Rare Sugars: Metabolic Impacts and Mechanisms of Action - a Scoping Review

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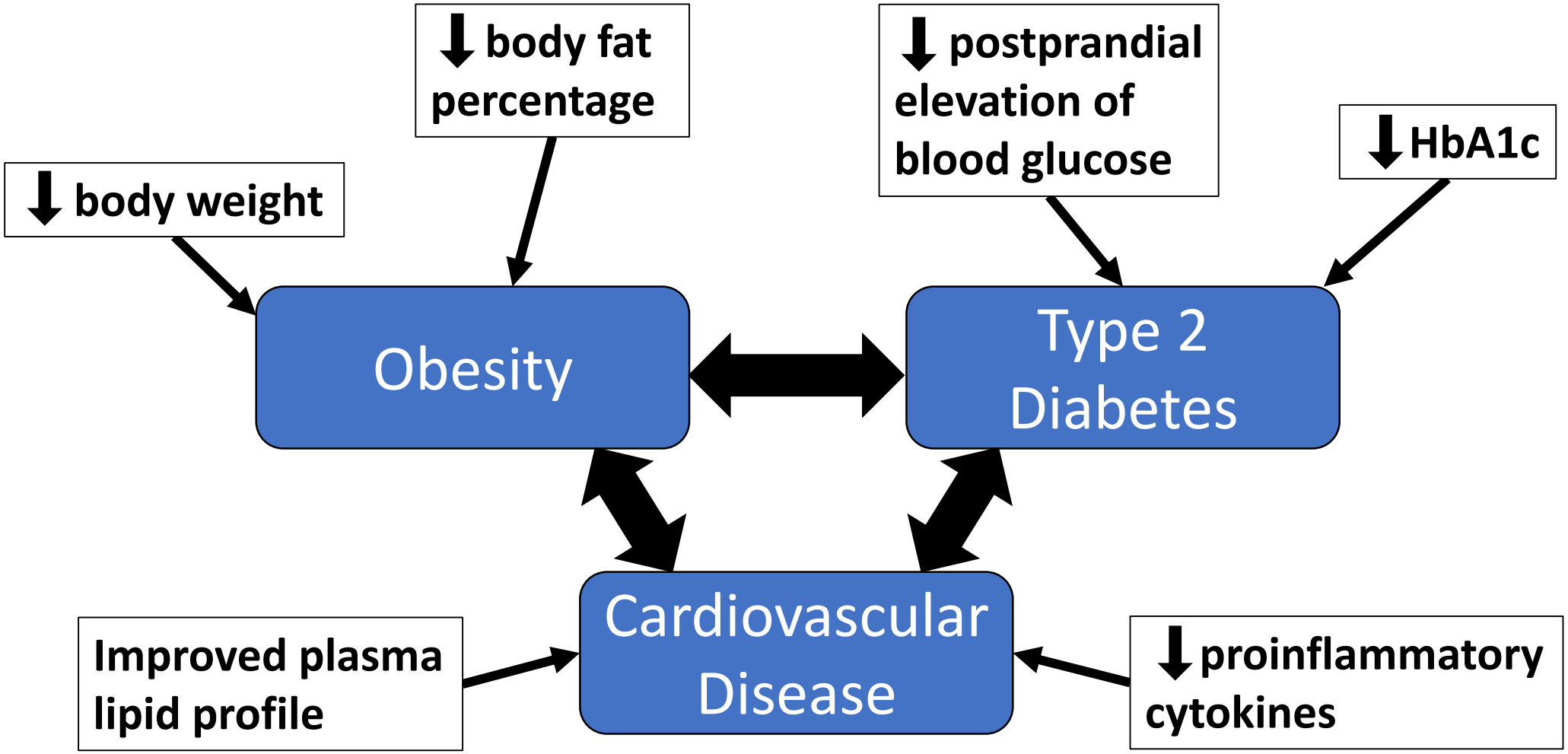
In vivo effects of rare sugars consumption



Rare sugars: Metabolic Impacts and Mechanisms of Action – a Scoping Review

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Abstract

Food manufacturers are under increasing pressure to limit the amount of free sugars in their products. Many have reformulated products to replace sucrose, glucose and fructose with alternative sweeteners, but some of these have been associated with additional health concerns. Rare sugars are "monosaccharides and their derivatives that hardly exist in nature", and there is increasing evidence that they could have health benefits. This review aimed to scope the existing literature in order to identify the most commonly researched rare sugars, to ascertain their proposed health benefits, mechanisms of action and potential uses, and to highlight knowledge gaps. A process of iterative database searching identified 55 relevant articles. The reported effects of rare sugars were noted, along with details of the research methodologies conducted. Our results indicated that the most common rare sugars investigated are D-psicose and D-tagatose, with the potential health benefits divided into three topics: glycaemic control, body composition and cardiovascular disease. All the rare sugars investigated have the potential to suppress postprandial elevation of blood glucose and improve glycaemic control in both human and animal models. Some animal studies have suggested that certain rare sugars may also improve lipid profiles, alter the gut microbiome and reduce pro-inflammatory cytokine expression. The present review demonstrates that rare sugars could play a role in reducing the development of obesity, type 2 diabetes, and/or cardiovascular disease. However, understanding of the mechanisms by which rare sugars may exert their effects is limited, and their effectiveness when used in reformulated products is unknown.

Introduction

There is increasing concern over the excess intake of metabolizable free sugars, which is associated with obesity and increased risk of non-communicable diseases[1-3]. Many food manufacturers are reformulating products to replace sucrose, glucose or fructose with dietary fibres, polyols or high-intensity sweeteners, but alternative sweeteners may be associated with health concerns such as appetite dysregulation and glucose intolerance[4]. Rare sugars, defined by the International Society of Rare Sugars as "monosaccharides and their derivatives that hardly exist in nature"[5], have attracted increasing interest as a result of recent advances in their commercial-scale biosynthesis[6; 7]. Rare sugars are low-calorie monosaccharides with similar sweetness to that of sucrose[6]. The rare sugars D-psicose (PSI, also known as allulose) and D-tagatose (TAG) have 'generally recognised as safe' (GRAS) status[8; 9]. Both are already in use in products such as biscuits, chocolate, jam[10], protein bars, soft drinks[11] and in commercial sweetener blends[12] in parts of Europe, Asia and the USA. Rare sugars have the advantage that, unlike high-intensity sweeteners, they can replace both the physical bulk and some of the sweetness of sucrose. They can therefore be used as a direct replacement for a significant portion of free sugars[13-15], allowing the production of confectionery with lower energy content. PSI in particular is an attractive option for food manufacturers as it is exempted from 'total sugars' and 'added sugars' figures on nutrition labelling in the USA[11].

The potential benefits of rare sugars go beyond simply replacing sucrose to reduce calorie intake. Research into the potential uses of rare sugars has been ongoing since the late 1990s, primarily in East Asia, with minimal research activity in the UK. They have been shown to have a range of beneficial biological functions[6], some of which could help to alleviate problems associated with the high consumption of free sugars. The biological actions of various rare sugars suggest they could contribute towards health improvements in a range of interlinked conditions, including obesity, type 2 diabetes (T2D) and cardiovascular disease (CVD)[6; 15; 16]. Rare sugars therefore have the potential to be used not only to replace sucrose in product reformulation, but also as functional ingredients with health promoting properties. Functional foods are foods or drinks which can have health benefits beyond their basic nutritional value[17]. In order for health claims

to be made about a food or ingredient, there must be robust evidence that it reaches its site of action, beneficially affects a physical function or biomarker, and has a direct impact on health status when consumed as part of a normal diet[17]. Research on rare sugars is in its early stages, and the evidence that would be required to make health claims is not yet available. More research is necessary before it can be claimed that rare sugars have health benefits in the general population.

The majority of research to date has focussed on measuring a limited range of outcomes, (for example body composition, glycated haemoglobin (HbA1c) levels or short-term glycaemic response) and the biological mechanisms underlying these outcomes are not yet clear. While there are several commercially available food products containing rare sugars[10; 11], there has been no research into the possible health benefits of these products. A detailed examination of the existing literature could help to explain mechanisms of action and highlight areas where further research is needed. Existing reviews on rare sugars have either focussed on a single sugar[9; 15; 16; 18; 19] or are broad summaries of potential uses, with little focus on mechanisms of action[6; 20]. The purpose of this scoping review is to provide an updated, comprehensive summary of the research into the potential health benefits of rare sugar consumption. The review identifies the most commonly researched rare sugars, explores their potential health benefits, mechanisms of action and possible uses, and highlights gaps in the evidence. Understanding the scope of the current evidence base and its limitations is critical to improving the design and implementation of future studies.

Methods

A scoping review differs from a systematic review, in that it aims to rapidly map the key concepts underpinning a research area. This scoping review aimed to identify primary research into the health benefits of the consumption of rare sugars, and employed the framework set out by Arksey and O'Malley[21]. While the objectives and methods were specified in advance, search terms and inclusion criteria were adapted during the process as the scope of the literature was identified.

Review Questions

This review seeks to answer the following questions:

1) Which rare sugars have been researched?
2) What are their known effects when consumed orally?
3) What are the mechanisms of action for these effects?
4) What are the proposed health benefits of rare sugars?
5) How might rare sugars be used to provide these health benefits?
6) What are the priorities for future research into rare sugars?

Identifying Relevant Studies

In order to test possible search terms, gain an overview of the literature and define the key concepts, a limited search of the literature was performed. The search term 'rare sugar AND (uses OR nutrition OR health)' was used in a search of Scopus. The titles and abstracts of the articles were scanned and several recent reviews were read in full[6; 16; 22], allowing the identification of key concepts: the most commonly-researched rare sugars, and broad areas of relevant research. These concepts were used to develop a search matrix for a systematic literature search (table S1), and to refine inclusion and exclusion criteria.

For the scoping review, all searches were performed in three databases (Scopus, PubMed and Web of Science) using identical search terms. The most recent searches were completed on 5th January 2021. Following title and abstract screening, the reference lists of relevant articles were searched to identify additional studies.

Study Selection

Inclusion and exclusion criteria

Preliminary literature searching revealed a wide range of uses for rare sugars[6]. While many of these are health-related, some involve the use of rare sugars in an industrial, pharmaceutical, or medical context. This review focuses on the health benefits of rare sugars in nutrition, therefore only includes studies where rare sugars have been administered orally *in vivo,* in humans or mammals. A significant milestone in rare sugars research was the discovery in 2004 of enzymatic methods by which rare sugars could be produced on an industrial scale[23]. This resulted in an increase in relevant research studies, particularly human trials. In order to rapidly identify the most relevant research, this review was therefore limited to articles published after 1st January 2004. Where relevant articles were unavailable in English, their abstracts were still included.

This review includes:

- Primary, *in vivo* research in humans or mammals in which rare sugars were administered orally.
- Studies published after 1st January 2004.

Studies were excluded if:

- The type or quantity of rare sugar were unclear (e.g. those using plant extracts)
- The rare sugar was not administered orally (e.g. solution injected or used in surgical procedures).

Study Screening

The process of article screening is summarised in Figure 1. Following database searching and removal of duplicates, title screening and abstract screening were carried out using the defined inclusion and exclusion criteria stated above.

Charting the Data

Included articles were read in full and data extracted. Microsoft Excel spreadsheets were used to allow methodical collection of available data, including the location, animal model or study population used, study design, rare sugar used, timescale, dosage, outcome measures and significant findings. Separate tables were used to record data from animal and human trials (table S2a and table S2b, respectively). As a scoping review aims to rapidly identify the parameters and gaps in a research area, quality of research is not a priority[24], therefore no systematic quality assurance was conducted and data from abstracts were included where full methods were not available.

Collating, Summarising and Reporting the Results

Study characteristics and available data were tabulated. A mapping diagram (Figure 2) was created to summarise the proposed health benefits described in the literature and their inter-relationships. Where several studies had similar methodology, additional tables were created to enable comparison of their methods, outcomes, and effect sizes.

Results

The outcomes of literature searching and article screening are summarised in figure 1. A total of 55 articles were included in this review (see tables S2a and S2b). The rare sugars identified as being most relevant from the included articles were PSI (also referred to as allulose), TAG, D-sorbose (SOR), D-allose (ALL) and rare sugar syrup (RSS, a syrup containing glucose and fructose along with around 5% PSI and small quantities of other rare sugars, which can be economically produced by isomerization of high fructose corn syrup (HFCS) under alkaline conditions). PSI, TAG and RSS are the most commonly researched rare sugars, and the only ones to have been used in human trials. There has been relatively little research into the health benefits of SOR, although some animal studies suggest it has the potential to improve glycaemic control[25; 26]. Much of the research involving ALL uses the compound in a pharmaceutical context (injected intravenously or as an antioxidant in irrigation fluid during surgery) and, therefore, is excluded from this review. There is limited research into the use of ALL as a dietary supplement, but one study in mice indicates that it has potential to improve fatty liver disease[27].

The reported *in vivo* effects of rare sugar consumption in humans included improved glycaemic control[28-39], reductions in body weight[36-39] and body fat[36; 39], and reduced low-density lipoprotein (LDL)-cholesterol and total cholesterol[40]. Similar effects were reported in animal studies. Additionally there is evidence from animal trials that rare sugar intake may also reduce hepatic lipid accumulation[27; 41-46], alter the gut microbiome[44; 45; 47] and improve inflammatory[45; 47] and oxidative status[48-50]. Therefore, results on the impact of PSI, TAG, RSS, SOR and ALL on these outcomes (glycaemic control, body weight and body fat, lipid metabolism, hepatic lipid accumulation and gut microbiome) will be presented. The effect of rare sugar consumption on appetite in humans has been monitored in some studies, with inconclusive results[51-53]. Table 1 summarises the key effects of rare sugar consumption as reported in the studies included in this review[54]. Taken as a whole, the evidence suggests that rare sugars may have the potential to improve or reduce the risk of obesity, T2D, CVD and fatty liver disease. The mapping diagram shown in figure 2 summarises how these interlinked conditions could be affected by rare sugar consumption. Importantly, the diagram highlights that the effect of

lowering postprandial glucose levels may lead to multiple health benefits. However, the majority of the evidence to date is from animal studies, and the mechanisms of action of the rare sugars are not understood. The extent to which rare sugars can affect pathways that lead to the alleviating of disease states is unclear.

Rare sugars and glycaemic control

There is evidence from human trials that both PSI and TAG, when consumed with a carbohydrate load, can reduce the resulting elevation in blood glucose in people with hyperglycaemia [28; 29; 33] (Table 2). Most of these studies involved a control group consuming the same carbohydrate load, so the effect can be attributed to the rare sugar rather than a simple decrease in carbohydrate intake. It should be noted that the reduction in the incremental area under the curve (iAUC) for glucose was relatively small (4-11% with PSI, 4% with TAG) compared to the effects of oral hypoglycaemic agents[55].

In studies where PSI[28; 56; 57] or TAG[33; 52] were consumed by healthy volunteers, no significant reductions in the iAUC for glucose were observed, although Kimura et al.[57] reported significantly lower blood glucose at 90 minutes after PSI was consumed before a standard meal. Some studies did report significant reductions in the postprandial elevation of blood glucose (PEBG) with PSI[30] or RSS[31; 34] consumption in healthy volunteers, but in these studies the experimental groups consumed reduced carbohydrate loads compared to control groups. The effects of SOR and ALL on glycaemic response have not been studied in humans, but one study in Wistar rats[25] reported a reduction in peak blood glucose concentration when SOR was given alongside a sucrose load.

The effect of longer-term rare sugar consumption on glycaemic control has also been investigated, with inconsistent results. Three studies examined the long-term effects of TAG in subjects with T2D[37; 38; 40] Of these, two found small but significant decreases in HbA1c after 12 months of regular TAG consumption [38; 40]. One study[36] investigated the effect of longer-term PSI consumption on glycaemic control in overweight individuals, and found no significant change in fasting blood glucose or HbA1c after 12 weeks.

The animal studies included in this review highlight the different effects of rare sugars on long-term glycaemic control in different animal models. Four studies investigated the effect of PSI consumption in animal models of metabolic syndrome (*db/db* mice[58] or Otsuka Long-Evans Tokushima Fatty (OLETF) rats[43; 59; 60]), and all found significantly reduced plasma glucose with PSI compared to control groups. A further 6 studies induced obesity and hyperglycaemia in wild-type animals by feeding high-sucrose or high-fat diets. Of these, three found no significant differences in blood glucose or insulin with PSI[61; 62] or RSS[63] feeding. Reductions in fasting blood glucose were reported in two studies feeding PSI to mice with diet-induced obesity (DIO)[41; 42], and Pongkan et al.[64], found significant reductions in fasting insulin levels and insulin resistance when PSI was fed to obese Wistar rats. Of the four studies in which there was no metabolic disorder, two reported a reduction in insulin levels with PSI[65] or RSS[66], with Iida et al. also reporting reduced fasting blood glucose[66]. The included animal studies using ALL[27; 67], SOR[26; 68] and TAG[68-70] found no significant difference in blood glucose, although Yamada et al.[26] reported a reduction in non-fasting serum insulin levels after 4 weeks of SOR feeding.

The effect of rare sugar consumption on body weight and body fat

Of the 27 animal studies where rare sugars were fed as part of the diet (typically 2-5% for PSI, RSS, ALL or SOR, 30% for TAG) or in drinking water (1-2% solution) for periods of 4 weeks or more, 22 studies found significant reductions in body weight with rare sugar consumption (see table 1). In 18 of the studies, where adipose tissue mass was an outcome measure, significant reductions were reported in 17 studies [41-46; 48; 49; 59; 62; 63; 66; 71-74]. Many of these studies were designed to reduce or eliminate the effect of differences in caloric intake, either using a paired-feeding approach or feeding isocaloric diets and carefully monitoring feed intake, but in some cases there was a calorie deficit in rare-sugar-fed animals.

Although few long-term clinical trials have been conducted, two trials in healthy adults found reductions in body mass index (BMI) and body fat percentage (BFP) when drinks containing PSI[36] or RSS[39] were consumed regularly over 12 weeks. Han et al.[36] reported modest but significant reductions in BMI (-0.38 kg/m^2) and BFP (-0.74%) in subjects consuming 14g PSI per day, with significant differences compared to a sucralose control group in which these

parameters were unchanged. Similarly, Hayashi et al.[39] found significant reductions in body weight (-1.85kg), BMI (-0.68 kg/m^2) and BFP (-1.72%) in subjects consuming 30g RSS per day, while no significant changes in these parameters were seen in control groups consuming isocaloric drinks containing 28g HFCS. In each of these studies food intake was recorded using 24 hour recalls[36] or 3-day food diaries[39], and no significant differences between groups were reported. Of three studies[37; 38; 40] where TAG was given regularly to adults with T2D, two found significant decreases in body weight from baseline, although neither of these studies had a control group[37; 38]. A large phase 3 clinical trial using the same dosing regimen (15g TAG three times daily before meals) found no significant differences in body weight between the TAG group and the control group who consumed a sucralose placebo[40]. None of the clinical trials using TAG reported food intake during the treatment period, so the potential contribution of calorie reduction and the effect of TAG on appetite are not known.

Some of the animal studies in this review reported that PSI consumption resulted in decreased food intake[43; 51; 60; 66], indicating a potential effect of PSI on appetite, although in most of the animal studies there was no significant difference in food intake.

Only one of the clinical trials in this review reported on differences in appetite with rare sugar consumption, and this was in the context of a study of gastrointestinal tolerance. Participants were given gradually increasing doses of 0.2-1g PSI per kg body weight, with gradually increasing daily frequency, over 1 week to find the maximum daily dose for regular ingestion. Diminished appetite, as one of a range of reported adverse effects, was self-reported by two of the 19 participants on day 8, after consuming the highest dose of 1g PSI per kg body weight[75].

Rare sugar consumption and lipid metabolism

Research methodologies used in animal studies include the measurement of plasma, hepatic and faecal triglycerides, cholesterol, and free fatty acids, as well as the expression and activities of enzymes involved in lipid metabolism. Of the 25 studies where blood lipids were measured, 17 used animal models of obesity (leptin deficient *ob/ob* mice or animals with DIO). The reported effects of rare sugar consumption on lipid metabolism are contradictory: of all the animal studies

measuring plasma lipids, only 13 found overall beneficial effects of rare sugar consumption (reduction in plasma triglyceride or total cholesterol, or increased ratio of high-density lipoprotein (HDL) to LDL cholesterol). Two of these were in Wistar rats without obesity[49; 76], although in both of these studies the diet of the PSI-fed rats was lower in energy than that of the control group. Nine studies reported reduced LDL cholesterol or non-HDL cholesterol with PSI consumption[42; 44; 45; 49; 60-62; 71; 76], and in four of these studies the HDL:LDL cholesterol ratio was increased[42; 45; 61; 71]. However three studies found no significant effects of PSI on plasma cholesterol[41; 58; 64], while two reported increased plasma total cholesterol and LDL cholesterol with PSI[72] or TAG[70] administration. It should be noted that all but one of these studies were carried out in rat or mouse models, in which cholesterol metabolism differs significantly from that of humans[61]. Kanasaki et al.[61] conducted a study in which PSI was fed to Syrian hamsters as part of a high fat diet over 8 weeks, and found no significant differences in plasma total cholesterol, although the HDL:LDL cholesterol ratio was increased.

There is more consensus in the reported effects of rare sugars on lipid metabolism enzyme activity. In general, PSI consumption tends to increase the activity of enzymes involved in β-oxidation of lipids and decrease the activity of enzymes involved in lipogenesis (Table 3). For example Do et al.[41] fed isoenergetic high fat diets with or without 5% PSI supplementation to mice for 8 weeks, and found that the livers of PSI-fed mice had reduced activity of phosphatidate phosphatase and glucose-6-phosphate dehydrogenase and increased activity of carnitine palmitoyltransferase 1. In several studies, the observed changes in enzyme activity were accompanied by reductions in adipose tissue weight[41; 48; 71; 73], although in two shorter studies the reductions did not reach significance[65; 68]. Interestingly when Nagata et al.[68] compared the effects of 3% PSI, TAG and SOR in the diets of rats, they found that lipid metabolism enzymes were affected differently by the different rare sugars, for example the activity of fatty acid synthase was decreased in PSI-fed rats but increased in the TAG-fed group.

Rare sugars and hepatic lipid accumulation

Although there are conflicting results concerning the effects of rare sugars on hepatic triglyceride and cholesterol content, there appears to be a consistent protective effect against hepatic lipid

accumulation with rare sugar consumption. All eight of the animal studies in which hepatic lipid was measured found that rare sugar consumption dramatically reduced lipid accumulation. In these studies, PSI[41-46; 49] or ALL[27] were fed to genetically obese or DIO animals and, while obese control groups developed hepatic fibrosis or ballooning degeneration, the livers of PSI-fed animals were found to be similar to non-obese controls[43-46].

Rare sugars and the gut microbiome

Two recent papers by Han et al.[44; 45] explored the effects of PSI consumption on the gut microbiome, as a possible mechanism for its observed anti-diabetic effects. In these studies PSI was fed as 5% of a high-fat diet to mice, with control groups pair-fed isocaloric high-fat diets. As well as reduced adipose tissue mass, serum lipids and hepatic lipids, these studies reported improved microbiome diversity; the microbiota of mice fed PSI with a high-fat diet was similar to that of mice fed a normal diet. TAG, too, has been found to be beneficial for gut microbiota in mice with induced colitis: in a study by Son et al.[47], TAG (25mg), *Lactobacillus rhamnosus* (109cfu) or a combination of the two treatments were administered every other day by oral gavage, with a control group given saline. Symptoms of colitis were reduced in TAG-fed groups, and synergistic effects were observed when TAG was fed alongside probiotics. There were significant reductions in the proinflammatory cytokines interleukin (IL)-6 and IL-10 with both TAG and *Lactobacillus* alone, and additionally a reduction in tumour necrosis factor α (TNFα) with combination treatment.

Discussion

This scoping review found that there is evidence, primarily from animal trials, for beneficial effects of dietary PSI consumption, particularly anti-hyperglycaemic and hypolipidemic effects. PSI, therefore, could be a useful alternative for free sugars and assist with prevention strategies for obesity and T2D. However, evidence from human trials is limited and research gaps remain. The actions of other rare sugars are less well-researched, but TAG has potential beneficial effects in the regulation of blood glucose. The mapping diagram (Figure 2) illustrates how the known actions of rare sugars could contribute to important health benefits linked to obesity, T2D and CVD. The majority of the studies reporting beneficial effects have involved animal models of metabolic disorders, or human subjects with hyperglycaemia, obesity or T2D (see Table 1). The potential health benefits of rare sugars as part of an ongoing normal diet in healthy individuals are unclear.

Unpacking the mechanisms of action of rare sugars

As outlined in figure 2, the observed *in vivo* effects of rare sugars are extensively interlinked. The reported effects of rare sugar intake could provide health benefits related to obesity, T2D, CVD and non-alcoholic fatty liver disease (NAFLD), but the precise mechanisms by which rare sugars exert their effects are not yet understood. Potential mechanisms of action include improvements in glycaemic control, altered lipid metabolism, reduced appetite, reduced inflammation and improvements in the gut microbiome. These factors will be discussed in the following sections.

The wide range of study types and methods used in researching rare sugars has resulted in some gaps in our understanding of their mechanisms of action, for example where one sugar has been shown to influence an outcome, biomarker, pathway, or gene, which may not have been investigated using other rare sugars. An understanding of the mechanisms of action is important when considering effects in different populations, and possible synergistic effects *in vivo.*

Glycaemic control: alteration in carbohydrate absorption and metabolism

As summarised in table 2, PSI and TAG have both been shown to reduce the elevation in blood glucose when given before or alongside a carbohydrate load. There have been several suggested mechanisms for this effect, including reduced digestion and absorption of dietary carbohydrates, enhanced glucose uptake from the plasma, and stimulation of insulin secretion.

SOR and TAG have both been found to inhibit sucrase and maltase enzymes from rat intestines[25], suggesting that reduced breakdown of disaccharides could be a mechanism by which rare sugars suppress PEBG. However it does not fully account for the reduction in PEBG when rare sugars are given with a carbohydrate load composed entirely of glucose, as observed by Noronha et al. [29] and in several animal studies [43; 58-60]. It is clear that other mechanisms of action also play a part.

Around 70% of ingested PSI is absorbed in the small intestine[60]. While glucose is transported largely by the sodium-glucose linked transporter (SGLT)1, both fructose and PSI enter enterocytes via the glucose transporter (GLUT)5. Efflux from enterocytes for all three monosaccharides involves the GLUT2 transporter[77]. This raises the possibility that PSI could reduce the absorption of both glucose and fructose by competition for sugar transporters. Indeed, TAG has been shown to reduce fructose absorption by 26% over 60 minutes when administered to rats alongside equal quantities of fructose[78]. It would be useful to determine the transport pathways of each rare sugar, and the extent to which they can slow the transport of fructose and glucose.

A further potential mechanism for the suppression of PEBG is through enhanced glucokinase (GK) translocation. GK catalyses the first step in the metabolism of glucose for the synthesis of glycogen and triacylglycerides, and is, therefore, critical in hepatic glucose metabolism. It is regulated by transcriptional changes and by translocation from the nucleus to the cytoplasm in the fed state[79]. This translocation of GK has been shown to be lower in hyperglycaemic or diabetic animal models, such as OLETF rats[59]. The translocation of GK was enhanced in both OLETF rats[43] and non-diabetic Wistar rats[74] fed PSI. An increase in translocation of GK to the

cytoplasm increases hepatic glucose uptake and contributes to better short-term regulation of blood glucose[79].

It is possible that the reduced PEBG observed with rare sugar administration is related to increased insulin secretion, stimulated by incretin hormones. These hormones, for example glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), are released in response to the presence of nutrients in the duodenum, and enhance the glucose-stimulated release of insulin from the pancreatic islets. One study in mice found that oral PSI administration stimulated GLP-1 release, leading to increased plasma insulin and reduced plasma glucose after intraperitoneal glucose injection[51]. Evidence from human trials, however, does not support this mechanism of action. One study in healthy volunteers reported that TAG stimulated GLP-1 release, but this did not lead to significant differences in blood glucose or insulin after a meal[52]. Additionally, several studies in humans have demonstrated that PSI[29; 57], TAG[33] or RSS[31; 34] consumption can reduce the iAUC for glucose following a carbohydrate load, but with no significant effect on plasma insulin. None of these trials reported measurements of incretin hormone levels. Insulin and incretin hormones play a vital role in glycaemic control, and the effect of rare sugar intake on insulin and incretin release in humans requires further investigation.

The relative contribution of these mechanisms *in vivo* is unknown, and may be different for different rare sugars. Postprandial blood glucose shows high inter-individual variation[56] and is affected by the action of insulin, glucagon and gut peptides, so the efficacy of rare sugars in suppressing PEBG is likely to vary between different animal species or human study participants. Future studies should aim to recruit sufficient participants to overcome the effects of inter-individual variation, and should measure not only blood glucose but also insulin and incretin hormone levels following the ingestion of rare sugars. Such studies should also trial the intake of rare sugars in food products, similar to those currently marketed, to ascertain whether significant differences in postprandial glycaemic response are observed compared to a standard product.

While regular TAG consumption has been shown to reduce HbA1c[38; 40], regular PSI consumption showed no significant effects on glycaemic control[36]. The factors affecting long-term glycaemic control are complex, and research in humans is complicated by changes in treatment regimes in subjects with T2D[38]. The HbA1c measurement commonly used in diabetes management reflects average plasma glucose over the previous 8-12 weeks, but does not take into account glycaemic variation during that time[80]. PSI and TAG can both reduce PEBG (see Table 2), so it is possible that dietary PSI or TAG could reduce damaging episodes of both hypo- and hyperglycaemia without significantly reducing HbA1c measurements. Further long-term, large scale studies are necessary to evaluate this, potentially using markers of short-term glycaemic control such as 1,5-anhydroglucitol[81].

Alterations in lipid metabolism

One consistently observed *in vivo* effect of rare sugar consumption, in both animals and humans, is a reduction in BFP and adipose tissue weight[36; 39; 41-46; 48; 49; 59; 62; 63; 66; 71-74]. Several animal studies have also reported a protective effect of rare sugars against the hepatic steatosis that results from a high-fat diet[27; 41-43; 45; 46; 49; 82]. The effects of rare sugars on serum and liver lipids are less consistent, and the precise mechanisms for the hypolipidemic effects of rare sugars are not well understood.

As shown in table 3, the intake of rare sugars appears to reduce the activity of lipogenic enzymes and increase the activity of those involved in β-oxidation. These changes are a plausible mechanism for the reduction in adipose tissue mass or BFP observed with regular rare sugar intake. Additionally, several studies observed significant reductions in the activity of enzymes involved in lipogenesis in the liver as a result of PSI feeding (Table 3). These changes, as well as contributing to reductions in hepatic lipid accumulation, could also affect plasma lipid profiles. An increase in the activity of hepatic lipase in serum and liver, for example, could contribute to the reduction in plasma triglyceride observed in several studies[41; 42; 48; 71].

Lipid metabolism is affected by blood glucose concentration, via both insulin-dependent and insulin-independent pathways[83]. Figure 3 outlines some of the pathways of fatty acid

metabolism in the liver and adipose tissue, showing potential mechanisms by which PSI could reduce lipid accumulation. Importantly, PSI appears to oppose the effect of insulin on several enzymes and pathways involved in lipid metabolism. A key question to be addressed is whether the observed changes in enzyme activity, and the resulting reduction in lipid accumulation, are direct effects of rare sugars or a result of changes in blood glucose and insulin.

The accumulation of lipid in non-adipose tissue is considered to be a factor in several non-communicable diseases. Fat infiltration in liver and muscle tissue is associated with insulin resistance[84], and in NAFLD lipid accumulates in hepatocytes causing liver damage[85]. NAFLD is closely associated with insulin resistance and obesity, and is one of the most common causes of chronic liver disease worldwide, with estimated global prevalence of 24%[86]. While rare sugars have been found to protect against lipid accumulation in the liver in DIO animals, the effect of rare sugars on lipid accumulation in muscle tissue does not appear to have been studied. Research in this area could provide useful insights into the potential therapeutic benefits of rare sugars.

Alterations in incretin response and appetite regulation

The question of whether rare sugars can affect appetite in people has not been extensively researched, and most of the animal studies in this review found no significant differences in food intake with rare sugar administration. However, some studies reported that PSI consumption results in decreased food intake[43; 51; 60; 66], and there are several mechanisms of action by which rare sugars could potentially affect appetite.

Leptin plays an important role in long-term appetite regulation; it suppresses appetite and increases energy expenditure[39]. Six animal studies found significantly decreased leptin levels with PSI supplementation[41; 42; 60; 65; 66; 71]. This could be explained by the decrease in body fat observed in each study, as leptin is mainly secreted by adipose tissue. The effect of rare sugars on leptin signalling in humans is not clear, with leptin levels found to increase[39] or remain the same[36] with daily PSI consumption despite significant reductions in body fat. Although generally correlated with adiposity, leptin levels show substantial inter-individual variation and

422 are affected by inputs from the sympathetic nervous system, insulin levels and long-term dietary
423 intake[87]. Further research is needed to investigate the potential effect of rare sugar intake on
424 leptin signalling.

425 Appetite is also regulated by gut hormones such as GLP-1 and GIP which, in addition to their
426 insulinotropic effects, slow gastric emptying. PSI has been shown to stimulate the release of
427 GLP-1 in animal studies[51; 88], an effect which could induce satiety and reduce food intake. TAG
428 has been found to stimulate GLP-1 release[52] and slow gastric emptying[52; 89] in human trials
429 but the effect of rare sugar intake as part of a mixed meal has not to our knowledge been
430 investigated.

431 Dietary monosaccharides are known to affect appetite-regulating peptides in the hypothalamus;
432 elevated glucose or fructose consumption have been shown to reduce the expression of the
433 appetite-suppressing signals peptide YY (PYY) and pro-opiomelanocortin (POMC) expression[90].
434 To our knowledge, the effects of rare sugars on hypothalamic appetite peptides have not been
435 studied. Further work is needed to investigate the effects of different rare sugars on appetite,
436 incretin release, gastric emptying and fullness in real-life conditions.

437 ***Effects on inflammatory markers and oxidative stress***

438 Obesity, T2D and CVD all involve inflammation and increased oxidative stress[83]. A reduction
439 in inflammatory cytokines and oxidative stress could therefore be a key mechanism by which
440 rare sugars may slow the progression of these conditions. Several animal studies have found
441 reduced markers of inflammation or oxidative stress when dietary sucrose or fructose were
442 replaced with PSI[71; 73; 82]. Although in all of these studies the control group consumed more
443 sucrose than the experimental group, the caloric intake was matched between groups so the
444 reduction in inflammatory cytokines is unlikely to be a result of caloric restriction. In one study
445 in which TAG (30% solution), fructose (30% solution) or plain drinking water were provided to
446 mice over 24 weeks, significantly increased TNFα and IL-1β levels were reported with fructose
447 intake[69]. There were also significant increases in these cytokines with TAG intake, but the
448 increase was around half of that with fructose. As fructose provides around 4kcal per gram and

TAG is estimated to provide 2kcal per gram[5], these differences in inflammatory cytokine levels could be explained by differences in caloric intake between groups[69]. Studies using OLETF rats, a model for T2D, have found that PSI-treated animals had reduced fibrosis and fatty degeneration of pancreatic islets compared to control OLETF rats. This protective effect was attributed to the reduced release of pro-inflammatory cytokines in PSI-fed animals[59; 60]. Similarly, the replacement of dietary sucrose with TAG has been found to reduce atherosclerosis in animals[70; 91], although once again the possible contribution of caloric restriction must be taken into account[92].

Effects on the gut microbiome

The composition of the gut microbiota can be affected by dietary change, and it is becoming increasingly clear that changes in the gut microbiome are linked to a wide range of health-related factors such as inflammatory state and adiposity[82]. Probiotics and polyphenol-rich fruit extracts, which improve the diversity of the gut microbiome, have been shown to also reduce visceral adiposity and obesity[45]. The impact of rare sugars on the gut microbiome has only recently been studied, but the results from animal studies indicate that PSI intake can increase the proportion of species such as *Lactobacillus,* thought to be protective against fructose-induced NAFLD[45]. TAG, as it is poorly absorbed, can act as a prebiotic, and has been shown to work synergistically with probiotics in reducing the susceptibility of mice to chemically-induced colitis[47]. This potential for changes to the gut microbiome requires further exploration in human studies, but should also be considered as a potential mechanism when interpreting the results of existing studies.

The potential use of rare sugars as functional foods

Functional foods are those containing ingredients which exert positive health effects, and therefore have health promoting properties besides their nutritional value[17]. The majority of the evidence suggesting health benefits from long-term rare sugar consumption comes from animal studies that, if replicated in humans, could provide significant health benefits. However, because of the very high-energy diets and large rare sugar dosages used in many of these trials,

there is doubt about whether similar effects would be seen in humans. For example, the dramatic reduction in lipid accumulation in the liver seen in studies of PSI[41-46; 49] or ALL[27] consumption suggests an application for rare sugars in preventing NAFLD. Only one of these studies[46] provides daily food intake data, stating that the *ob/ob* mice in the experimental group consumed 3-4g PSI per kg body weight per day, with control groups consuming an isocaloric diet of normal CE2 pellet food. This quantity would equate to an intake of at least 210g PSI per day for an average 70kg human- a quantity clearly unrealistic for PSI consumption in foods.

In this review the effects of long-term consumption in humans have been reported in only three studies using TAG in the USA and India[37; 38; 40], two studies using PSI in Korea and Japan[28; 36] and one study in Japan using RSS[39]. Although these trials did report significant benefits from rare sugar consumption, it is important to note that they involved relatively large doses of rare sugars taken as daily dietary supplements. If rare sugars are to be promoted for their health benefits, research studies must take into account that they are more likely to be consumed in smaller quantities as part of reformulated food products.

The rare sugar TAG is currently used as a sweetener (branded 'Tagatesse') in products sold by Damhert Nutrition in Belgium, the Netherlands and Luxembourg[10]. A typical product, gluten-free spiced biscuits, contains 0.6g TAG per 10g portion. In contrast, participants in the 2015 trial conducted by Ensor et al.[40] consumed 15g of TAG three times per day. Products containing PSI are also available, primarily in the USA, where items such as soft drinks, protein bars and cookies are sweetened with PSI[11]. For example, Quest hero bars, marketed as low-carbohydrate snacks, contain 11g PSI per 60g bar (along with erythritol and soluble fibre)[93]. This quantity is more comparable to the amounts used in clinical trials, for example Han et al.[36] reported significant reductions in body weight and BFP when overweight participants consumed 7g PSI twice daily for 12 weeks, compared to a control group consuming a sucralose placebo.

The cost of rare sugar production has been reduced by advances in biotechnology. The cost of PSI is now estimated at $7/kg, comparable with erythritol[94]. Recent advances in genetic engineering have produced yeasts that can generate TAG from whey waste from yogurt making,

greatly reducing its cost[7]. Rare sugars are therefore becoming attractive alternatives to other sweeteners in the reformulation of products.

Another important consideration if rare sugars are to be used in the reformulation of foods is their sensory properties. Rare sugars tend to be slightly less sweet than sucrose but have similar sweetness profiles, suggesting that the temporal sweetness profile and sweetness quality may be similar to sucrose but the intensity will be lower[14; 95]. When used in combination with sucrose, some rare sugars can provide desirable sensory characteristics whilst also reducing calories[14; 95].

In considering the use of rare sugars within functional foods and in the reformulation of foods, it is also vital to consider the safety of long-term rare sugar intake. Both PSI and TAG have been given GRAS status[8; 9]. In tolerance testing in healthy volunteers, the maximum single dose of PSI that resulted in no severe gastrointestinal symptoms was 0.4g per kg body weight[75] although Hayashi et al.[28] reported no evidence of toxicity with a single dose of PSI at 0.5-0.6g per kg body weight. A large clinical trial investigating the safety and efficacy of TAG for treating patients with T2D reported no toxic effects on renal or hepatic function, although there were transient mild gastrointestinal symptoms[37]. One consideration in the assessment of the safety of sugars is their natural presence in a typical human diet. PSI exists in small amounts in wheat and Itea plants as a free sugar, but more substantial amounts (up to 135mg/100g) are formed when fructose undergoes cooking processes, such as in Worcester sauce, brown sugar, maple syrup, ketchup, and cola[15]. TAG occurs naturally in Sterculia setigera gum and small quantities have been found in sterilized and powdered cow's milk, a variety of cheeses, and other dairy products[96]. Nonetheless, it is vital to consider the effects of large-scale increases in the intake of these sugars in a population. The rare disaccharide trehalose appears naturally in small amounts in mushrooms, honey and other foods and was considered GRAS. However, when it begun to be widely used in the manufacture of baked goods and cereals, average intakes increased from less than 0.3g per day to over 30g per day. This change in nutrient availability led to the evolution of strains of the pathogenic bacterium *Clostridium difficile* which were able to utilise trehalose as an energy source, and therefore outcompete other gut microbiota[97]. The

effects of increased intake of rare monosaccharides on the gut microbiome should be carefully considered before encouraging increased general intake of rare-sugar-containing products.

The GRAS status, suitable sensory characteristics and reasonable costs of both PSI and TAG make them attractive options as novel sugar replacers in the reformulation of food products. However there is a need for further long-term human trials in different populations, using realistic dosages within real food matrices, with careful monitoring of adverse effects and impact on gut microbiome before any of the promising results from animal studies can be translated into health claims for rare sugars as functional foods.

Implications for research

This review has highlighted gaps in the research on the use of rare sugars. Studies in this field have tended to focus on either postprandial glucose metabolism, long-term glycaemic control, or lipid metabolism. As a result, there is a lack of research linking these different areas. Research to date has been predominantly conducted in animals, often using DIO animals consuming high-energy diets, for example several studies[41-45] involved PSI intake as 5% of a weight-promoting diet (replacing sucrose), with control diets typically containing 20% fat and 37% sucrose by weight[41]. This is a widely-used method to model obesity in rodents[98], but may not accurately represent the complexities of energy metabolism in humans consuming an unhealthy diet. The small number of human studies to date have been carried out in limited populations (PSI and RSS primarily in East Asian subjects, TAG mainly in subjects with T2D). The details of how rare sugars are absorbed, metabolised and excreted in humans are not yet known. PSI and ALL are both found in human urine at levels higher than would be expected considering extremely low levels in the diet, highlighting gaps in our knowledge of their metabolism[99]. The mechanisms by which rare sugars exert their effects are not fully understood, therefore it is not possible to draw conclusions on their potential health benefits in different populations. The majority of the human trials have involved rare sugar solutions as a supplement, and there is no evidence to date for health benefits of rare sugar consumption in reformulated products as part of a normal diet. In order for rare sugars to be classed as functional foods, robust evidence would be required demonstrating measurable improvements

559 in health markers or outcomes from regular consumption of reformulated foods containing rare
560 sugars.

561 One of the key differences in research methodology highlighted by this review is the nature of
562 the control conditions. While many researchers took steps to reduce or eliminate the effect of
563 differences in caloric intake between groups, some studies used rare sugars to replace other
564 carbohydrates in the diet, and thus there was a difference in energy intake between groups. In
565 some cases this difference was substantial, for example in one study in mice where all of the
566 sucrose in a Western diet (34% of the diet by weight) was replaced by TAG[91]. It is possible
567 therefore that the reduced serum lipids, reduced atherosclerotic lesions and reduced adipose
568 tissue weight observed in this study were partly a result of caloric restriction. Reduced calorie
569 intake can rapidly lead to decreased triglyceride levels in tissues including the liver, reduced
570 visceral fat and increased insulin sensitivity in people with obesity[92], therefore it is vital that
571 studies exploring similar effects with rare sugar intake ensure that experimental and control
572 diets are isocaloric. Overall food intake should also be monitored and reported. Several animal
573 studies in this review reported reduced food intake with PSI[43; 46; 51; 60; 62] or RSS[66; 74]
574 supplementation, suggesting a possible effect on appetite. In long-term studies in people, where
575 there may be large differences in energy intake between different participants, small changes in
576 appetite with rare sugar intake could result in differences in energy intake which may not be
577 detected even with careful dietary monitoring. Even in studies with isocaloric diets and
578 monitored food intakes, the type and quantity of carbohydrates in experimental and control diets
579 should be considered carefully. Consumption of fructose and HFCS are known to have
580 detrimental effects on lipid metabolism and insulin sensitivity[100], and have been linked to
581 increased cardiovascular risk and diabetes prevalence[101]. It is important when examining the
582 benefits of a rare sugar to consider whether rare sugar consumption is 'better than nothing' or
583 only 'better than other free sugars'.

584 Short-term studies in both healthy volunteers and subjects with T2D have demonstrated a
585 reduction in PEBG when a single dose of PSI or TAG is consumed alongside a carbohydrate
586 load[28; 29; 31-34; 52; 57]. However, it is not clear whether this effect persists when rare sugars are

consumed regularly[36; 39]. Additionally, the importance of the timing of rare sugar consumption relative to the carbohydrate load, and the effects of rare sugar consumption on appetite, have not to our knowledge been investigated in humans. These are important considerations if health claims are to be made for products containing rare sugars as replacements for free sugars.

Many animal studies[36; 39; 41-46; 48; 49; 59; 62; 63; 66; 71-74], and two studies in humans[36; 39], have reported reductions in body fat with PSI or RSS intake. This hypolipidemic effect appears to be mediated by changes in the expression or activity of enzymes involved in lipid metabolism (see Figure 3). Importantly, the *in vivo* effects of PSI tend to oppose the effects of insulin. It is possible that reduced circulating insulin is the primary factor leading to reduced lipogenesis and increased oxidation of fatty acids. However, there were no significant changes in fasting insulin levels in the human studies[36; 39], or in the animal studies in which it was measured[62; 63; 70]. While both PSI and TAG have been shown to stimulate GLP-1 release[51; 52; 88], it is only in mice that this has been linked to increased insulin release[51]. It is possible that rare sugars may potentiate insulin release in the short term, while improving insulin sensitivity and thus reducing basal insulin levels in the longer term. Further large-scale, long-term trials in different human populations would help to clarify the effect of rare sugars on insulin secretion and shed light on the mechanisms for the hypolipidemic effects of rare sugars.

Limitations of this review

The process of a scoping review, as distinct from a systematic review, has certain limitations. In order to rapidly map the existing literature, inclusion criteria were broad and study selection was not subject to the quality assurance typical in a systematic review. The quality of individual studies has not been formally assessed, and some evidence has been extracted from abstracts of papers, so detailed methods cannot be examined.

When attempting to collate and report data from a range of different studies there is necessarily a degree of over-simplification. This review has largely reported on significant effects and their direction, but has not attempted to quantitatively compare effect sizes. Studies are not always

directly comparable because of differences in animal models or subjects, rare sugar dosages and timescales.

When considering the results of human trials, it is significant that most of the studies carried out to date have been in East Asian populations. Differences in genetics and habitual diet could limit the extent to which these results can be generalised to other populations. Additionally, most studies have involved the acute administration of rare sugars in drinks or syrups. The effects of rare sugars as part of a typical human diet, and in different food matrices, are largely unknown.

Summary

This scoping review has summarised the research into the observed health benefits of rare sugars. The majority of research has focussed on PSI, but other rare sugars have been shown to have beneficial effects.

Rare sugars have been shown to improve glycaemic control and reduce body fat in human clinical trials as well as in animal studies. The effect of lowering postprandial glucose levels could lead to multiple health benefits, and rare sugars may also affect other pathways linked to obesity, T2D, NAFLD and CVD, for example by altering lipid metabolism, improving the gut microbiome or reducing inflammation. Therefore the consumption of rare sugars, whether as sugar replacers, dietary supplements or in functional foods, could potentially provide health benefits. However, the number and scale of human studies is still limited, and the dosage, timing and frequency of consumption required to see beneficial effects in humans is not known. There are questions to be answered about the long-term efficacy of rare sugars and their effects on health outcomes in different populations. A clearer understanding of the absorption and metabolism of rare sugars in humans, their effects when consumed in realistic doses as part of reformulated foods, and their mechanisms of action, is vital when considering the potential benefits of rare sugars in the human diet.

Author declaration and contribution

The authors declare that they have no conflicts of interest. AS, PJ, AA contributed to the conception, design and drafting of the review. AS carried out literature searching, data extraction and analysis and wrote the paper. RF, QY, DN, NM and AG were involved in conception and reviewing the manuscript. PJ had primary responsibility for the final manuscript.

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Tables

Table 1: Summary of the reported health benefits of rare sugar consumption (including only studies reporting significant results)

Observed Effect of Rare Sugar	Human studies				Animal studies			
	Subjects with T2D, hyperglycemia or obesity		Healthy subjects		Animal models of metabolic disease		Normal animals	
Reduced PEBG	PSI	Hayashi 2010[28] Noronha 2018[29]	PSI	Matsuo 2011[30]#* Yamada 2018[31]#* Iida 2008[32]#	PSI	Hossain 2011[43], 2012[59] Iwasaki 2018[51] Pongkan 2020[64]	SOR RSS	Oku 2014[25] Shintani 2017[74]
	TAG	Kwak 2013[33]	RSS	Nakamura 2017[34]#*				
Improved long-term glycaemic control	TAG	Ensor 2014[38], 2015[40]			PSI	Baek 2010[58] Do 2019[41]+ Han 2016[42] Hossain 2011[43]. 2012[59]. 2015[60]	PSI	Iida 2013[66]+
Reduced body weight	PSI TAG	Han 2018[36] Donner 2010[37] Ensor 2014[38]	RSS	Hayashi 2014[39]+	PSI	Han 2016[42]+, 2020[44]+, 2020[45]+ Baek 2010[58] Choi 2018[71]*+ Chung 2012[72] Do 2019[41]+ Hossain 2011[43], 2012[59] Itoh 2015[46] Kim 2017[73]+ Ochiai 2013[62] Hossain 2015[60]	PSI RSS ALL	Huang 2018[76]# Nagata 2015[65]+* Yagi 2009[54] Iida 2013[66]+ Shintani 2017[74] Iga 2010[67]
					TAG	Williams 2015[91]*+		
Reduced body fat	PSI	Han 2018[36]	RSS	Hayashi 2014[39]+	PSI	Han 2020[44]+ Choi 2018[71]*+ Hossain 2011[43] Itoh 2015[46] Kim 2017[73]+ Ochiai 2013[62]	PSI	Chen 2017[48]*+# Chen 2019[49]*+
					RSS	Ochiai 2017[63]+*		
Improved plasma lipid profile	TAG	Ensor 2015[40]			PSI	Han 2016[42]+, 2020[44]+, 2020[45]+ Baek 2010[58] Choi 2018[71]*+ Do 2019[41]+ Ochiai 2013[62] Hossain 2015[60] Kim 2017[73]+ Kanasaki 2019[61]*+	PSI	Chen 2017[48]*+# Chen 2019[49]*+

	TAG	Williams 2015[91]*+		
Reduced hepatic lipid accumulation	PSI	Han 2016[42]+, 2020[44]+, 2020[45]+ Do 2019[41]+ Hossain 2011[43] Itoh 2015[46]	PSI	Chen 2019[49]*+
	ALL	Yamamoto 2017[27]		
Improved gut microbiome	PSI	Han 2020[44]+, 2020[45]+		
	TAG	Son 2019[47]		
Reduced inflammation	PSI	Han 2020[45]+		
	TAG	Son 2019[47]		
Improved oxidative status	PSI	Pratchayasakul 2020[50]#	PSI	Chen 2017[48]*+# Chen 2019[49]*+

Studies reporting inconclusive or non-significant results have not been included. PEBG, postprandial elevation of blood glucose.
* indicates studies in which there was a possible calorie deficit in the experimental group. + indicates studies in which the rare sugar replaced another carbohydrate in the experimental diet. # indicates studies available as abstracts only.

Table 2: Summary of human trials examining the effect of rare sugars on postprandial blood glucose elevation

Study & Location	Study population	Trial design	RS dose	CHO load	Ratio RS:CHO	Control	Difference in AUC	p value	Conclusions
Braunstein et al., 2018[56] *Canada*	Healthy volunteers (n= 25) age 37 ± 16 BMI 24.7 ± 3.4	Randomised, controlled, double-blind, multiple-crossover	5g PSI in glucose solution	75g glucose solution	1:15	No addition to CHO load	-35 ± 22 mmol/L*min (15.6% reduction)	0.11	No significant effect on plasma glucose iAUC compared to 0g PSI control.
			10g PSI in glucose solution		2:15		-23 ± 22 mmol/L*min (10.3% reduction)	0.07	
Hayashi et al., 2010[28] *Japan*	Borderline diabetes (n=15) and healthy volunteers (n=11) age 55.0 ± 11.4 BMI 24.9 ± 4.4	Randomised, controlled, double-blind, crossover	5g PSI single dose in tea given with meal	Standard meal (425kcal, 84.5g CHO, 13.3g protein, 3.7g fat)	1:17	Aspartame	-743.3 mg*min/dl overall for meal (11.5% reduction)	<0.01	AUC for PSI meal was significantly less than control aspartame meal overall and in subgroup of subjects with borderline diabetes but not in subgroup of healthy participants.
Kimura et al, 2017[57] *Japan*	Healthy volunteers (n=13) age 35.7 ± 2.0 BMI 20.9 ± 0.7	Randomised, controlled, single-blind, crossover	5g PSI single dose in solution, 30min before meal	Standard meal (571kcal; 61% of energy as CHO, 25% as fat, 14% as protein. (Estimated 93g CHO)	1:19	Aspartame	NA	NA	PSI supplementation gave significantly lower change in plasma glucose at 90 min only, compared to aspartame control. No significant difference in plasma insulin.
Noronha et al., 2018[29] *Canada*	Subjects with T2D, controlled with diet or OHAs, not insulin (n=24) age 66 ± 1.2 BMI 27.0 ± 0.9	Randomized controlled, double-blind, crossover	5g PSI in glucose solution	75g glucose solution	1:15	No addition to CHO load	-48.1 mol*min/l (6.2% reduction)	0.051	Significant linear dose response gradient for reduction in AUC for glucose.

			10g PSI in glucose solution		2:15		-60.1 mol*min/l (7.7% reduction)	0.015	
Matsuo & Lu, 2011[30] *Japan*	Healthy volunteers (n=44)	No crossover, no info on randomisation or blinding	6g PSI single dose before meal	Normal lunch selected by subjects (636kcal, 87.6g CHO for males, 513kcal, 18.9g CHO for females)	1:15 male, 1:3 female	6g D-fructose	NA	NA	Postprandial glycaemic response significantly lower after PSI compared to D-fructose control.
Iida et al., 2008[32] *Japan*	Healthy volunteers (n=20)	Randomised, single-blind crossover	2.5, 5 or 7.5g PSI	75g maltodextrin solution	1:10, 1:15 or 1:30	No addition to CHO load	NA	NA	Dose-dependent reduction in postprandial blood glucose, with significant effects at doses of 5g or greater.
Tanaka et al., 2020[35] *Japan*	Healthy volunteers (n=?)	Randomised, single blind crossover	0, 1.8, 3.6 or 12.5g PSI in 50g chocolate	50g chocolate (carbohydrate content not provided)	NA	NA	NA	NA	Reduction in postprandial blood glucose and insulin with PSI compared to control.
Nakamura et al., 2017[34] *Japan*	Healthy volunteers (n=10)	Randomised, single-blind, placebo-controlled crossover	0, 15, 25 or 35g RSS	Total 50g CHO-sucrose with part replaced by RSS	3:7, 5:5 or 7:3	sucrose	NA	NA	Compared to 100% sucrose control, 5:5 and 7:3 ratios gave significant reduction in iAUC for glucose and insulin. 3:7 ratio gave significant reduction in iAUC for insulin but not glucose.
	Healthy volunteers (n=12)		5g RSS	Total 10g CHO-sucrose with half replaced by RSS	1:1	sucrose			Significant reduction in iAUC for glucose and insulin with 1:1 RSS:sucrose compared to sucrose alone.

Yamada et al., 2018[31] *Japan*	Healthy volunteers (n=14)	Randomised, single blind, placebo-controlled crossover	Half sucrose replaced with RSS	Sucrose (no info on amount)	1:1	sucrose	NA	NA	Significant reduction in iAUC for glucose compared to sucrose control.
	Healthy volunteers (n=10)		Sucrose replaced with RSS		3:10 and 5:5	sucrose			Significant reduction in iAUC for glucose compared to sucrose control.
Kwak et al., 2013[33] *Korea*	Healthy volunteers (n=52) Age 35.8 ± 1.45 BMI 23.7 ± 0.54	Randomised, double-blind, placebo-controlled crossover	5g or 10g TAG in drink before a meal	Standard meal, 356kcal of which 60% (53g) CHO	1:10 or 1:5	Sucralose-erythritol drink	-3.3 mg/dL/h (1.32% reduction)	NS	Significant reduction in iAUC only in hyperglycaemic subjects.
	Hyperglycaemic subjects (impaired fasting glucose or newly-diagnosed T2D, n=33) Age 57.2 ± 1.71 BMI 25.0 ± 0.46						-15.4 mg/dL/h (4.0% reduction)	<0.05	
Wu et al., 2012[52] *Australia*	Healthy volunteers (n=10) Age 28.2 ± 4.0 BMI 25.5 ± 1.5	Randomised, single-blind, placebo-controlled crossover	40g TAG-isomalt mixture (16g TAG), 20 mins before meal	Standard meal containing 63g CHO	1:4	Sucralose preload	+0.5 mmol/L*min (0.25% increase)	NS	Significant increase in iAUC with glucose preload, but no significant differences between TAG and control.

Difference in iAUC (incremental area under curve) for glucose is the difference between rare sugar treatment group vs control group in 120 minutes following ingestion of carbohydrate load. P-values are for significance of difference as stated in the referenced article. Ages are given in years, body mass index (BMI) is given in kg/m^2. Shaded rows are articles not available in English. RS, rare sugar; PSI, D-psicose; CHO, carbohydrate; T2D, type 2 diabetes; OHAs, oral hypoglycaemic agents; NA, not available; RSS, rare sugar syrup; TAG, D-tagatose; NS, not significant.

Table 3: the effects of *in vivo* PSI administration on the enzymes involved in lipid metabolism.

Enzyme	Role	Effect of PSI	References
Hepatic lipase	Hydrolysis of triacylglyceride	Increased activity	48
Hepatic CPT1	Catalyses the rate-limiting step in the beta-oxidation of long chain fatty acids.	Increased expression or activity	73, 71, 41
Hepatic ME	Catalyses conversion of malate to pyruvate, replenishing TCA cycle intermediates. Provides a source of NADPH for lipogenesis.	Decreased activity	71
Hepatic G6PDH	Provides a source of NADPH for lipogenesis.	Decreased activity	73, 71, 65, 68
ACC	Catalyses the committed step in fatty acid synthesis	Reduced expression	48
FAS	Catalyses the synthesis of long-chain fatty acids.	No significant difference in activity	41
		Decreased activity or expression	48, 71, 76, 41, 68
Adipose tissue CPT1	Catalyses the rate-limiting step in the beta-oxidation of long chain fatty acids.	Increased expression	71
HSL	Hydrolysis of long-chain fatty acids- inhibited by insulin.	Increased expression	48, 41
PAP	Catalyses the conversion of phosphatidate to diacylglycerol, regulates TAG synthesis.	Decreased activity	73, 68
LPL	Hydrolyses triglycerides in lipoproteins	Decreased expression	41
ACAT	Catalyses key step in the mevalonate pathway, promotes cholesterol storage.	Decreased activity	73
PCSK9	Binds to LDL receptor, reducing LDL-R recycling.	Lower serum level	61
HMGCR	Catalyses the rate-limiting step in cholesterol synthesis.	Increased activity	73

CPT: carnitine palmitoyltransferase, ME: malic enzyme, G6PDH: glucose 6-phosphate dehydrogenase, ACC: acetyl-CoA carboxylase, FAS: fatty acid synthase, HSL: hormone-sensitive lipase, PAP: phosphatidate phosphatase, LPL: Lipoprotein lipase, ACAT: Acetyl-coenzyme A acetyltransferase, PCSK9: Proprotein convertase subtilisin/kexin type 9 HMGCR: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, TAG: triacylglycerol.

Figures

Figure 1: Identification and selection of relevant research. PSI: D-psicose, TAG: D-tagatose, SOR: D-sorbose, RSS: rare sugar syrup, ALL: D-allose.

Figure 2: Mapping diagram to show the health benefits of rare sugars and how they are interlinked. Blue text indicates actions of rare sugars demonstrated in at least one study included in this review. Letters in brackets indicate the rare sugars involved, with capital letters denoting human studies and lower-case letters denoting animal studies: A/a – allose, P/p – psicose, S/s – sorbose, T/t – tagatose.

Figure 3: Outline of fatty acid metabolism in the liver (A) and adipose tissue (B), highlighting the effects of insulin and PSI. Green (+) or (-) indicates increased or decreased expression or activity stimulated by insulin. Red (+) or (-) indicates increased or decreased expression or activity as a result of PSI consumption. TG: triacylglycerol, VLDL: very low density lipoprotein, ACS: acyl-CoA synthase, ACC: acetyl-CoA carboxylase, CPT-1: carnitine-palmitoyl transferase 1, ME: malic enzyme, GLUT2: glucose transporter 2, GLUT4: glucose transporter 4, LPL: lipoprotein lipase. Diagrams adapted from Frayn, 2019[83], p131 & 133.

Supplementary Data (provided separately)

Table S1: Search terms and results of literature searching.

Table S2a: Summary of included *in vivo* animal studies.

Table S2b: Summary of included studies in human subjects.

Table S1: Search Terms and Results of Literature Searching

Search	Search terms	Scopus	Web of Science	PubMed
1	D-psicose OR psicose OR D-psi OR allulose OR D-allulose	551	687	303
2	D-tagatose OR tagatose OR D-tag	650	688	335
3	D-sorbose or sorbose OR D-sor	529	499	282
4	D-allose OR allose	381	437	246
5	'rare sugar' OR 'novel sweetener' OR 'new sweetener' OR ketohexose OR aldohexose	77	536	404
6	?Glyc?emi* OR 'blood sugar' OR insulin OR diabetes OR HbA1c	356,952	680,350	703,422
7	Lipid OR adipose OR fat OR 'body composition' OR obesity OR lipo* OR NAFLD OR NASH OR 'fatty liver'	80,712	1,301,826	1,264,128
8	'Cardiovascular disease' OR CVD OR 'heart disease' OR stroke OR atherosclerosis	503,577	700,494	537,047
9	Antioxidant OR 'oxidative stress' OR redox OR 'reactive oxygen species' OR 'free radical' OR thioredoxin OR glutathione	42,011	846,983	706,203
10	1 AND (6 OR 7 OR 8 OR 9)	69	333	87
11	2 AND (6 OR 7 OR 8 OR 9)	40	272	79
12	3 AND (6 OR 7 OR 8 OR 9)	12	110	70
13	4 AND (6 OR 7 OR 8 OR 9)	23	213	84
14	5 AND (6 OR 7 OR 8 OR 9)	20	147	117
Unique references identified in database		**123**	**613**	**425**

Table S2a: Summary of included *in vivo* animal studies.

Ref	Authors	Location	Animal model	Sugar used	Timescale and dosage	Overview of methods	Outcome measures	Key results and conclusions
25	Oku et al., 2014	Japan	Wistar rats	SOR	0.0495g single oral dose.	Test solutions (0.45g sucrose, 0.45g sucrose + 0.0495g SOR, 0.45g sucrose + 0.0495g L-SOR) given orally in solution, plasma glucose and insulin measured every 30 minutes for 3 hours.	Plasma glucose and insulin.	With SOR: elevation of plasma glucose was suppressed after 30 and 60 minutes. Plasma insulin was also lower at 30 and 60 minutes in SOR group compared to sucrose-only group.
26	Yamada et al., 2014	Japan	Sprague-Dawley rats	SOR	3% of diet for 28 days.	2 groups (n=7) given control diet or 3% SOR (replacing cornstarch) diet ad libitum for 28d. BW monitored. At sacrifice, non-fasting blood collected for biochemical analysis and organ weights measured.	BW and composition, organ and tissue weights, serum insulin, glucose, lipids and biochemical parameters.	No significant differences observed in BW, food intake or adipose tissue weights. Cecum weight increased and cecal pH reduced in SOR group. Serum insulin reduced, but no significant change in serum glucose, in SOR group. Uric acid and aspartate aminotransferase reduced in SOR group. No other significant differences observed.
27	Yamamoto et al., 2017	Japan	STAM mice (C57BL/6J injected with STZ then fed high fat diet to induce NASH)	ALL	2% of high fat diet for 3 weeks.	2 groups (n=5-8) of STAM mice given high fat diet or high fat diet with 2% ALL. Control group of C57BL/6J mice given normal diet. BW monitored. At sacrifice, organ weights and serum biochemical parameters measured. Liver sections examined microscopically.	BW, liver weight. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride and glucose. Liver injury (NAFLD activity score)	STAM mice had reduced BW, increased liver weight, and 7-fold higher fasting serum glucose compared to control mice. No significant differences were observed between ALL-fed STAM and control STAM groups. Serum ALT and AST were increased in STAM mice compared to control, indicating liver injury. ALT level was reduced in ALL-fed STAM group compared to control STAM group, but was still significantly higher than control group. No significant differences in serum triglyceride were seen between any groups. Hepatic lipid accumulation was increased in STAM mice compared to control, but in

								STAM mice given ALL this was completely suppressed. Scores of hepatic pathology were reduced in ALL-fed STAM mice compared to the STAM group.
41	Do et al., 2019	Korea	Male C57BL/6J mice	PSI	5% of high fat diet for 8 weeks.	2 groups (n=8), given either a high fat diet with 5% PSI (replacing sucrose), or an isoenergetic amount of high fat diet. BW monitored. At sacrifice body composition and organ weights measured, plasma, hepatic and fecal lipids, plasma adipokines and cytokines and hepatic enzyme activities measured. Liver histopathology examined.	BW and composition, feed efficiency ratio, plasma adipokines and cytokines, plasma, hepatic and fecal lipids, organ weights and histopathology, hepatic enzyme activities.	With PSI: lower weight gain and feed efficiency ratio. Reduced adipose tissue. Reduced liver weight, increased kidney and muscle weight. Reduced plasma glucose, resistin and leptin. Reduced fecal fatty acids and triglycerides, reduced plasma triglycerides, reduced hepatic triglycerides, fatty acids and cholesterol. Reduced activities of G6PDH, PAP, ACAT but no significant difference in FAS or enzymes involved in β-oxidation. Smaller and fewer lipid droplets in liver, smaller adipocytes.
42	Han et al., 2016	Korea	Male C57BL/6J mice	PSI	5% of high fat diet for 16 weeks.	6 groups (n=10), given normal diet (control), high fat diet (control) or high fat diet with 5% PSI, erythritol, glucose or fructose (replacing sucrose). BW monitored. At sacrifice body composition measured, plasma, hepatic and fecal lipids, plasma adipokines and hepatic enzyme activities measured.	BW and composition, plasma adipokines, plasma, hepatic and fecal lipids, hepatic enzyme activities.	With PSI: lower weight gain and feed efficiency ratio. Reduced plasma leptin and resistin. Reduced liver weight, increased kidney and muscle weight. Reduced white adipose tissue. Values in PSI group close to normal diet control. Reduced plasma triglycerides, total cholesterol and LDL-cholesterol. Reduced hepatic free fatty acids, triglycerides and cholesterol. Reduced fatty acid synthase activity and increased β-oxidation activity in adipose tissue.
43	Hossain et al., 2011	Japan	OLETF rats	PSI	5% solution in drinking water for 14 weeks.	OLETF rats (n=15 per group) given plain water, 5% PSI solution or 5% glucose solution. Blood glucose measured periodically, OGTT at 14 weeks, liver and pancreas histology at sacrifice, immunostaining of	BW and composition, AUC for glucose and insulin in OGTT, hepatic steatosis, pancreas morphology.	With PSI: lower weight gain and food intake. Reduced abdominal fat. Reduced AUC for glucose and insulin. Although periodical blood glucose increased gradually in OLETF control and glucose-fed groups, it was static in LETO control and PSI-fed OLETF rats from 3 weeks.

						liver tissue for glucokinase (GK).		GK translocation to cytoplasm impaired in OLETF control rats, but no significant difference between LETO control, PSI-fed and glucose-fed groups.
44	Han et al., 2020	Korea	Male C57BL/6J mice	PSI	5% of high fat diet for 16 weeks.	4 groups (n=10) given normal diet, high fat diet, high fat diet + 5% PSI or 5% erythritol (substituted for sucrose). BW monitored and energy expenditure measured. At sacrifice body composition measured, plasma lipids and adipokines measured, gut microbiota and short chain fatty acids measured.	BW and composition, plasma lipid profile, plasma adipokines, energy expenditure, gut microbiota and short chain fatty acids. Liver histopathology.	With PSI: lower BW compared to high fat diet and erythritol groups. Adipose tissue weight dramatically reduced compared to high fat diet group. Total cholesterol, HDL and non-HDL cholesterol decreased compared to high fat diet. Fatty acid synthase activity reduced and β-oxidation activity increased in white adipose tissue. Significant increase in energy expenditure. PSI and normal diet groups showed higher diversity in gut microbiota than high fat diet group. Reduced accumulation of lipid droplets in hepatic tissue with PSI compared to high fat diet group. Fibrotic tissue absent in normal diet and PSI groups, present in high fat diet and erythritol groups.
45	Han et al., 2020	Korea	Male C57BL/6J mice	PSI	5% of high fat diet for 16 weeks.	3 groups (n=9) given normal diet, high fat diet or high fat diet + 5% PSI (substituted for sucrose). BW monitored. At sacrifice body composition and plasma inflammatory markers measured. Expression of genes in liver and white adipose tissue measured.	BW and composition, plasma inflammatory markers, up/downregulation of gene expression in liver and white adipose tissue, gut microbiota.	With PSI: reduced BW and adipose tissue weight, no significant difference in food intake. Reduced hepatic lipid content. PSI supplementation reversed the differences in organ weights seen with high fat diet. Groups of up/downregulated genes identified as associated with obesity-related inflammation, reduced to near normal-diet levels with PSI. PSI diet increased beneficial bacteria Lactobacillus and Coprococcus.
46	Itoh et al., 2015	Japan	C57BL/6J mice (*ob/ob* and wild-type)	PSI	2.5% or 5% of diet for 15 weeks.	3 groups (n=14) of *ob/ob* mice given 0, 2.5 or 5% PSI, control group (wild-type) given normal diet. BW monitored,	BW and composition, hepatic steatosis.	BW gain lower in 5% PSI group than in *ob/ob* control. Liver weight, visceral fat and fat mass lower in PSI groups than *ob/ob* control, with no difference in fat-free mass. Livers of

						hepatic steatosis and fat deposition measured by MRI. Body composition and histological examination at sacrifice.		*ob/ob* mice showed signs of hepatic steatosis not present in wild-type mice- this was inhibited in 5% PSI group.
47	Son et al., 2019	Korea	BALB/c mice	TAG	25mg every other day for 3 weeks, with or without 109 cfu/ml *Lactobacillus rhamnosus GG* (LGG), by oral gavage.	4 treatment groups (n≥3) given PBS, TAG, LGG or LGG+TAG for 3 weeks. In 3rd week dextran sulphate sodium (DSS) added to drinking water to induce colitis.	BW, food intake and colitis disease activity index assessed daily, fecal microbiota analysed and classified. At sacrifice, morphological and histological analysis of colon undertaken, serum IL-6, IL-10 and TNFα determined.	DSS induced colitis symptoms (reduced BW, diarrhoea, bloody stools), as well as reduced colon length, irregular crypt structure, inflammatory cell infiltration, increased serum IL-6, IL-10 and TNFα. Group given LGG+TAG were less susceptible to colitis than LGG group or TAG group- had higher BW, higher food intake and reduced diarrhoea scores. BW was higher in TAG, LGG and LGG+TAG groups than in DSS group. In all 3 'treatment' groups, the reduced colon length and acute inflammation seen with DSS treatment were attenuated, with a synergistic effect with LGG+TAG. All 3 treatments reduced serum IL-6 and IL-10, but only LGG+TAG reduced serum TNFα. The effects of DSS-induced colitis on the intestinal bacterial communities were reduced in the LGG+TAG group.
48	Chen et al., 2017 ABSTRACT ONLY	China	Wistar rats	PSI	5% of diet for 4 weeks.	5 groups given 5% glucose, fructose, cellulose or PSI. At sacrifice, blood lipid profile, tissue morphology and genes involved in lipid metabolism measured.	BW, body fat, plasma lipid profile, expression of genes related to lipid metabolism.	With PSI: lower weight gain, reduced epididymal fat, smaller adipocyte size, improved blood lipid profile and antioxidant level. Increased expression of succinate dehydrogenase and hepatic lipase.
49	Chen et al., 2019[j]	China	Male Wistar rats	PSI	5% of diet for 4 weeks.	5 groups (n=6) given AIN-76A diet or the same diet with CHO partially replaced with 5% glucose, fructose, cellulose or PSI. BW measured every two days. At	BW, body fat, plasma lipid profile, hepatic gene expression.	With PSI: lower weight gain, reduced abdominal and epididymal fat, reduced plasma triglyceride, free fatty acids and LDL cholesterol compared to control. Increased

					sacrifice body fat, plasma lipids and hepatic gene expression measured.		hepatic expression of catalase and succinate dehydrogenase.
50	Pratchayasakul et al., 2020 ABSTRACT ONLY	Thailand	Rats	PSI	1.9g per kg BW per day for 12 weeks	Rats (n=56) fed control diet or HFD for 12 weeks. HFD-fed rats then given PSI or metformin for 12 weeks. Cognition and brain parameters determined at 24 weeks.	Brain oxidative stress, mitochondrial dysfunction, microglial hyper-activation, apoptosis, insulin insensitivity, hippocampal synaptic dysfunction, cognitive decline.	All stated cognition and brain parameters were observed in HFD rats. Both PSI and metformin attenuated brain oxidative stress, mitochondrial reactive oxygen species production and hippocampal apoptosis and improved learning. Metformin gave greater improvement than PSI in brain mitochondrial dysfunction and microglial hyper-activation, and improved both learning and memory.
51	Iwasaki et al., 2018	Japan	C57BL/6J mice (HFD-induced obese, *GLP1r* knockout)	PSI	0.3, 1 or 3g per kg BW single dose.	PSI given orally or by intraperitoneal injection. Food intake monitored. Blood glucose, insulin and GLP-1 measured before and after intraperitoneal glucose injection.	Food intake, GLP-1 secretion, response in glucose tolerance test.	Oral PSI administration decreased food intake for 6 hours without aversion. Cumulative intake normalised after 24 hours. This effect was not seen in *GLP1r*-knockout mice, nor when PSI given by injection. Oral PSI administration 60 minutes before glucose injection attenuated increases in blood glucose at 15, 30 and 60 minutes without affecting basal blood glucose, and increased insulin release at 15 minutes.
					1g per kg BW per day for 10 days.	PSI given orally at onset of light or dark period. Food intake monitored, blood glucose and insulin measured before and after intraperitoneal glucose injection.		Daily oral PSI administration at onset of light period reduced food intake during light period, reduced fasting blood glucose and attenuated hyperinsulinaemia in diet-induced obese mice. Blood glucose and insulin after glucose injection were also reduced. Effects were not significant in *GLP-1r* knockout mice, nor if PSI was given at onset of dark period.
54	Yagi and Matsuo, 2009	Japan	Wistar rats	PSI	3% of diet for 12-18 months.	2 groups (n=18) given diet with 3% sucrose or D-psi ad libitum. BW, food intake and	BW, organ weight and morphology, haematological and	BW not significantly different between groups at 12 months but reduced in PSI group at 18 months. With PSI: liver and

						symptoms of toxicity monitored. At sacrifice, organ weight and morphology examined, blood biochemical parameters measured.	biochemical measurements.	kidney weights increased at 12 and 18 months, brain, lung and pancreas and cecum weights increased at 18 months, intra-abdominal adipose tissue weight reduced at 18 months. No significant differences in chemical values. Fatty degeneration & hepatocellular fibrosis observed in PSI but not sucrose group, slight increase in pathological lesions in liver at 18 months. Overall effects not suggestive of overt PSI toxicity.
58	Baek et al., 2010	Korea	Male C57BL/6J *db/db* mice	PSI	200mg per kg BW for 4 weeks.	4 groups of *db/db* mice (n=10) given water, PSI, D-glucose or fructose orally. Wild-type control group given water. BW, plasma glucose and insulin, plasma, liver and fecal lipids measured. OGTT at 28 days.	BW, plasma glucose and insulin, AUC for glucose in OGTT, lipid profiles.	With PSI: lower weight gain, lower plasma glucose compared to all groups. No significant difference in AUC for glucose in OGTT compared to control. Lower liver triglyceride and total cholesterol, no significant difference in plasma or fecal lipids.
59	Hossain et al., 2012	Japan	OLETF rats	PSI	5% solution in drinking water for 13 weeks.	OLETF rats (n=15 per group) given plain water, 5% PSI solution or 5% glucose solution. BW and composition monitored. Periodical fasting blood glucose and OGTT measurements. At sacrifice serum adipokines measured and adipose tissue and pancreas morphology examined.	BW and composition, AUC for glucose in OGTT, degree of insulin resistance (HOMA), histopathology of pancreatic islets, adipose tissue morphology.	With PSI: lower weight gain with no change in food intake. Reduced total fat and % fat mass. Reduced fasting blood glucose and AUC for glucose in OGTT. Reduced insulin resistance. OLETF control group had evidence of fibrosis and fatty degeneration in islets, absent in PSI-fed group.
60	Hossain et al., 2015	Japan	OLETF rats	PSI	5% solution in drinking water for 60 weeks.	OLETF rats (n=10 per group) given 5% PSI solution or normal drinking water. LETO control rats fed normal diet. Fasting and postprandial	AUC for glucose in OGTT, degree of insulin resistance (HOMA), plasma lipids, cytokines and	With PSI: reduced postprandial blood glucose from 35 weeks. Reduced plasma insulin and reduced insulin resistance (PSI-fed OLETF similar to LETO rats). Reduced inflammatory cytokines. Fibrotic,

						blood glucose measured periodically. OGTT, plasma lipids, adipokines and cytokines measured. At sacrifice adipose tissue and pancreas morphology examined.	adipokines, histopathology of pancreatic islets, adipose tissue morphology.	disorganised islets observed in OLETF control group, much less prominent and severe in PSI-fed group.
61	Kanasaki et al., 2019	Japan	Golden Syrian hamsters	PSI	3% of normal diet or high fat diet for 8 weeks.	2 groups (n=8) given normal diet with or without 3% PSI. 2 groups (n=8) given high fat diet for 4 weeks then high fat diet with or without 3% PSI for 4 weeks. BW monitored, serum glucose, insulin, lipids and PCSK9 measured.	BW, serum glucose, insulin, lipids and PCSK9.	Normal diet hamsters: no significant differences in BW, serum glucose or insulin. Reduced cholesterol in VLDL and medium LDL, increased cholesterol in very small LDL and HDL, reduced LDL/HDL ratio. High fat diet hamsters: Reduced cholesterol in LDL, particularly medium and small LDL. Reduced LDL/HDL ratio. Both groups had reduced serum PCSK9 with PSI compared to control. PSI seems to improve cholesterol metabolism, possibly by reducing serum PCSK9.
62	Ochiai et al., 2013	Japan	Wistar rats	PSI	5% of diet for 8 weeks.	Rats fed high sucrose diet for 7 weeks, then 4 groups (n=8) given high starch diet with PSI (NP) or cellulose (NC) or high sucrose diet with PSI (SP) or cellulose (SC). BW monitored, serum lipids, insulin and leptin measured, liver glycogen and lipids measured at sacrifice.	BW, serum lipids, insulin and leptin, hepatic CHO and lipid content.	With PSI, reduced BW gain and adipose tissue weight. For rats on high sucrose diet, PSI reduced serum HDL and LDL cholesterol and increased non-esterified fatty acids. No significant differences in serum glucose, insulin or leptin. Hepatic triglyceride and cholesterol higher with PSI in high-starch diet groups, but no significant differences in hepatic glycogen.
63	Ochiai et al., 2017	Japan	Wistar rats	RSS or modified glucose syrup (MGS)	30% of diet for 8 weeks.	4 groups (n=8) given high sucrose control, HFCS, RSS or MGS in ad libitum diet. Sucrose (approx. 30% of diet w/w) replaced with HFCS, RSS (PSI 1.5%, SOR 2.9%, TAG/ALL	BW & composition, serum fasting glucose, insulin, triglycerides, total	With RSS, reduced adipose tissue weight and body fat percentage compared with sucrose group. Reduced food efficiency with RSS and MGS. Increased liver and kidney weights

						1.1% of diet) or MGS (PSI 3.3% of diet) for 8 weeks. Food intake and BW monitored. At sacrifice, organ weights recorded and biochemical analysis of serum conducted.	cholesterol. Liver lipid profile.	with both RSS and MGS compared to sucrose. No significant differences in blood biochemical parameters.
64	Pongkan et al., 2020	Thailand	Male Wistar rats	PSI	1.9g per kg BW per day (3% solution in drinking water) for 12 weeks	4 groups (n=6). 3 groups fed HFD for 12 weeks (control group fed ND). HFD groups then given PSI, metformin (300mg/kgBW/day) or sterile drinking water for 12 weeks. Cardiac function measured at 12 and 24 weeks. Plasma glucose, insulin and lipids measured and insulin resistance estimated, OGTT carried out, markers of cardiac dysfunction measured at 24 weeks.	Electrocardiograph for cardiac function, heart rate variability, cardiac mitochondrial function and oxidative stress, plasma glucose, insulin and cholesterol, homeostasis model assessment of insulin resistance, plasma and cardiac malondialdehyde.	No significant difference in food intake per body weight, but HFD animals had increased body weight and visceral fat. No significant difference in body weight or visceral fat with PSI compared to HFD group. PSI and metformin both attenuated insulin resistance, metformin improved lipid profile but no significant difference in lipids with PSI. Both PSI and metformin improved cardiac function, reduced cardiac oxidative stress, reduced evidence of cardiac mitochondrial dysfunction and reduced levels of cardiac apoptotic proteins compared to HFD group.
65	Nagata et al., 2015	Japan	Sprague-Dawley rats	PSI	3% of diet for 4 weeks.	2 groups (n=24) given control diet or 3% PSI diet for 4weeks then 5-6 animals sacrificed every 6h over 24h without fasting. 2 groups (n=8) fed as above and energy expenditure measured over 24hrs.	Serum glucose, insulin, lipids and leptin, hepatic enzyme activity, gene expression in liver, small intestine, muscle and adipose tissue. Total energy expenditure, fat oxidation and CHO oxidation.	With PSI: reduced BW and food intake. Reduced serum insulin, leptin and total cholesterol at some timepoints, no significant difference in serum glucose. With PSI: decrease of G6PDH and ME (sig at 9am). Expr of PPARa sig higher in liver, Exp of MTP sig lower. . Total EE per kg BW sig higher during late light period Fat ox sig enhanced and carb ox sig reduced during dark period.
66	Iida et al., 2013	Japan	Male Wistar rats	RSS	30% of diet (replacing	3 groups (n=10), given diets containing 60% starch, 30% starch:30% HFCS or 30%	BW and composition, plasma glucose,	With RSS: Lower weight gain, reduced intra-abdominal fat (dose-dependent effect).

					50% of starch) for 8 weeks.	starch:30% RSS. BW monitored. At sacrifice, body composition measured, fasting blood taken and plasma glucose, insulin, lipids and adipokines measured.	insulin, lipids and adipokines.	Fasting blood glucose reduced in HCFS and RSS groups compared to starch group. Plasma insulin reduced in RSS group compared to HCFS and starch. No differences in plasma total cholesterol or triglycerides. Leptin in RSS group lower than starch, in HCFS group higher than starch.
67	Iga et al., 2010	Japan	Wistar rats	ALL	Acute administration study: 15-25g per kg BW in single dose.	Acute administration study: rats (n=4 per group) given single dose after 12h fast, fasted for 12h then observed for 48h.	Acute administration study: number of deaths, LD50.	Acute administration study: LD50=20.5g per kg BW.
					Subchronic feeding study: 0-3% in food for 6 months.	Subchronic feeding study: rats (n=10 per group) given ALL in food. BW and food intake monitored. At sacrifice, haematological parameters and tissue weights measured.	Subchronic feeding study: BW, food intake, haematology, organ and tissue weights.	Subchronic feeding study: BW and feed efficiency ratio reduced in 3% ALL group compared to control. Lungs, soleus and gastrocnemius muscle weights reduced in 3% ALL group. No significant differences in haematological parameters. ALL concluded to be non-toxic in rats.
68	Nagata et al., 2018	Japan	Sprague-Dawley rats	PSI, TAG, SOR	3% of diet for 4 weeks.	5 groups (n=6) given AIN-93G diet with or without 3% rare sugar or fructose replacing cornstarch. Sacrificed without fasting. Serum and fecal lipids, hepatic enzyme activity and gene expression in liver and small intestine measured.	Serum lipids, faecal lipids, hepatic enzyme activity, gene expression in liver and small intestine.	No significant differences in BW, feed efficiency ratio or liver weight. TAG-fed group had increased serum free fatty acids compared to fructose-fed group. Faecal excretion of fatty acids was decreased by PSI but increased by SOR. Activity of fatty acid synthase was decreased by PSI but increased by TAG. G6PDH and PAP expression was decreased in PSI-fed group compared to control. Rare sugars affect lipid metabolism differently in rats.
69	Collotta et al. 2018	Italy	C57BL/6J mice	TAG	30% of solid diet or 30% syrup drink for 24 weeks.	5 groups (n=6) given a 30% TAG or fructose solid diet, a control diet with 30% TAG or fructose syrup or a control diet with water. BW and	BW, fasting glucose, HbA1c. Plasma lipids, leptin, inflammatory markers and MDA	Fructose-fed groups had higher weight gain, increased plasma fasting glucose and %HbA1c, increased leptin, serum triglyceride and LDL and decreased HDL, and a 3-fold increase in MDA. No significant differences

						glycaemia monitored. Plasma lipids, adipokines, cytokines and markers of myocardial oxidative stress measured.	(marker of myocardial oxidative stress) measured.	were seen with TAG compared to control. Both fructose and TAG caused increased TNF-α and IL-1β, but the increase with TAG was half that of fructose.
70	Police et al., 2009	USA	C57BL/6J *LDLr-/-* mice	TAG	30% of diet for 16 weeks.	2 groups (n=12, equal m/f) given TAG or sucrose diet for 16weeks. Control (n=10) given standard murine diet. TAG/sucrose introduced gradually over 3 weeks before 16 week feeding period. BW and food intake measured. At sacrifice, organ weights measured, blood biochemistry analysed. Aorta and adipose tissue morphology examined.	BW and composition, fasting blood glucose, plasma lipids and lipoproteins. Atherosclerotic lesion area of aorta, morphology of adipose tissue, macrophage infiltration.	High sucrose diet group had increased BW, energy intake, adipose tissue mass and adipocyte size, TAG-fed group similar to control. Total cholesterol, VLDL and LDL increased with both sucrose and TAG compared to control, levels in the sucrose group higher than the TAG group. Atherosclerotic lesion area increased with sucrose compared to TAG and control, and in females in the TAG group compared to control. Macrophage positive immunostaining seen in adipose tissue and aortic root of sucrose but not control or TAG groups. TAG as a CHO source leads to increased total cholesterol and atherosclerosis, but significantly less than sucrose.
71	Choi et al., 2018	Korea	Male C57BL/6J mice	PSI	3% of diet (PSI substituted for sucrose in high fat diet), with or without probiotics, for 12 weeks.	7 groups (n=10), given high fat diet and two different probiotics with or without PSI. Control group given normal diet. At sacrifice, after 16h fast, BW and composition, plasma lipids, adipokines and cytokines, hepatic lipids, enzyme activity and gene expression measured.	BW and composition, plasma and hepatic lipids, plasma adipokines and cytokines, hepatic enzyme activities & expression.	With PSI: lower weight gain, reduced white adipose tissue. PSI and probiotics worked synergistically. Reduced plasma leptin, resistin and IL-1β in all groups fed PSI. Reduced activities of enzymes involved with fatty acid synthesis; increased activity of enzymes involved in β-oxidation in all groups fed PSI.
72	Chung et al., 2012	Korea	Male Sprague-Dawley rats	PSI	2.5 or 5% of diet for 52 days.	Rats (n=10 per group) fed high fat diet for 4weeks to induce obesity, then either switched to normal diet or	BW and composition, feed efficiency ratio, plasma lipids, organ	With PSI: lower weight gain (dose-dependent), food efficiency ratio and fat accumulation (greater effect in animals fed normal diet). Increased serum total

						kept on high fat diet with 5% sucrose, 5% eryrthritol or 2.5/5% PSI for 52 days. BW monitored, at sacrifice plasma lipids, body composition and organ weights measured.	weights and histopathology.	cholesterol, LDL-cholesterol and HDL-cholesterol and liver weight in PSI-ND group compared to ND group. No apparent differences in liver histopathology.
73	Kim et al., 2017	Korea	C57BL/6J *ob/ob* mice	PSI	5% of diet (replacing sucrose) for 12 weeks.	2 groups (n=15) given AIN-93G diet or same diet with half of sucrose replaced with PSI (equivalent to 5% of diet). BW monitored, at sacrifice body composition, plasma lipids measured, adipose tissue morphology and gene expression examined.	BW and composition, plasma lipids, adipose tissue histology and gene expression.	With PSI: reduced final BW, white adipose tissue weight and adipocyte size. Lower plasma total cholesterol, LDL cholesterol and LDL/HDL ratio. No significant differences in triglycerides, free fatty acids or HDL cholesterol. Reduced expression of markers of inflammation (TNFα, IL-6, MCP-1) and adipogenesis (PPARs, SREBP-1c, LPL, FAS), increased expression of markers of lipolysis (HSL) and beta oxidation (CPT-1).
74	Shintani et al., 2017	Japan	Wistar rats	RSS	RSS diluted to give 7% fructose (equates to around 1.4% PSI in solution) in drinking water for 10 weeks.	3 groups (n=10), given water, HFCS or RSS. BW monitored. OGTT (2g per kg BW glucose) and insulin tolerance test carried out at 8 weeks. At 10 weeks, 4 rats per group sacrificed before and 30 min after a glucose load and livers examined for glucokinase translocation. At sacrifice, tissue weights measured and liver analysed for glycogen content.	BW and composition, AUC for glucose and insulin in OGTT, hepatic glucokinase distribution before and after glucose load, liver glycogen content.	With RSS: reduced weight gain, decreased total abdominal fat compared to control. (HFCS had no effect on BW but increased abdominal fat). RSS decreased AUC for glucose and insulin in OGTT compared to control (AUC for glucose was increased by HFCS). Insulin sensitivity increased by RSS (decreased by HFCS). Hepatic glycogen before glucose load was 3-fold higher with RSS than control or HFCS. Glycogen in HFCS group was reduced after glucose load compared to control and RSS. GK translocation to cytoplasm was increased with RSS compared to HFCS or control, both before and after glucose load.
76	Huang et al., 2018	China	Wistar rats	PSI	unknown	5 groups (n=?), given normal diet or supplemented with	BW, plasma lipids, liver histology,	With PSI: reduced BW, serum triglycerides, free fatty acids and LDL-cholesterol.

	ABSTRACT ONLY					PSI, cellulose, glucose or fructose.	hepatic gene expression.	Increased expression of PPARα, reduced expression of fatty acid synthase.
78	Williams et al., 2013	USA	Male Sprague-Dawley rats	TAG	0, 0.6, 2 or 6g per kg BW, single dose by oral gavage along with ^{14}C-labelled fructose	5 groups (n=8) given oral gavage containing 2g/kg ^{14}C-labelled fructose and varying doses of TAG. Blood samples from femoral vein catheter at regular intervals for 60 mins.	Blood glucose, plasma scintillation count to determine ^{14}C fructose.	2 and 6g/kg TAG reduced AUC of fructose absorption by 26 and 30% respectively. No difference in blood glucose with 0.6 or 2g/kg TAG, but 6g/kg TAG caused increased blood glucose from 30 mins (this attributed to stress caused by malabsorption effects from large doses of fructose and TAG)
88	Hayakawa et al., 2018	Japan	Male C57BL/6J mice	PSI	0.5 – 2g per kg BW single oral dose.	PSI, resistant maltodextrin, dextrin, fructose or water administered orally, with or without inhibitors of glucose/fructose transport. Plasma GLP-1, portal GLP-1 and GIP measured. Luminal contents measured at 60 and 150min after administration.	Plasma and portal GLP-1 and GIP, rate of PSI absorption, with and without inhibitors of glucose/fructose transport.	Oral PSI administration increased plasma GLP-1 in dose-dependent manner, and stimulated GLP-1 but not GIP in the portal vein. Intraperitoneal injection of PSI did not stimulate GLP-1. PSI absorption was slower than glucose (25% PSI remaining in stomach after 60 mins compared to 2.6% with glucose). Inhibitors of SGLT1 and sweet receptor did not lower PSI-induced GLP-1 secretion.
91	Williams et al., 2015	USA	ApoE knockout mice	TAG	34% of diet by weight (entirely replacing sucrose) for 8 weeks.	5 groups (n=8), given standard diet, Western diet (high fat & sucrose), Western diet with TAG, Western diet with BSN723 or Western diet with TAG and BSN723. BW monitored. At sacrifice body composition and evidence of atherosclerotic plaques measured.	BW and composition, serum lipids, extent of atherosclerosis.	TAG groups on Western diet showed lower BW gain than control Western diet group. Addition of TAG prevented the increase in adipose tissue caused by Western diet. Surface area of atherosclerotic lesions was greater in Western diet compared to standard diet; this was inhibited in TAG groups. The increase in serum cholesterol as a result of Western diet was significantly less in the groups receiving TAG.

Reported differences are statistically significant unless stated otherwise. BW: body weight, PSI: D-psicose, TAG: D-tagatose, SOR: D-sorbose, ALL: D-allose, RSS: rare sugar syrup, HFCS: high fructose corn syrup, CHO: carbohydrate, AUC: area under curve, OGTT: oral glucose tolerance test, LDL: low density lipoprotein, HDL: high density lipoprotein, HFD: high fat diet, TNF-α: tumour necrosis factor α, NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, ND: normal diet, IL: interleukin, OLETF: Otsuka Long-Evans Tokushima Fatty, LETO: Long-Evans Tokushima Otsuka.

Table S2b: Summary of included studies in human subjects

Ref	Authors	Location	Study population	Type of study	Sugar used	Timescale and dosage	Overview of methods	Outcome measures	Key results and conclusions
28	Hayashi et al., 2010[j]	Japan	Borderline diabetes (fasting blood glucose 100-126mg/dl) (n=15) or healthy (n=11) volunteers Age 22-69yrs	Randomized placebo-controlled, double-blind parallel-group study	PSI	Meal-loading study: 5g, with meal	Meal-loading study: 5g PSI given with meal, blood taken at 30min intervals for 120 min.	Meal-loading study: plasma glucose, AUC glucose for meal.	Meal-loading study: Plasma glucose was significantly lower at 30 and 60 min with all subjects after PSI meal compared to control meal. AUC for glucose (mg/ml/dl) for test meal 578.8+/-2509.9, for control meal 6482.1+/-2953.8 ($p<0.01$ for difference) Plasma glucose and AUC glucose significantly reduced with PSI, overall and in subjects with borderline diabetes but not in subgroup of healthy subjects.
						Safety study: 5g, 3x daily for 12 weeks	Long-term safety study: 5g with meals for 12 weeks. Fasting urine & blood taken at 2, 4, 8 and 12 weeks.	Long-term safety study: reported adverse effects.	Long-term safety study: No significant differences observed in nutritional intake. No persistent or serious adverse effects.
29	Noronha et al., 2018	Canada	Subjects (n=24) 12m, 12f with T2D (controlled with diet or OHAs, not insulin) Age 66+/-1.2yrs BMI 27+/-0.9kg/m^2	Randomized controlled, double-blind crossover acute feeding equivalence	PSI	0, 5 or 10g in 75g glucose solution	75g OGTTs with 0, 5 or 10g fructose or PSI added (6 visits 1 week apart). Blood taken every 30 minutes for 120 minutes, plasma glucose and insulin measured.	iAUC for plasma glucose, iAUC for plasma insulin, absolute maximum concentrations (C_{max}) for glucose and insulin.	With 10g PSI, significantly reduced iAUC for glucose (mol*min/l): 5g PSI -48.1 (SE24.7, p=0.051) 10g PSI -601.1 (SE24.7, p=0.015) Significant linear dose response gradient for reduction. Significantly reduced absolute mean plasma glucose with 5g. Equivalence test shows results within 20% equivalence boundaries, and reductions in glycaemic response were modest compared to oral antihyperglycaemic agents e.g. acarbose.

30	Matsuo and Lu, 2011 ABSTRACT ONLY	Japan	Healthy subjects, (n=44) 15m, 29f	no details available	PSI	6g, single dose before meal	6g PSI or fructose given with normal lunch. Blood taken regularly for 120 minutes after meal.	Plasma glucose and insulin.	Significantly lower glycaemic response after PSI compared with fructose.
31	Yamada et al., 2018 ABSTRACT ONLY	Japan	Healthy subjects (three trials, n=6, n=14, n=10)	Randomized , controlled single-blind crossover	RSS	0, 30 or 50% of sucrose in test food/drink, single dose	Half of sucrose in drink (n=6) or food (n=14) replaced with RSS, or 0, 30 or 50% sucrose replaced with RSS in test drink (n=10). Blood collected at 5 time-points before and after ingestion.	iAUC for plasma glucose and insulin.	All foods and drinks containing RSS showed significantly reduced iAUC for glucose compared to sucrose control. No significant changes in iAUC for insulin were observed.
33	Kwak et al., 2013	Korea	Healthy (n=52) and hyper-glycaemic (n=33) Korean subjects	Randomised controlled, double-blind crossover	TAG	5g, single dose before meal	5g or 10g TAG or placebo (sucralose or erythritol) consumed before standard meal (356kcal, of which 59.57% - 53g - was CHO). Blood taken every 30 mins for 120 mins	Plasma glucose and insulin.	In subjects with hyperglycaemia, TAG significantly reduced AUC for glucose (4% decrease) and plasma glucose at 120 mins compared to placebo. With high dose TAG in healthy subjects there was a non-significant reduction in blood glucose, and significantly lower AUC for insulin and c-peptide.
34	Nakamura et al., 2017 ABSTRACT ONLY	Japan	Healthy subjects (n=10, n=12)	Randomized placebo-controlled, single blind crossover	RSS	0-35g single dose	50g tolerance test: 50g sucrose replaced with RSS in ratio 0:10, 3:7, 5:5, 7:3. 10g tolerance test:	Blood glucose and insulin. AUC for glucose and insulin.	Significant reductions in AUC for glucose were seen with RSS:sucrose in ratios of 5:5 and 7:3. Significant reductions in AUC for insulin were seen with ratios of 3:7, 5:5 and 7:3.

							10g sucrose or 5g RSS with 5g sucrose. Blood glucose and insulin measured.		
35	Tanaka et al., 2020 ABSTRACT ONLY	Japan	Young, healthy Japanese women	Single-blind, randomised crossover	PSI	0, 1.8, 3.6 or 12.5g single dose in 50g chocolate	Blood taken before consumption of chocolate and at 1, 2, 4 and 6hours afterwards.	Free fatty acids, blood glucose and insulin and GLP-1 measured.	Post-prandial free fatty acids were increased and glucose and insulin decreased after consuming chocolate containing PSI compared to placebo. Enhanced GLP-1 secretion observed after PSI intake.
36	Han et al., 2018	Korea	Overweight Asian subjects (n=144) Age 20-40yrs BMI >/= 23	Randomised double-blind placebo-controlled parallel study	PSI	4g or 7g, 2x daily for 12 weeks.	Placebo (sucralose) or PSI given 2x daily after meals. Anthropometric measurements and blood samples taken every 4 weeks.	BMI, body composition, fasting blood glucose, HbA1c and lipids.	With PSI: significantly lower body fat percentage, body fat mass and BMI. Significantly lower total fat area, particularly subcutaneous fat, in high-dose PSI group compared to placebo. No significant differences observed in plasma lipids, fasting blood glucose, HbA1c or leptin.
37	Donner et al., 2010	USA	Subjects (n=8, 4m, 4f) with T2D- poor glycaemic control. Age 50.7 +/- 10.9yrs BMI 36.7 +/- 5.1kg/m^2	Pilot intervention study, no control, no blinding.	TAG	15g, 3x daily for 14 months.	TAG taken with regular, non-standardised meals. Body weight and vital signs recorded and blood taken every 2 months. Subjects questioned about adverse effects.	Body weight, plasma glucose, insulin, glycated haemoglobin, lipids.	Significant weight loss compared to baseline after 12 months (p=0.01). Significant overall decrease in glycated haemoglobin, but this was non-significant when two patients who had started or increased medication were excluded. Significant increases in HDL-cholesterol, no changes in plasma triglycerides, total cholesterol or LDL-cholesterol. All subjects experienced transient mild GI symptoms in the first two weeks, these were persistent in one subject.
38	Ensor et al., 2014	USA and India	Asian subjects (n=161) with T2D controlled	Prospective randomised parallel	TAG	2.5, 5 or 7.5g 3x daily	After 8-week stabilisation period subjects	Reduction in HbA_{1c} , fasting blood glucose	Treatment success (defined as a 0.5 or greater decrease in %HbA1c) was greatest for 7.5g dose, but difference between doses was not statistically

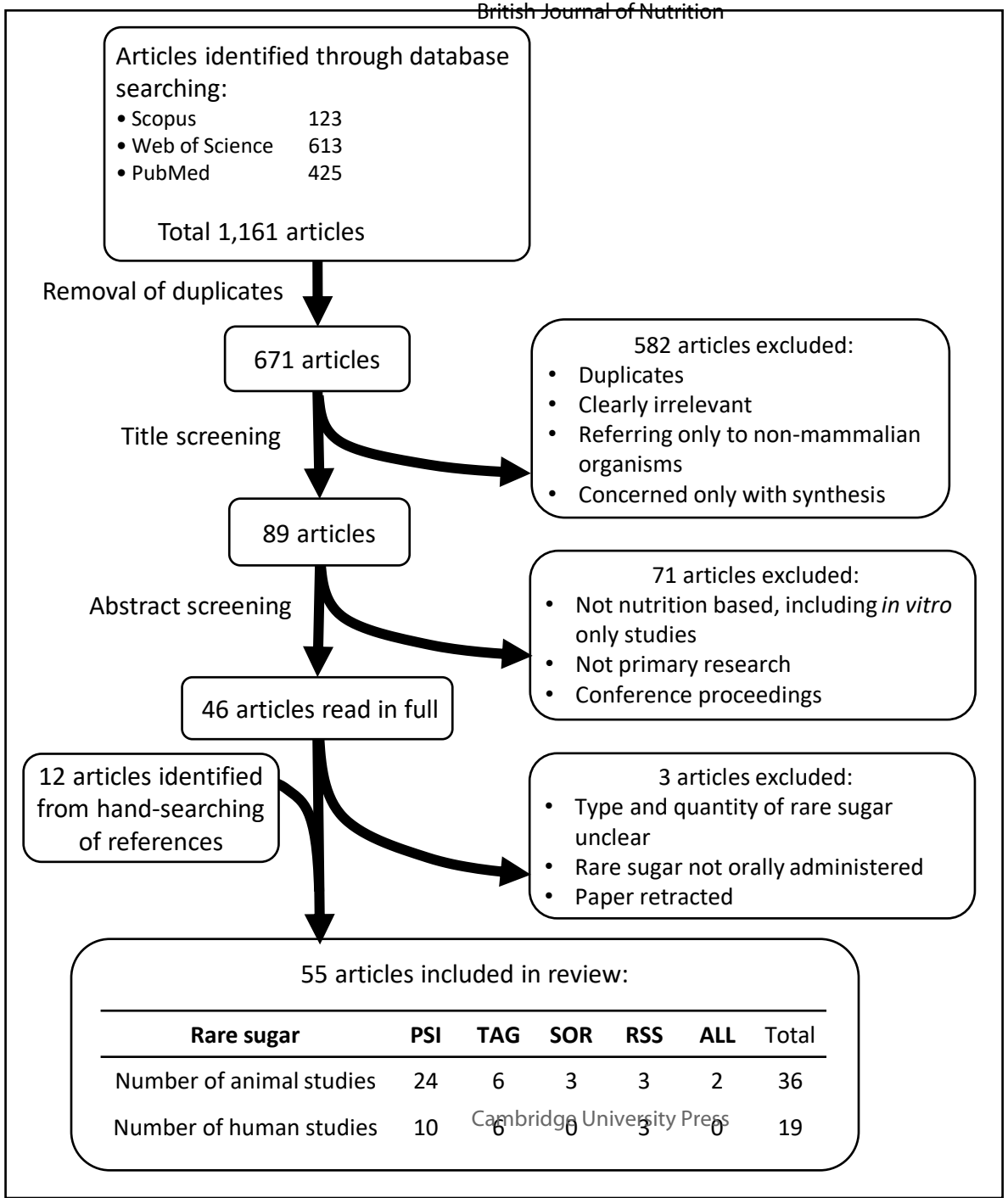
			with diet and exercise only. Majority male, around 50 yrs.	dose-ranging trial, single-blind (subjects blind to dosage)		for 6 months.	randomised into three groups and given TAG 3x daily for 6 months. Medical examination at start and end of trial, regular blood tests.	and insulin, serum lipids, body weight.	significant. Only 7.5g dose reduced fasting blood glucose after 6 months. Plasma triglyceride increased in 5.0g group, but no significant differences in total, LDL or HDL cholesterol. Dose-dependent reduction in body weight observed.
39	Hayashi et al., 2014[j]	Japan	Healthy volunteers (n=34) Age 42 +/- 2.7yrs BMI 25.5 +/- 0.6kg/m^2	Randomised placebo-controlled, double-blind parallel-group study	RSS (6% PSI)	30g RSS or 28g HFCS (each 114 kcal) given daily for 12 weeks	Test (RSS) or control (HFCS) drink taken 30mins before breakfast each day. Body weight, body fat ratio, blood pressure measured and blood samples taken after 0, 2, 4, 8 and 12 weeks.	BMI, body fat ratio, hip and waist circumference, plasma glucose, insulin, HbA1c, lipids, leptin and other biochemical parameters.	With RSS, hip circumference was significantly reduced compared to baseline after 4 weeks. Body weight BMI, body fat ratio and waist circumference were significantly reduced compared to baseline from week 8, however differences between RSS and HFCS groups were non-significant. Retinol-binding protein (highly expressed in visceral fat) significantly reduced in RSS group at week 12 compared to baseline, and leptin significantly increased in RSS group at week 12 compared to baseline.
40	Ensor et al., 2015	USA and India	Asian subjects (n=480) with T2D controlled with diet and exercise only.	Placebo-controlled, randomised, double-blind, parallel-group phase 3 clinical trial.	TAG	15g, 3x daily for 12 months.	After 8-week stabilisation period subjects randomised into two groups and given TAG or placebo (Splenda) 3x daily before meals. Medical examination on initial visit, blood taken every 2 months.	Reduction in HbA_{1c} , fasting blood glucose and insulin, serum lipids, body weight.	Significantly greater reduction in HbA1c observed in TAG group compared to placebo. Significant difference was seen earlier in the subgroup with baseline HbA1c <7.5%. Effect of lowering HbA1c was more pronounced in US population versus Indian population. No observed effect of TAG on changes in body weight or BMI compared to placebo. TAG group showed better reductions in total cholesterol and LDL compared to placebo from 4 months.

52	Wu et al., 2012	Australia	Healthy subjects (n=10) 7m, 3f Age 28.2+/-4yrs BMI 25.5+/-1.5	Randomized single-blind crossover	TAG	40g TAG-isomalt mixture (TIM) (16g tag), single dose before CHO-based meal	Subjects given preload of 40g glucose, TIM, OMG (non-metabolizable SGLT1 substrate) or 60mg sucralose, 20 min before meal (potato, glucose and egg yolk labelled with 13C octanoic acid). Breath samples and blood taken and GI sensations recorded.	Plasma glucose, insulin, GLP-1 and GIP, gastric emptying.	Glucose preload increased blood glucose immediately and iAUC for glucose was significantly higher at 30 mins after the meal, but there were no significant differences in iAUC for glucose over 240 mins. iAUC for insulin was significantly higher with glucose preload over 240min. No significant differences were observed between TIM and sucralose in terms of blood glucose or insulin iAUC. Plasma GLP-1 was significantly higher with glucose, OMG and TIM preloads than with sucralose. Plasma GIP was significantly higher with glucose and OMG preloads than with sucralose or TIM. Gastric emptying was slower with OMG and TIM preloads than with sucralose preload. Fullness after meal was reduced with sucralose. Nonnutrient substrates of SGLT1 or poorly absorbed sweeteners (TIM) could be used instead of protein or fat preloads to stimulate GLP-1 and slow gastric emptying, therefore reduce post-prandial elevation in blood glucose in people with T2D.
53	Van Opstal et al., 2019	Netherlands	Caucasian men, age 18-25yrs, BMI 20-23	Double-blind crossover	PSI	23g single dose in 'milkshake' containing 0.33g protein, 5g fat.	Resting-state functional MRI carried out immediately before and for 15mins after consumption of shake containing glucose, fructose, sucralose or PSI (matched for sweetness). Visual analogue scores used to	Changes in blood oxygen level dependent signal, functional network connectivity and voxel-based connectivity in brain.	No significant differences in visual analogue scores between sweeteners. Glucose and fructose decreased blood oxygen level dependent signal, and glucose increased eigen vector centrality throughout brain but decreased eigen vector centrality in mid-brain. PSI and sucralose had no effect on blood oxygen level dependent signal, but sucralose increased eigen vector centrality in some brain regions. The brain reward and satiety responses to low-calorie sweeteners was minimal compared to glucose and fructose.

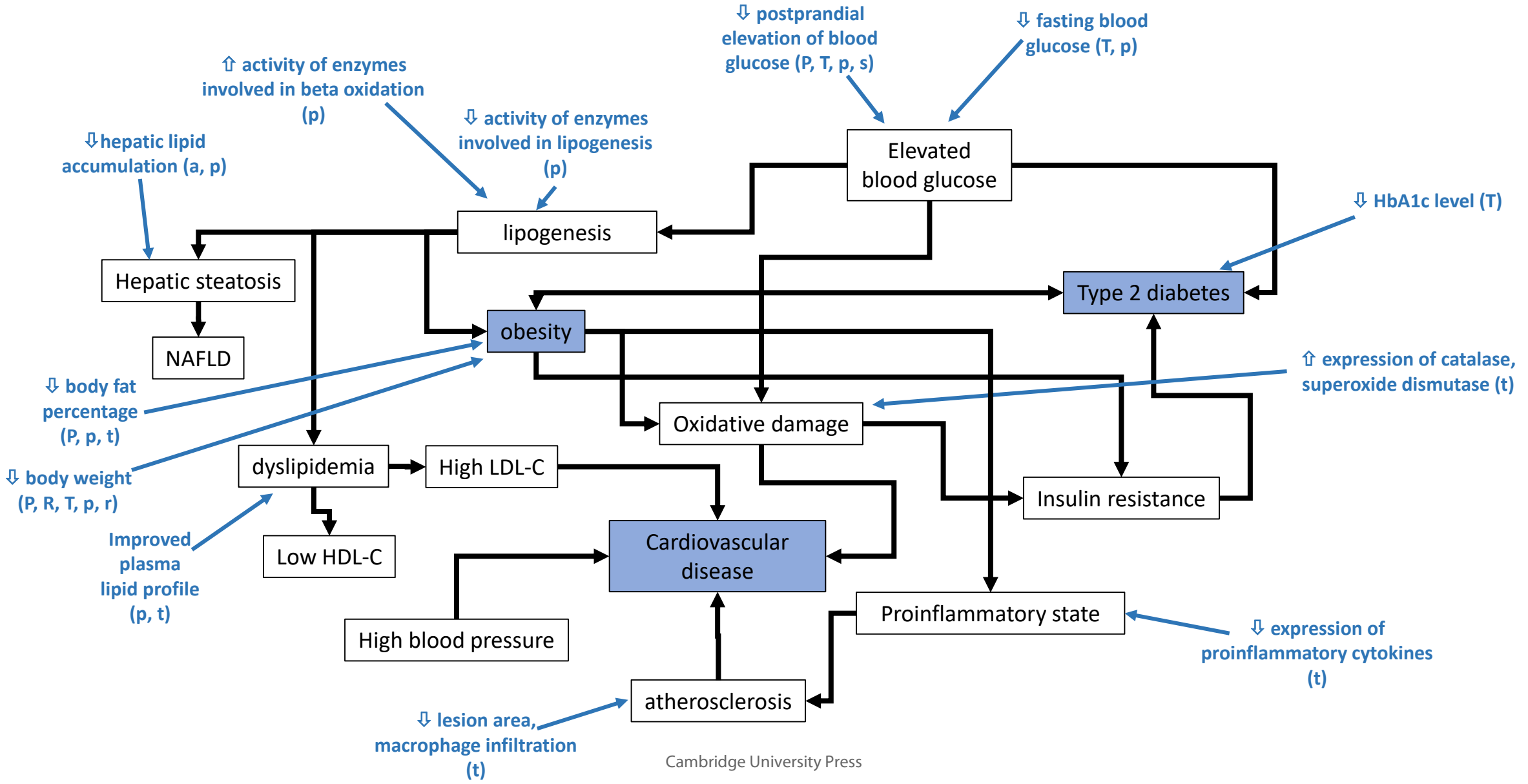
							measure hunger and fullness.		
56	Braunstein et al., 2018	Canada	Healthy volunteers (n=25, 13m, 12f) Age 37+/-16yrs BMI 24.7+/-3.4kg/m^2	Randomized controlled, double-blind, crossover acute feeding equivalence	PSI	0, 5 and 10g added to 75g glucose in 500ml water.	OGTTs with fructose or PSI (6 visits 1 week apart).	iAUC for plasma glucose, iAUC for plasma insulin, absolute maximum concentrations (C_{max}) of glucose and insulin.	iAUC for glucose (mmol/L*min) was reduced but effect was not significant. 5g PSI: -35 +/-22 (p=0.11). 10g PSI: -23 +/-22 (p=0.30) Pooled PSI: -29=+/-16 (p=0.07) No significant effect of PSI on iAUC for insulin, or C_{max} for glucose or insulin. Direction and magnitude of lowering of glycaemic response was similar to previous studies, but not significant because of high within-subject variability.
57	Kimura et al., 2017	Japan	Healthy volunteers (n=13, m5, f8) Age 35.7 +/-2yrs BMI 20.9 +/-0.7 kg/m^2	Randomized crossover, single blind	PSI	5g, single dose before meal	5g PSI or 10mg aspartame given 30 min before standard meal after 12h fast. Energy metabolism and blood biochemical parameters measured.	REE, CEE and FEE, RQ. Plasma glucose, insulin and lipids.	No significant differences in REE. AUC for FEE increased and CEE reduced with PSI compared to control. With PSI, plasma glucose significantly reduced at 90 minutes, plasma free fatty acids significantly increased from 180 minutes.
66	Iida et al., 2008 ABSTRACT ONLY	Japan	Healthy Asian subjects (n=20) 11m, 9f Age 20-39yrs	Randomised single-blind crossover	PSI	0, 2.5, 5 or 7.5g single dose in solution with 75g maltodextrin	Subjects visited at intervals of >1week. Blood sampled before consumption of PSI/maltodextrin and at 30, 60, 90 and 120mins after.	Blood glucose, insulin.	PSI dose-dependently reduced the elevation of blood glucose and insulin after maltodextrin load, with significant effects at doses of 5g or greater. 7.5g PSI administered alone did not affect blood glucose or insulin.
75	Han et al., 2018	Korea	Healthy Asian subjects (n=30)	Placebo-controlled	PSI	0.1g – 0.6g daily, or	Gradually increasing single	Max single dose for occasional	Maximum single dose with no reports of severe GI symptoms was 0.4g per kg body weight.

			Age 21-30yrs BMI 18.5-23	tolerance testing		0.2g-1g per kg body weight, 2-5 times daily, increasing over 1 week.	daily dose over 6 weeks with 1-week washout to find max single dose for occasional consumption, or gradually increasing daily dose and frequency over 1 week to find max daily dose for regular ingestion.	ingestion, max daily dose for regular consumption.	Maximum total daily intake for regular consumption with no reports of severe GI symptoms was 0.9g per kg body weight per day.
89	Little et al., 2010	UK	Healthy subjects (n=31) 16m, 15f, age 32.5 (SEM4.2), BMI 23.2 (SEM 0.7)	Single-blind, randomised.	TAG	22.5 or 45g in 500ml water, single dose	Hexose sugars (glucose, galactose, fructose or TAG) at various osmolalities given alongside 13C-labelled sodium acetate, breath samples taken before ingestion and at 5min intervals for 45mins.	Gastric emptying (13C:12C ratio in breath samples)	At 22.5g dose (250mOsmol) TAG slowed gastric emptying, with no difference between glucose, fructose and water. At 45g dose (500mOsmol), glucose, fructose and TAG all slowed gastric emptying compared to water, with no differences between different hexoses. This effect was reduced when a CCK1 inhibitor was administered. Gut-brain signalling affecting gastric emptying involves hexose-specific effects, independent of osmolality. TAG seems to slow gastric emptying more than other hexoses at physiological osmolalities.

All reported differences are significant unless stated otherwise. PSI: D-psicose, TAG: D-tagatose, RSS: rare sugar syrup, HFCS: high-fructose corn syrup, TIM: TAG-isomalt mixture, OMG: O-methylglucose, T2D: type 2 diabetes, OHAs: oral hypoglycaemic agents, OGTT: oral glucose tolerance test, AUC: area under curve, BMI: body mass index, CHO: carbohydrate, HDL: high density lipoprotein, LDL: low density lipoprotein, HbA1c: glycated haemoglobin, GI: gastrointestinal, REE: resting energy expenditure, CEE: CHO energy expenditure, FEE: fat energy expenditure, RQ: respiratory quotient, GLP-1: glucagon-like peptide-1, GIP: gastric inhibitory polypeptide, SGLT1: sodium-glucose cotransporter 1.



Rare sugar	PSI	TAG	SOR	RSS	ALL	Total
Number of animal studies	24	6	3	3	2	36
Number of human studies	10	6	0	3	0	19


⇩ postprandial elevation of blood glucose (P, T, p, s)
⇩ fasting blood glucose (T, p)
⇧ activity of enzymes involved in beta oxidation (p)
⇩ activity of enzymes involved in lipogenesis (p)
⇩hepatic lipid accumulation (a, p)
Elevated blood glucose
lipogenesis
⇩ HbA1c level (T)
Hepatic steatosis
Type 2 diabetes
obesity
NAFLD
⇧ expression of catalase, superoxide dismutase (t)
⇩ body fat percentage (P, p, t)
Oxidative damage
dyslipidemia
High LDL-C
⇩ body weight (P, R, T, p, r)
Insulin resistance
Improved plasma lipid profile (p, t)
Low HDL-C
Cardiovascular disease
Proinflammatory state
High blood pressure
⇩ expression of proinflammatory cytokines (t)
atherosclerosis
⇩ lesion area, macrophage infiltration (t)