favorably affected glucose regulation and appetite variables at the following breakfast: a randomized controlled study in healthy subjects. *PLoS One.* (2016) 11:e0151985. doi: 10.1371/journal.pone.0151985
50. Sandberg JC, Björck IME, Nilsson AC. Impact of rye-based evening meals on cognitive functions, mood and cardiometabolic risk factors: a randomized controlled study in healthy middle-aged subjects. *Nutr J.* (2018) 17:102. doi: 10.1186/s12937-018-0412-4
51. Sandberg JC, Björck IME, Nilsson AC. Effects of whole grain rye, with and without resistant starch type 2 supplementation, on glucose tolerance, gut hormones, inflammation and appetite regulation in an 11–14.5 hour perspective; a randomized controlled study in healthy subjects. *Nutr J.* (2017) 16:1–11. doi: 10.1186/s12937-017-0246-5
52. Lappi J, Mykkänen H, Knudsen KEB, Kirjavainen P, Katina K, Pihlajamäki J, et al. Postprandial glucose metabolism and SCFA after consuming wholegrain rye bread and wheat bread enriched with bioprocessed rye bran in individuals with mild gastrointestinal symptoms. *Nutr J.* (2014) 13:104. doi: 10.1186/1475-2891-13-104
53. McIntosh GH, Noakes M, Royle PJ, Foster PR. Whole-grain rye and wheat foods and markers of bowel health in overweight middle-aged men. *Am J Clin Nutr.* (2003) 77:967–74. doi: 10.1093/ajcn/77.4.967
54. Juntunen KS, Laaksonen DE, Poutanen KS, Niskanen LK, Mykkänen HM, Mykkänen HM. High-fiber rye bread and insulin secretion and sensitivity in healthy postmenopausal women. *Am J Clin Nutr.* (2003) 77:385–91. doi: 10.1093/ajcn/77.2.385
55. Laaksonen DE, Toppinen LK, Juntunen KS, Autio K, Liukkonen K-H, Poutanen KS, et al. Dietary carbohydrate modification enhances insulin secretion in persons with the metabolic syndrome. *Am J Clin Nutr.* (2005) 82:1218–27. doi: 10.1093/ajcn/82.6.1218
56. Juntunen KS, Laaksonen DE, Autio K, Niskanen LK, Holst JJ, Savolainen KE, et al. Structural differences between rye and wheat breads but not total fiber content may explain the lower postprandial insulin response to rye bread. *Am J Clin Nutr.* (2003) 78:957–64. doi: 10.1093/ajcn/78.5.957
57. Östman JR, Müllner E, Eriksson J, Kristinsson H, Gustafsson J, Withöft C, et al. Glucose appearance rate rather than the blood glucose concentrations explains differences in postprandial insulin responses between wholemeal rye and refined wheat breads—results from a cross-over meal study. *Mol Nutr Food Res.* (2019) 63:1800959. doi: 10.1002/mnfr.201800959
58. Philip Karl J, Meydani M, Barnett JB, Vanegas SM, Goldin B, Kane A, et al. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. *Am J Clin Nutr.* (2017) 105:589–99. doi: 10.3945/ajcn.116.139683
59. Stamataki NS, Yanni AE, Karathanos VT. Bread making technology influences postprandial glucose response: a review of the clinical evidence. *Br J Nutr.* (2017) 117:1001–12. doi: 10.1017/S0007114517000770
60. de Angelis M, Damiano N, Rizzello CG, Cassone A, Di Cagno R, Gobbetti M. Sourdough fermentation as a tool for the manufacture of low-glycemic index white wheat bread enriched in dietary fibre. *Eur Food Res Technol.* (2009) 229:593–601. doi: 10.1007/s00217-009-1085-1
61. Iversen KN, Johansson D, Brunius D, Andlid T, Andersson R, Langton M, et al. Appetite and subsequent food intake were unaffected by the amount of sourdough and rye in soft bread—a randomized cross-over breakfast study. *Nutrients.* (2018) 10:1594. doi: 10.3390/nu10111594
62. Karusheva Y, Koessler T, Strassburger K, Markgraf D, Mastroiataro L, Jelenik T, et al. Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: a randomized controlled crossover trial. *Am J Clin Nutr.* (2019) 110:1098–107. doi: 10.1093/ajcn/nqz191
63. Mustafa A, Aman P, Andersson R, Kamal-Eldin A. Analysis of free amino acids in cereal products. *Food Chem.* (2007) 105:317–24. doi: 10.1016/j.foodchem.2006.11.044
64. Oishi K, Yamamoto S, Itoh N, Nakao R, Yasumoto Y, Tanaka K, et al. Wheat alkylresorcinols suppress high-fat, high-sucrose diet-induced obesity and glucose intolerance by increasing insulin sensitivity and cholesterol excretion in male mice. *J Nutr.* (2015) 145:199–206. doi: 10.3945/jn.114.202754
65. Kwon DY, Kim DS, Yang HJ, Park S. The lignan-rich fractions of *Fructus Schisandrae* improve insulin sensitivity via the PPAR- γ pathways in *in vitro* and *in vivo* studies. *J Ethnopharmacol.* (2011) 135:455–62. doi: 10.1016/j.jep.2011.03.037
66. Savolainen O, Lind MV, Bergström G, Fagerberg B, Sandberg A-S, Ross A. Biomarkers of food intake and nutrient status are associated with glucose tolerance status and development of type 2 diabetes in older Swedish women. *Am J Clin Nutr.* (2017) 106:ajcn152850. doi: 10.3945/ajcn.117.152850
67. Jawhara M, Sørensen SB, Heitmann BL, Andersen V. Biomarkers of whole-grain and cereal-fiber intake in human studies: a systematic review of the available evidence and perspectives. *Nutrients.* (2019) 11:2994. doi: 10.3390/nu11122994
68. Adlercreutz H. Lignans and human health. *Crit Rev Clin Lab Sci.* (2007) 44:483–525. doi: 10.1080/10408360701612942
69. Morisset AS, Lemieux S, Veilleux A, Bergeron J, John Weisnagel S, Tcherno A. Impact of a lignan-rich diet on adiposity and insulin sensitivity in post-menopausal women. *Br J Nutr.* (2009) 102:195–200. doi: 10.1017/S0007114508162092
70. Peterson J, Dwyer J, Adlercreutz H, Scalbert A, Jacques P, McCullough ML. Dietary lignans: physiology and potential for cardiovascular disease risk reduction. *Nutr Rev.* (2010) 68:571–603. doi: 10.1111/j.1753-4887.2010.00319.x
71. Eelderink C, Noort MWJ, Sozer N, Koehorst M, Holst JJ, Deacon CF, et al. The structure of wheat bread influences the postprandial metabolic response in healthy men. *Food Funct.* (2015) 6:3236–48. doi: 10.1039/c5fo00354g
72. Eelderink C, Noort MWJ, Sozer N, Koehorst M, Holst JJ, Deacon CF, et al. Difference in postprandial GLP-1 response despite similar glucose kinetics after consumption of wheat breads with different particle size in healthy men. *Eur J Nutr.* (2017) 56:1063–76. doi: 10.1007/s00394-016-1156-6
73. Liljeberg H, Granfeldt Y, Björck I. Metabolic responses to starch in bread containing intact kernels versus milled flour. *Eur J Clin Nutr.* (1992) 46:561–75.
74. Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. *Arch Public Health.* (2015) 73:1–9. doi: 10.1186/s13690-015-0088-6
75. Kimura Y, Hyogo H, Ishitobi T, Nabeshima Y, Arihiro K, Chayama K. Postprandial insulin secretion pattern is associated with histological severity in non-alcoholic fatty liver disease patients without prior known diabetes

- mellitus. *J Gastroenterol Hepatol.* (2011) 26:517–22. doi: 10.1111/j.1440-1746.2010.06567.x
76. Baltali M, Korkmaz ME, Kiziltan HT, Muderris IH, Ozin B, Anarat R. Association between postprandial hyperinsulinemia and coronary artery disease among non-diabetic women: a case control study. *Int J Cardiol.* (2003) 88:215–21. doi: 10.1016/S0167-5273(02)00399-6
 77. Åberg S, Mann J, Neumann S, Ross AB, Reynolds AN. Whole-grain processing and glycemic control in type 2 diabetes: a randomized crossover trial. *Diabetes Care.* (2020) 43:1717–23. doi: 10.2337/dc20-0263
 78. Nordlund E, Katina K, Mykkänen H, Poutanen K. Distinct characteristics of rye and wheat breads impact on their *in vitro* gastric disintegration and *in vivo* glucose and insulin responses. *Foods.* (2016) 5:24. doi: 10.3390/foods5020024
 79. Hartvigsen ML, Gregersen S, Laerke HN, Holst JJ, Knudsen KEB, Hermansen K. Effects of concentrated arabinoxylan and beta-glucan compared with refined wheat and whole grain rye on glucose and appetite in subjects with the metabolic syndrome: a randomized study. *Eur J Clin Nutr.* (2014) 68:84–90. doi: 10.1038/ejcn.2013.236
 80. Breen C, Ryan M, Gibney MJ, Corrigan M, O'Shea D. Glycemic, insulinemic, and appetite responses of patients with type 2 diabetes to commonly consumed breads. *Diabetes Educ.* (2013) 39:376–86. doi: 10.1177/0145721713479675
 81. Bondia-Pons I, Nordlund E, Mattila I, Katina K, Aura A-M, Kolehmainen M, et al. Postprandial differences in the plasma metabolome of healthy Finnish subjects after intake of a sourdough fermented endosperm rye bread versus white wheat bread. *Nutr J.* (2011) 10:116. doi: 10.1186/1475-2891-10-116
 82. Rosén LA, Östman EM, Shewry PR, Ward JL, Andersson AAM, Piironen V, et al. Postprandial glycemia, insulinemia, and satiety responses in healthy subjects after whole grain rye bread made from different rye varieties. 1. *J Agric Food Chem.* (2011) 59:12139–48. doi: 10.1021/jf2019825
 83. Rosén LA, Östman EM, Björck IM. Postprandial glycemia, insulinemia, and satiety responses in healthy subjects after whole grain rye bread made from different rye varieties. 2. *J Agric Food Chem.* (2011) 59:12149–54. doi: 10.1021/jf2019837
 84. Rosén LA, Östman EM, Björck IM. Effects of cereal breakfasts on postprandial glucose, appetite regulation and voluntary energy intake at a subsequent standardized lunch; focusing on rye products. *Nutr J.* (2011) 10:7. doi: 10.1186/1475-2891-10-7
 85. Kallio P, Kolehmainen M, Laaksonen DE, Pulkkinen L, Atalay M, Mykkänen H, et al. Inflammation markers are modulated by responses to diets differing in postprandial insulin responses in individuals with the metabolic syndrome. *Am J Clin Nutr.* (2008) 87:1497–503. doi: 10.1093/ajcn/87.5.1497
 86. Heinonen MV, Karhunen LJ, Chabot ED, Toppinen LK, Juntunen KS, Laaksonen DE, et al. Plasma ghrelin levels after two high-carbohydrate meals producing different insulin responses in patients with metabolic syndrome. *Regul Pept.* (2007) 138:118–25. doi: 10.1016/j.regpep.2006.08.011
 87. Juntunen KS, Niskanen LK, Liukkonen KH, Poutanen KS, Holst JJ, Mykkänen HM. Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects. *Am J Clin Nutr.* (2002) 75:254–62. doi: 10.1093/ajcn/75.2.254
 88. Leinonen K, Liukkonen K, Poutanen K, Uusitupa M, Mykkänen H. Rye bread decreases postprandial insulin response but does not alter glucose response in healthy Finnish subjects. *Eur J Clin Nutr.* (1999) 53:262–7. doi: 10.1038/sj.ejcn.1600716
 89. Liljeberg H, Björck I. Bioavailability of starch in bread products. Postprandial glucose and insulin responses in healthy subjects and *in vitro* resistant starch content. *Eur J Clin Nutr.* (1994) 48:151–63.
 90. Elliott RM, Morgan LM, Tredger JA, Wright J. The effects of cereal source and processing on the metabolic responses to commercially available breakfast cereals and breads. *Int J Food Sci Nutr.* (1994) 45:217–22. doi: 10.3109/09637489409166161
 91. Hagander B, Björck I, Asp NG, Efeandia S, Holm J, Nilsson-Ehle P, et al. Rye products in the diabetic diet. Postprandial glucose and hormonal responses in non-insulin-dependent diabetic patients as compared to starch availability *in vitro* and experiments in rats. *Diabetes Res Clin Pract.* (1987) 3:85–96. doi: 10.1016/s0168-8227(87)80012-8
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