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Impact of acute consumption of beverages containing plant-based or alternative sweetener blends on postprandial appetite, food intake, metabolism, and gastro-intestinal symptoms: Results of the SWEET beverages trial

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ABSTRACT

Project SWEET examined the barriers and facilitators to the use of non-nutritive sweeteners and sweetness enhancers (hereafter "S&SE") alongside potential risks/benefits for health and sustainability. The Beverages trial was a double-blind multi-centre, randomised crossover trial within SWEET evaluating the acute impact of three S&SE blends (plant-based and alternatives) vs. a sucrose control on glycaemic response, food intake, appetite sensations and safety after a carbohydrate-rich breakfast meal. The blends were: mogroside V and stevia RebM; stevia RebA and thaumatin; and sucralose and acesulfame-potassium (ace-K). At each 4 h visit, 60 healthy volunteers (53% male; all with overweight/obesity) consumed a 330 mL beverage with either an S&SE blend (0 kJ) or 8% sucrose (26 g, 442 kJ), shortly followed by a standardised breakfast (~2600 or 1800 kJ with 77 or 51 g carbohydrates, depending on sex). All blends reduced the 2-h incremental area-under-the-curve (iAUC) for blood insulin ($p < 0.001$ in mixed-effects models), while the stevia RebA and sucralose blends reduced the glucose iAUC ($p < 0.05$) compared with sucrose. Post-prandial levels of triglycerides plus hepatic transaminases did not differ across conditions ($p > 0.05$ for all). Compared with sucrose, there was a 3% increase in LDL-cholesterol after stevia RebA-thaumatin ($p < 0.001$ in adjusted models); and a 2% decrease in HDL-cholesterol after sucralose-ace-K ($p < 0.01$). There was an impact of blend on fullness and desire to eat ratings (both $p < 0.05$) and

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sucralose-acesulfame K induced higher prospective intake vs sucrose ($p < 0.001$ in adjusted models), but changes were of a small magnitude and did not translate into energy intake differences over the next 24 h. Gastrointestinal symptoms for all beverages were mostly mild. In general, responses to a carbohydrate-rich meal following consumption of S&SE blends with stevia or sucralose were similar to sucrose.

1. Introduction

Obesity is a major health problem adding to the global burden of disease. Sugar intake is one dietary component that has gained attention as a major contributor to the overall energy density of diets, with excess intake promoting weight gain (WHO, 2018). In 2015, the World Health Organization recommended that free sugar intake should constitute <10% of total daily energy intake (E%) and preferably <5 E% for optimised health (WHO, 2015). However, due to the palatability of sweet foods and their ubiquitous presence, a large part of the population does not comply with this recommendation. For example, in the UK, added sugars (excluding those found naturally in fruit, vegetables and milk) contribute about 10 E% (Public Health England, 2020), while in Denmark the average intake of free and/or added sugars is 10–16 E% (Nordic Council of Ministers., n.d.). In Spain, half of the total sugar consumption (average 17 E%) is estimated to be free sugars (which include sugars naturally present in foods) (Ruiz et al., 2017)(WHO, 2015).

Epidemiological data reveal that sugar-sweetened beverages (SSBs) are one major source of added sugar intake across all age groups (Malik & Hu, 2022; Singh et al., 2015). To reduce dietary sources of added sugars, one recommended approach is to consume water instead of SSBs (Ebbeling et al., 2012). Another strategy is to choose beverages containing low- or non-calorie sweeteners in place of sugar (i.e. sugar replacers or non-nutritive sweeteners and sweetness enhancers - S&SEs). S&SEs have been shown to provide desired sweetness with little to no calories and contribute to reduced energy intake plus potentially, to better weight management (Lee et al., 2021; Rios-Leyvraz & Montez, 2022). S&SEs have also shown beneficial effects on blood glucose control and are used in the management of diabetes (British Dietetic Association, 2016; EFSA, 2011).

There is currently inconsistent evidence on the short-term effects of S&SE-containing products and limited data on the long-term effects, in particular on safety aspects and efficacy, with studies suggesting either benefits or adverse effects (Higgins & Mattes, 2019; Rios-Leyvraz & Montez, 2022; Suez et al., 2014; Sylvetsky & Rother, 2018). These controversies likely arise due to differences in study design and perhaps also because S&SE represent a variety of substances that act in different ways and may not collectively share the same mechanisms of action. This is possibly linked to each sweetener's unique chemical structure (Buchanan et al., 2022; Dalenberg et al., 2020; Higgins & Mattes, 2019; Yunker et al., 2021). Recent work suggests altered neural food cue responsivity for some S&SEs (Yunker et al., 2021), highlighting that not all S&SEs behave equally.

While some sweeteners could potentially increase subjective appetite, short-term randomised controlled trials show a consistent reduction in energy intakes when S&SEs replace sugars, although the effects are typically associated to single S&SEs rather than blends (Lee et al., 2021; O'Connor et al., 2021; Rios-Leyvraz & Montez, 2022). Acute and long-term effects may also differ and the role of reverse causality in observational studies cannot be ruled out (Rios-Leyvraz & Montez, 2022; Rogers et al., 2016). Taken as a whole, there is currently insufficient evidence to determine the extent of any undesirable effects of particular S&SE and S&SE blends on appetite, glucose metabolism and safety parameters.

As part of SWEET (SWEET Project, 2019), this study employed a multi-centre trial involving an acute intervention to explore initial acceptance, safety and post-prandial effects of S&SE blends delivered in beverage form prior to a meal. An *a priori* approach with comprehensive selection criteria was used to determine which blends to include in the trial considering regulatory status, sensory attributes, food and beverage functionality, industry use, and market/consumer trends. The three selected blends were: stevia rebaudioside M 80% purity (RebM) and mogroside V 50% purity (luo han Guo, monk fruit extract); stevia rebaudioside A 95% purity (RebA) and thaumatin; and sucralose and acesulfame-potassium (ace-K). Stevia RebA and RebM are both steviol rebaudiosides from the *Stevia rebaudiana* plant, which exist at different concentrations. Stevia RebM is noted to have more sweetness and less bitterness than can be found in RebA which is the most widely used stevia. Mogroside V is also a glycoside extracted from the monk fruit plant (*Siraitia Grosvenorii),* while thaumatin is a sweet tasting protein derived from the African *Thaumatococcus daniellii* plant (Mora & Dando, 2021). To our knowledge, the stevia RebM and mogroside V blend is used commercially with limited global prevalence (but not necessarily in the ratio used in SWEET); however, the stevia RebA and thaumatin blend is not and is therefore relatively novel.

The null hypothesis tested in the present study was that the consumption of beverages sweetened with S&SE blends prior to a carbohydrate-rich meal would not significantly affect responses (including glycaemic response markers) relative to sucrose. Acute effects of different S&SE blends on appetite sensations, food intake (including energy intake, energy compensation and prospective food intake), safety (including gastro-intestinal (GI) symptoms, lipid and hepatic markers), and initial acceptance, were also investigated.

2. Methods

2.1. Study design

The study was designed as a double-blind, multicentre randomised cross-over acute intervention study across three European centres (Spain, Denmark and UK). Participants were recruited and involved in the study between August 2020 and June 2021 and the study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the corresponding Research Ethics Committees for Denmark, the University of Copenhagen (ref. H-19085058); Spain, the University of Navarra (ref. 2019.213 mod1); and UK, the University of Liverpool (ref. 6273). All participants provided signed informed consent and were compensated for their time with the equivalent of between €100 and €200.

The trial was registered in ClinicalTrials.gov under registration number NCT04483180.

Each participant attended four laboratory sessions (Clinical Investigation Days; CIDs), where one of four beverages (three with S&SE blends and a sucrose control) was tested. Wash-out periods between sessions were 6–10 days, but longer periods (12–21 days) were allowed under special circumstances (e.g. COVID-19 diagnosis).

Participants were randomised to one of four sequences created by the University of Leeds, based on a balanced block design to ensure equal number of comparable subjects under each treatment order at each centre. Each sequence of exposure was stratified by sex (female/male), and age group (18–45 years/46–60 years) and intervention site (UNAV, UCPH, ULIV). In addition, a female/male ratio of minimum 60/40 was considered to reflect the target population characteristics. The person responsible for generating the sequence did not have any study related tasks (e.g. inclusion or examination of participants). Blinding of the beverages was applied by the manufacturers and both participants and researchers including the data analyst were blinded.

2.2. Participants

Participants were healthy men and women, aged 18–60 y, with overweight or obesity (BMI 25–35 kg/m^2), regular consumers of sugar-containing foods and drinks and willing to consume plant-based or alternative non-caloric sweeteners (i.e. from chemical synthesis). Furthermore, participants also had to consume breakfast ≥5 days/week and like the control beverage (sucrose).

Exclusion criteria included lifestyle habits (i.e. physical activity, eating out patterns), medical conditions and medication affecting appetite and body weight, GI health, sweetener intake and conduct of the study (further details in Supplementary Material).

2.3. Procedures

2.3.1. Screening session

Written informed consent was obtained prior to the screening session in the laboratory. During screening, medical history and concomitant medication were registered, and body weight and height measured to verify BMI criteria. Lack of eating disorders was confirmed with the Eating Attitudes Test-26 (EAT-26) (Garner & Garfinkel, 1979) for which a score <20 was required. Hip and waist circumference and waist-to-hip ratio (WHR) were also measured. A short questionnaire was used to confirm that participants were habitual consumers of sweetened products and liked sweet beverages. Candidates also rated their liking for 50 mL of the control beverage on an electronic anchored line scale or VAS (visual analogue scale) (a score of ≥40/100 mm was required). All eligible candidates completed the International Physical Activity Questionnaire (IPAQ) (Booth, 2000) and a socio-demographic questionnaire (all questionnaires described below).

2.3.2. Clinical Investigation Days

Fig. 1 shows the procedures for the CIDs.

Prior to each CID, participants fasted for a minimum of 12 h (excluding up to 500 mL still water) and high-intensity physical activity, alcoholic beverages and coffee were not allowed for 12 h before arriving to the laboratory. These requirements were monitored at arrival and participants not complying with the protocol were scheduled for a later date (within a maximum of four days).

CID starting times were scheduled between 08:00 and 10:30 a.m., however participants had to attend at the same time on each CID. To standardise thirst levels, participants drank 200 mL water at arrival. On the last CID before drinking the water, participants were weighed in light clothing. Before participants saw the intervention foods, a cannula was inserted and after 10 min of resting a fasting blood sample was drawn. Following this, subjective appetite sensations, nausea and bloating ("sensations questionnaire" on Fig. 1) were registered using electronic VAS.

One of the four beverages was then served and the participant was instructed to consume it all within 5 min (Time point 0 min). The participant then recorded appetite sensations, liking and desire for more beverage (Time point 5 min). Following this, participants consumed the complete breakfast within a maximum of 10 min. The breakfast consisted of customary items and was standardized across countries (see details below). For participants who refused to consume all the food, the reason and weight of any left-overs (measured covertly) were registered.

Participants remained seated in the intervention area completing questionnaires for a period of 180 min, during which no food or beverage were allowed. The same sensations questionnaire (VAS) was completed at times ~15, 30, 45, 60, 120 and 180 min. In addition, at time 20 min participants completed the Leeds Food Preference Questionnaire (LFPQ) (reported separately). Postprandial blood samples were drawn at 30, 60, 90 and 120 min. Before leaving the laboratory, the participant received an End of Day questionnaire to register food cravings at home. On the next day participants undertook a telephone interview where GI symptoms plus all consumed foods and beverages between leaving the laboratory and until 24 h after consuming the test beverage on the CID were registered. On CID4, participants were offered

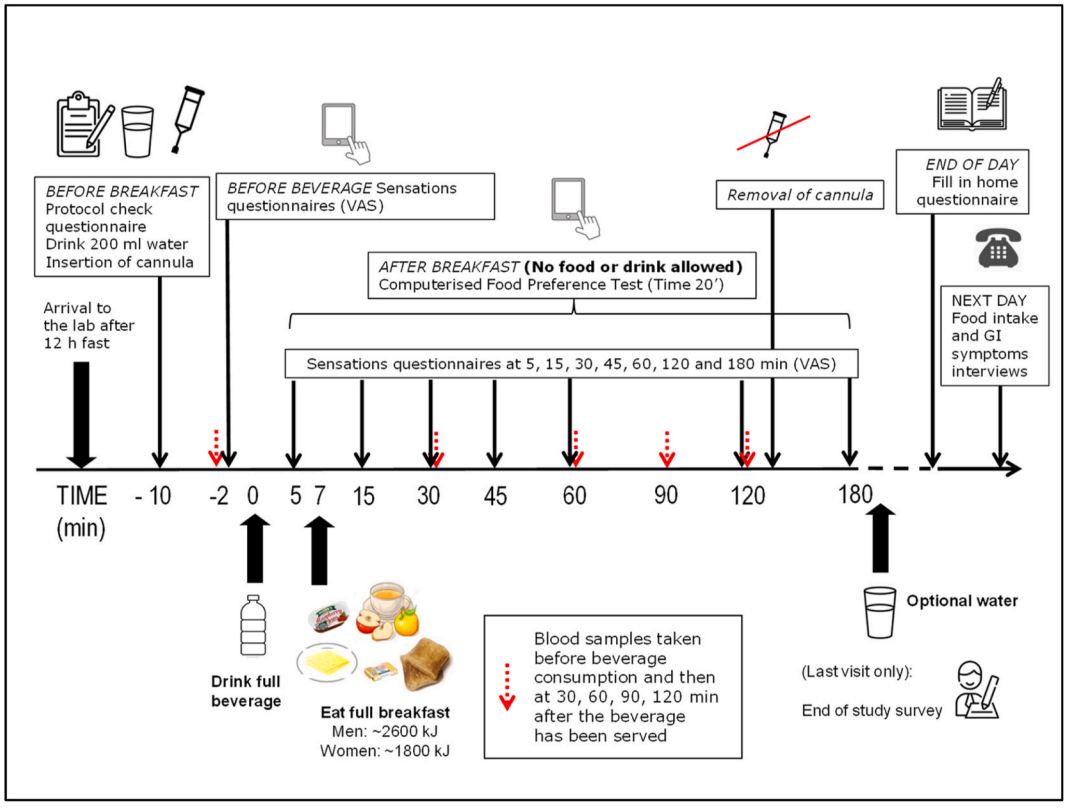

Fig. 1. Clinical Investigation Day procedures. Abbreviations: GI, gastro-intestinal; VAS, visual analogue scale.

to complete an End of study survey asking about the study design, treatment by staff, materials and compensation.

2.4. Breakfast and test beverages

Table 1 lists the composition of each of the beverages used in the trials. Blends are hereafter referred to as: StM_Mog (stevia RebM 80% purity and Mogroside V 50% purity); StA_Tha (stevia RebA 95% purity and thaumatin); Suc_Ace (sucralose and ace-K). For plant extracts (stevia and mogroside) the purity ranges from 50% to 95% based on what is commercially available. The other sweeteners are synthesized (except for thaumatin which is a protein) and all are >95% pure.

The S&SE used have previously been approved for human consumption and have been granted EU or USA regulatory food status. The selected S&SE represented a diverse array including common commercial and consumer known sweetener blends, plus novel sweetener blends that have not been well studied yet, and were chosen based on their properties and/or existing data.

S&SE amounts were determined using the Beidler equation (prediction of sweetness intensities) (Graaf & Frijters, 1986; Schiffman et al., 2003), to match a sucrose equivalent (SEV) of 8%, an acceptable level chosen to represent the ranges of 5–12%, typically found in sugar sweetened beverages. An 8% SEV level can be matched with the use of S&SE and avoids inclusion of amounts of S&SE that can introduce bitter, metallic or off tastes.

Test beverages were all water-based, non-carbonated and lemon flavoured, supplied in identical 330 mL clear, lidded bottles, labelled with a numerical code. Beverages were served in their original container alongside an empty 250 mL glass for optional use. The control, sucrose beverage (8% sucrose), provided 442 kJ (105.6 kcal) in total and contained 26.4 g sucrose (amount needed to produce a SEV of 8% in a volume of 330 ml). The three S&SE beverages provided 0 kJ. All four beverages were designed to be matched for sweetness intensity, flavour and physical appearance. Pre-study sensory analysis confirmed reasonable acceptance for all four intervention beverages (see Supplementary Material).

Crystalline sucrose and food grade stevia RebA and stevia RebM were obtained from Cargill B.V., (Vilvoorde, Belgium). Mogroside V was purchased from Anderson Advanced Ingredients (Irvine, CA, USA). Thaumatin was kindly provided as a gift from Natex (Letchworth Garden City, UK). Food grade Ace-K was purchased from Sigma-Aldrich Inc. (St Louis, MO, USA) and sucralose was purchased from Prinova-Spectrum (London, UK). Shortly after consuming the S&SE beverages, male or female subjects consumed a standardized breakfast containing ~2600 or 1800 kJ and 77 or 51 g glycemic carbohydrates, respectively. Nutrient and energy information for the breakfasts is provided in Table S1 in the Supplementary Material. All breakfast products were free from non-caloric and low-calorie sweeteners and were commercially available.

Table 1
Composition of the 330 mL test beverages (per 100 mL) by sweetener type.

Ingredients (in 100 mL)	StM_Mog	StA_Tha	Suc_Ace	Sucrose
Water (g)	94.77	94.81	94.82	86.83
Sucrose (g)	0	0	0	8.00
Mogroside V (g)	0.04	0	0	0
Stevia RebM (g)	0.02	0	0	0
Stevia RebA (g)	0	0.024	0	0
Thaumatin (g)	0	0.00012	0	0
Sucralose (g)	0	0	0.01	0
Ace-K (g)	0	0	0.01	0
Potassium Citrate (g)	1.04	1.04	1.04	1.04
Citric Acid (g)	3.93	3.93	3.93	3.93
Sodium Benzoate (g)	0.02	0.02	0.02	0.02
Natural Lemon flavour (g)	0.18	0.18	0.18	0.18

2.5. Data collection

2.5.1. Questionnaires

All common questionnaires were developed in English and translated to local languages. Where available, previously validated, translated versions for the corresponding study populations were preferentially used (i.e. Danish, Spanish). Questionnaires were delivered by the Questionnaire Delivery Platform (QDP), implemented by NetUnion (Lausanne, Switzerland), except for the LFPQ, implemented in E-Prime (Psychology Software Tools, Sharpsburg, PA, USA).

The sensations questionnaire consisted of a total of 11 electronic VAS related to pleasantness, desire for, appetite, satiety and GI symptoms and was administered using a tablet/PC with a link accessing the QDP. Validated questions for liking of the taste and desire for drinking more beverage, hunger, fullness, thirst, desire to eat, prospective intake, nausea, bloating, appetite for something savoury and appetite for something sweet (Finlayson, King, & Blundell, 2008; Flint, Raben, Blundell, & Astrup, 2000; Hill & Blundell, 1982) were shown on separate screens and the response was automatically registered standardised to 100 (based on a 100 mm VAS). Data for thirst, nausea, bloating, appetite for something savoury and for something sweet were all similar across conditions and are not reported further. The remaining set of appetite VAS (hunger, fullness, desire to eat and prospective food consumption) are referred to as "appetite sensations". The full questionnaire can be accessed by contacting the authors.

Additional questionnaires were used to measure habitual consumption of sweet foods, physical activity, socio-demographic characteristics, perceptions of the intervention (end of study survey in Fig. 1), food preference, food cravings and consumer S&SE perceptions (see Supplementary Material for details). The last 3 sets of data will be presented in a separate publication.

2.5.2. Gastro-intestinal symptoms interview

The GI health assessment (presence of symptoms, duration and intensity) was carried out via a telephonic, standardised, 24-h interview using a tool based on the validated Gastro-Intestinal Symptom Rating Scale (Svedlund, Sjodin, & Dotevall, 1988). Participants were asked about any experienced GI symptoms since they consumed the test beverage and up to 24 h later and to report whether they believed symptoms were associated with the test beverage. Any GI symptoms that had not been reported at screening were recorded as an adverse event.

2.5.3. Dietary intake interview

Dietary assessment was carried out via a telephonic, standardised, 24-h recall (interview) following an adaptation of the validated 24-h recall method for NHANES (Centers for Disease Control and Prevention, n.d.). Participants were asked to verbally report everything they ate and drank (including recipe description and amounts) over the 24 h after drinking the test beverage in the laboratory. To facilitate the interview, participants were allowed to take photographs and/or keep food packaging, and to use portion size measuring guides. The Australian Health Survey (AHS) food model booklet (Australian Bureau of Statistics, 2010), a piloted Danish food model booklet (Tjønneland et al., 2007) and the AHS plus the Young Persons Food atlases (Foster et al., 2017) were used in Spain, Denmark and the UK, respectively. The information from the 24-h food recall was converted to dietary intakes by using national nutrient composition data tables and software, specific to each country (Forestfield Software Ltd, 2021; Healthcare Software Solutions S.A., 2021; Kraftaerk Foodtech, n.d.).

2.6. Blood sampling and processing

Blood samples were only collected from Spanish (n = 22) and Danish (n = 20) participants due to unavailability of medical staff at the UK site caused by the COVID-19 pandemic.

Blood parameters analysed at each CID included glucose, insulin,

lipid profile (triglycerides and total, HDL-plus LDL-cholesterol), and liver function markers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), plus gamma-glutamyltransferase (GGT)). All processed samples were stored at −80 °C until shipment and analysed at the Bioiatriki Central Laboratory in Athens, Greece. For details of sample collection procedures see Supplementary Materials.

All biochemistry analyses were performed using a HITACHI cobas 800c system/701 and the corresponding reagents (ROCHE). Insulin concentrations were determined by electrochemiluminescence immunoassay (ROCHE, Basel, Switzerland) using a HITACHI cobas e801 automated immunoassay system (ROCHE). Glucose concentrations were determined by the hexokinase test (enzymatic ultra-violet); triglycerides were determined by the enzymatic colorimetric method (end point); total cholesterol was determined by colorimetric, oxidase, esterase, and peroxidase analysis; HDL- and LDL-cholesterol were determined by homogeneous enzymatic colorimetric analyses (direct polyethylene glycol method for HDL-cholesterol); AST and ALT were determined by enzymatic colorimetric assays, and GGT by enzymatic colorimetric G glutamyl-carboxy-nitroanilide according to the International Federation of Clinical Chemistry guidelines.

2.7. Data management and processing

The majority of the data were collected electronically and uploaded onto a common datahub. Other data were collected using either an electronic case report form (e-CRF) (Xolomon Tree, SL, Madrid, Spain) or on paper CRFs and later entered into the e-CRF system.

The trapezoid method (Wolever, Jenkins, Jenkins, & Josse, 1991) was used for calculation of the incremental area under the curve (iAUC, excluding fasting values to remove bias or differences at baseline) for glucose, insulin and the triglyceride and glucose (TyG) index. For appetite ratings, the net incremental AUC (niAUC) was used to account for negative values (Brouns et al., 2005; Douglas & Leidy, 2019).

The TyG index, a marker of insulin resistance and metabolic syndrome; the homeostatic model assessment for insulin resistance (HOMA-IR) score; and the fatty liver index (FLI) were calculated as reported previously (Ascaso et al., 2001; Bedogni et al., 2006; Simental-Mendía, Rodríguez-Morán, & Guerrero-Romero, 2008).

Percent energy compensation (%EC) was derived from the dietary recall data and calculated as:

$$\%EC = [\ (EI_{\text{Low Calorie Preload}} - EI_{\text{Regular Preload}})/\ |EP|]\ *100$$

Where EI = energy intake subsequent to eating the low calorie or the regular preload (in this case, beverage with sucrose), over the 24 h after preload administration (that is, excluding the breakfast and beverage); and |EP| = difference in the energy provided by each low-calorie preload vs the sucrose (control) condition, in absolute value (Almiron-Roig et al., 2013). See Supplementary Material for interpretation procedures applied.

2.8. Sample size and statistical analyses

Sample size was estimated based on previous literature on low-calorie sweeteners (Anton et al., 2010; Brandt, Sünram-Lea, & Qualtrough, 2006; Green, Taylor, Elliman, & Rhodes, 2001; Jiménez-Domínguez et al., 2015; Tey, Salleh, Henry, & Forde, 2017b) and on validation studies for subjective appetite scales (Almiron-Roig et al., 2009; Flint et al., 2000). These studies have used sample sizes of 12–48 participants. To detect a minimum difference of 8 mm in appetite ratings on a 100 mm VAS with 80% power, alpha 0.05, and a within-subject SD of 14.4 mm (Almiron-Roig et al., 2009), an overall sample of 54 participants was needed (Jones & Kenward, 2015). The 54 participants would also cover effect sizes for blood glucose and insulin (a minimum of 16 was needed) (Green et al., 2001), energy intake and compensation (Almiron-Roig & Drewnowski, 2003), liking and desire (Rogers & Hardman, 2015).

All study hypotheses as well as the analytic plan were specified prior to data collection, except when otherwise stated. This included subgroup analyses for men vs women and younger (18–45 y) vs. older (46–60 y) participants, when applicable.

Data are presented as means ± SD or SE as stated, for all continuous variables. Qualitative data are summarized with a narrative synthesis (e.g. observations related to adverse events).

Extreme points were defined based on the literature (Kassambara, 2022) as values above {Q3 + 3 × IQR} or below {Q1 - 3 × IQR} where Q1 and Q3 are the first and third quartile, respectively. IQR is the interquartile range (IQR = Q3 - Q1). Only extreme points (but not outliers) were excluded from analyses except for nausea ratings (no data were excluded as it contained a too large number of extreme points).

Change in body weight over the course of the intervention was analysed by paired-samples *t*-tests.

The impact of S&SE or sucrose condition (hereafter referred to as "blend") on all outcome variables was analysed with linear mixed effects regression models including a random intercept to account for the repeated observations for each individual, and fitted using maximum likelihood estimation, likelihood ratio tests (REML). Fixed effects explored included blend and time when appropriate. All models were adjusted *a priori* for intervention site, sex, age group, and breakfast energy intake when applicable. Tukey's post-hoc tests were applied to control the error rate for multiple pairwise comparisons between blends when an overall impact of blend was detected or suspected..

Effect sizes and 95% CIs were computed as Cohen's *d* (Cohen, 1988) using a correction factor to account for the cross-over nature of the study (Lakens, 2013) and assuming a correlation of 0.8 between visits (Robinson et al., 2014). Effect sizes were defined as trivial ($d < 0.2$), small (0.2–0.49), moderate (0.5–0.79) or strong (≥0.8) (Cohen, 1988).

The potential presence of carry-over effects on appetite ratings was investigated by comparing mean 3-h niAUC ratings for hunger, fullness, desire to eat and prospective intake across the 4 potential treatment orders with ANOVA. Sensitivity analyses were then performed on those variables where the mean ratings differed across treatment order.

Differences in beverage liking and desire were detected as part of the main results, therefore, a data-driven, post-hoc analysis was performed to rule out unplanned effects of desire/liking on main study variables (i.e. hunger, fullness, desire to eat, prospective intake, 24 h *ad libitum* and total energy intakes). All analyses were carried out using the R-language free software, RStudio 2022.12.0 + 353 (R Project for Statistical Computing, www.r-project. org). Statistical significance was set at $p < 0.05$ or $p < 0.01$ for multiple comparisons.

3. Results

A total of 308 interested participants were contacted across the three sites of which 79 were screened and 69 were enrolled. Of those, 59 completed the four CIDs. There were 10 drop-outs in total, largely due to personal and medical reasons (Fig. 2).

The analyses are based on participants completing the first visit i.e. CID1 (N = 60). This sample is composed of 47% women and 53% men with a mean (SD) age and BMI of 32.1 (11.0) y and 28.9 (2.8) kg/m^2 respectively. The distribution of anthropometric and other baseline data was similar across countries. Weight at the end of the study was not different from weight at baseline (p = 0.405) (Table 2).

The sample populations were ≥75% of white European descent, except in the UK where 35% were of East-Asian descent. Most participants in Spain and the UK reported holding or studying for a university-degree, while 48% of Danish participants reported secondary education as the highest level attained. One-third were employed full-time while 40% were on full-time education (Table S2 in Supplementary information). Chronic-disease risk markers (waist circumference, WHR, TyG, FLI, and HOMA-IR) were overall within the healthy range or close (Bedogni et al., 2006; Gayoso-Diz et al., 2013; Simental-Mendía et al.,

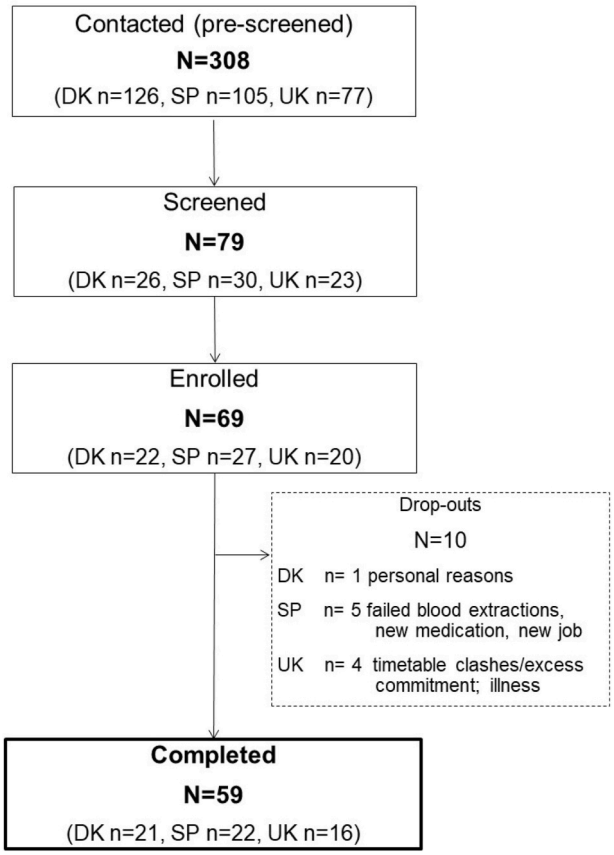

Fig. 2. Recruitment flowchart for the Beverages multi-centre trial. Abbreviations: DK, Denmark (University of Copenhagen); SP, Spain (University of Navarra); UK, United Kingdom (University of Liverpool).

2008).

3.1. Glycaemic impact

There was an overall impact of blend on the 2-h iAUC for both glucose and insulin (Table 3). Calculated effect sizes (95%CI) for the glucose were small at best at −0.17 (−0.39, 0.04), −0.31 (−0.52, −0.09) and −0.32 (−0.53, −0.11) for the comparison of StM_Mog, StA_Tha and Suc_Ace vs. sucrose, respectively. Insulin iAUC effect sizes were small at −0.39 (−0.60, −0.18), −0.40 (−0.62, −0.19) and −0.44 (−0.66, −0.22), respectively. Post-hoc Tukey's adjusted tests revealed significant differences in insulin iAUC for all three blends vs. sucrose ($p < 0.001$ for all comparisons), but not for glucose iAUC ($p > 0.01$). There were no differences between non-caloric blend pairs for either glucose nor insulin iAUCs ($p > 0.05$ all comparisons). There was an impact of blend condition on the 2-h iAUC for the TyG index with StA_Tha and Suc_Ace reducing the TyG vs sucrose (overall effect of blend $p < 0.05$), with trivial effect sizes (−0.17 to 0.01; 95%CI -0.38 to 0.23) (Table 3).

Post-prandial blood glucose and insulin levels are shown in Fig. 3. In contrast with the AUC analysis, for glucose, the main effect of blend was non-significant ($p = 0.286$). For insulin however, there was a significant impact of blend ($p < 0.001$) and a Tukey's adjusted post-hoc analysis revealed lower concentrations after any of the S&SE blends vs. sucrose ($p < 0.001$ for all comparisons), with no differences between non-caloric blend pairs.

Mean values and details of B coefficients for the glucose and insulin 2-h iAUC models can be found in Supplementary Tables S3 and S4. Sex and intervention site remained significant covariates in the glucose but not in the insulin models (see Supplementary Materials for details, Additional Results).

3.2. Appetite response

Fig. 4 shows the temporal profiles for subjective hunger, fullness, desire to eat and prospective intake ratings across blend condition.

Different effects of the S&SE blends on the appetite response were detected. While there was no major impact of any of the preloads containing S&SE over sucrose on appetite ratings, the Suc_Ace blend performed differently. In particular, the Suc_Ace blend elicited higher prospective intake sensations than the StA_Tha blend and the sucrose (both $p < 0.001$). An overall impact of blend was also detected for desire to eat and fullness ratings (both $p < 0.05$). These effects were all of small magnitude. Indeed, hunger, fullness, desire to eat and prospective intake effect sizes calculated using the 3-h niAUC were all trivial ($d < 0.22$) despite differences seen in the 3-h curves.

In terms of "rebound" hunger, there was no increase in the 2-h niAUC for hunger after any of the S&SE conditions compared with sucrose ($p = 0.442$).

Treatment order effects were detected only for fullness ($p < 0.001$). Including treatment order as covariate in the model for fullness ratings did not change the results.

3.3. Beverage liking and desire for more beverage scores

There were significant differences in both liking and desire ratings across blends ($p < 0.001$ for both models). Post-hoc analyses (Tukey's-adjusted) confirmed that the sucrose and Suc_Ace-containing beverages were more liked and desired than both stevia-containing beverages (Table 4). Effect sizes (95%CI) for liking scores of each S&SE blend vs. sucrose ranged from trivial to moderate: StM_Mog −0.67 (−0.85, −0.49); StA_Tha −0.60 (−0.79, −0.42) and Suc_Ace −0.12 (−0.30, 0.06). For desire scores, effect sizes were similar: StM_Mog −0.53 (−0.71, −0.36); StA_Tha −0.63 (−0.81, −0.45) and Suc_Ace −0.15 (−0.32, 0.03).

Exploratory post-hoc tests for the influence of liking and desire revealed no significant effect of either liking or desire on hunger and prospective intake ratings, nor on energy intake outcomes. Desire for more beverage attenuated the impact of blend on fullness and desire to eat ratings, while liking (pleasantness) attenuated the impact on fullness ratings (further details included in Supplementary Material, Additional Results).

3.4. Energy and macronutrient intake

There were no blend-associated differences in ad libitum energy intake over the next 24 h or in total energy intake (including additionally the breakfast and beverage) ($p > 0.05$ both) (Fig. 5).

Mean (SD) total energy intakes by blend were: StM_Mog 11152 (86384) kJ; StA_Tha 11321 (86957) kJ; Suc_Ace 11283 (87399) kJ; sucrose 11480 (88922) kJ. These values were not statistically different in adjusted models, with the maximum difference corresponding to around 328 kJ (78 kcal) between the StM_Mog and the sucrose conditions.

There was a significant impact of intervention site and sex (both $p < 0.01$), on both 24 h and total energy intakes. As expected, men consumed more total energy. Also, Spanish participants consumed less total energy than British and Danish ones.

3.4.1. Energy compensation

Taking as reference the sucrose condition, no significant differences in percent energy compensation were detected across adjusted means (effect of blend $p = 0.214$).

3.4.2. Twenty-four h ad libitum macronutrient intake

Analysis of the 24 h dietary recall data revealed no significant impact of beverage on nutrient intakes over the 24 h period following preload consumption in adjusted models. However, intervention site remained a

Table 2
Characteristics of participants completing CID1. Values are means (SD) unless otherwise indicated. Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; EAT-26, Eating attitudes test-26; IPAQ, International physical activity questionnaire; FL index, Fatty liver index; GGT, Gamma-glutamyltransferase; TyG, Triglyceride and glucose index; VAS, Visual analogue scale; WHR, waist-to-hip ratio; N/A: not applicable (no blood samples collected).

	All centres (N = 60)[a]		Spain (n = 22)		Denmark (n = 21)		U.K. (n = 17)[a]	
Sex								
Female (n)	28		11		8		9	
Male (n)	32		11		13		8	
Age (years)	32.1	(11.0)	33.5	(11.6)	33.1	(11.5)	28.9	(9.6)
Weight at baseline (kg)	85.9	(14.0)	80.3	(13.5)	93.1	(12.9)	84.3	(12.7)
Weight at study end (kg)	86.0	(14.0)	80.1	(13.6)	92.9	(13.0)	85.3	(12.6)
Height (cm)	171.5	(9.8)	168.1	(8.2)	177.0	(9.7)	169.6	(9.6)
BMI (kg/m^2)	28.9	(2.8)	28.2	(2.7)	29.3	(2.6)	29.3	(3.3)
EAT-26 score (0–78)	5.4	(3.9)	6.5	(3.7)	4.5	(3.1)	5.1	(4.8)
Waist circumference (cm)	93.9	(12.1)	89.8	(13.4)	96.2	(10.9)	96.3	(11.0)
Hip circumference (cm)	108.7	(7.1)	107.0	(6.7)	108.5	(7.2)	111.1	(7.2)
WHR (cm)	0.86	(0.10)	0.84	(0.10)	0.89	(0.10)	0.87	(0.08)
Fasting glucose (mg/dL)	92.6	(6.5)	90.1	(6.1)	95.3	(5.9)	N/A	
Fasting insulin (μU/mL)	10.6	(5.5)	10.6	(5.9)	10.6	(5.1)	N/A	
Fasting triglycerides (mg/dL)	93.1	(45.6)	79.4	(32.0)	108.1	(53.9)	N/A	
Fasting total cholesterol (mg/dL)	165.9	(29.7)	172.1	(31.6)	159.1	(26.6)	N/A	
Fasting HDL-cholesterol (mg/dL)	52.9	(12.2)	56.6	(13.2)	48.9	(9.7)	N/A	
Fasting LDL-cholesterol (mg/dL)	102.5	(26.4)	107.7	(28.2)	96.8	(23.8)	N/A	
Fasting AST (IU/L)	23.4	(6.9)	24.1	(7.5)	22.6	(6.3)	N/A	
Fasting ALT (IU/L)	22.4	(13.9)	21.8	(11.9)	23.0	(16.1)	N/A	
Fasting GGT (IU/L)	25.8	(22.9)	30.1	(29.5)	21.1	(10.9)	N/A	
TyG index (cut off 4.65 points)	4.48	(0.2)	4.40	(0.2)	4.57	(0.2)	N/A	
FL index (cut off 60 points)	40	(27)	37	(29)	41	(26)	N/A	
HOMA-IR[b]	2.45	(1.3)	2.4	(1.4)	2.5	(1.3)	N/A	
Physical activity (IPAQ, Total MET-minutes/week)[c]	5636	(4531)	5068	(3595)	5809	(5116)	6110	(4932)
Habitual intake of sweet foods (short sugar FFQ score, 0–11)	8.3	(1.7)	7.2	(1.7)	9.1	(1.4)	8.8	(1.3)
Liking of control beverage (Taste test, 100 mm VAS)	80.5	(15.4)	82.6	(15.4)	77.2	(15.9)	81.8	(15.0)
Conduct of intervention (end of study survey score, 0–10)	9.30	(0.8)	9.46	(0.7)	8.81	(0.8)	9.71	(0.4)

[a] Includes one female who dropped out after CID3 due to illness (COVID-19 diagnosis).
[b] Cut-off value for HOMA-IR is 3.8 for healthy population and 2.1 for high risk population (Ascaso et al., 2001; Gayoso-Diz et al., 2013).
[c] Sample size for All centres N = 45; Spain n = 15; Denmark n = 19; U.K. n = 11.

Table 3
Incremental area under the curve (iAUC) for glucose and insulin blood levels, and the triglyceride and glucose index (TyG), after preload consumption (breakfast plus beverage). Values are mean (SD) across centres.

		StM_Mog	StA_Tha	Suc_Ace	Sucrose	Overall impact of blend[a]
Glucose iAUC (mg/dL x min) N = 42	Mean (SD)	1132 (1002)	985 (788)	967 (781)	1322 (1144)	p = 0.028
Insulin iAUC (μU/mL x min) N = 42[b]	Mean (SD)	5120 (2391)	5095 (3015)	4965 (2580)	6429 (3480)	p = 0.000
TyG Index iAUC (points x min) N = 42[c]	Mean (SD)	8.545 (8.670)	7.180 (6.548)	7.272 (5.872)	8.444 (7.742)	p = 0.013

[a] Linear mixed effects regression adjusted with intervention site, sex, age group and breakfast energy intake (intervention site and sex remained significant in the final glucose and TyG models).
[b] An extreme value was detected for StA_Tha and for sucrose; plus, two for Suc_Ace. These values were excluded.
[c] An extreme value was detected for Suc_Ace and this value was excluded.

significant variable in all carbohydrate models (total carb, fibre and sugar), while sex remained a significant variable in the fat models (total fat, saturated and unsaturated fat intake).

3.5. Safety parameters

3.5.1. Blood lipids

There was a small impact of some S&SE blends on some blood lipids, however, changes were of a very small magnitude (Table S5). Adjusted models showed an overall impact of blend on total and LDL-cholesterol (both $p < 0.001$); and on HDL-cholesterol ($p < 0.01$), but not on triglycerides ($p = 0.371$). StA_Tha increased LDL-cholesterol levels by 2.9% vs sucrose ($p < 0.001$), and increased total cholesterol vs StM_Mog ($p < 0.001$) but not vs. sucrose ($p = 0.076$). Also, compared with sucrose, all three S&SE blends reduced HDL-cholesterol by between 1.9 and 2.3% but the reduction was only significant for Suc_Ace (−2.3%, $p < 0.01$). These small effects were not due to differences in fasting values ($p > 0.05$ all comparisons).

3.5.2. GI symptoms, other adverse events and medication

There were no serious adverse events and most reported GI symptoms were mild although some were more frequent/intense such as belching, rumbling and altered frequency of opening bowels. Changes in concomitant medication during the study were accounted for in the analyses as was the presence of adverse events. There were no changes in medication that related to study procedures. Overall, no beverage was associated with important undesired metabolic or behavioural outcomes and there were no drop-outs related to adverse events.

4. Discussion

The results of this study show that a range of plant-based and alternative sweeteners were comparable to sucrose in their metabolic effects after acute consumption in liquid form. Despite the co-ingestion of the beverages with a standardised breakfast, blood insulin rose higher after the sucrose vs all S&SE blends, suggesting an attenuation effect of the breakfast-induced insulin peak with all three S&SE blends. As

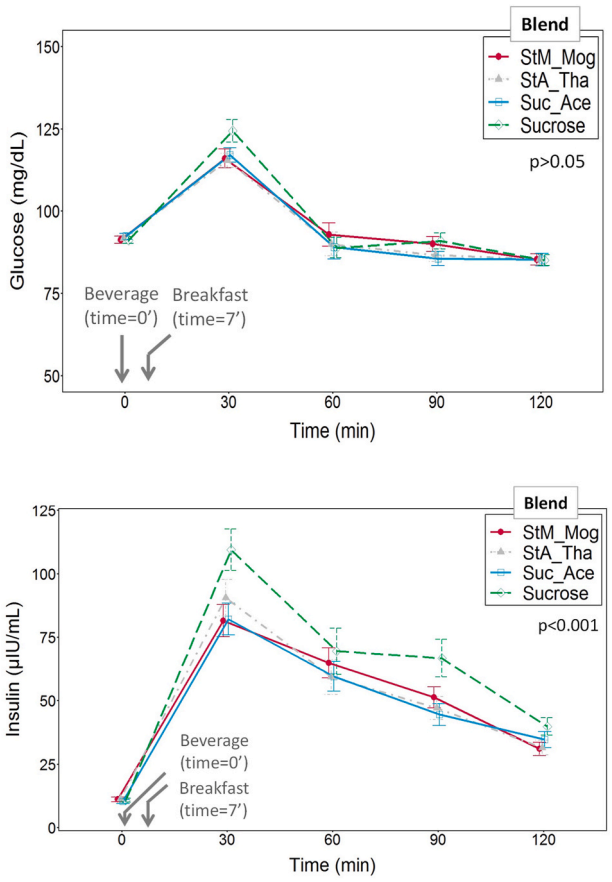

Fig. 3. Fasting and post-prandial blood glucose (top) and insulin levels (bottom) across blend condition (N = 42). Data points are means with SE. Overall impact of blend (linear mixed effects models results shown on the right upper corner).

expected, glucose and insulin iAUC values were higher after sucrose consumption, however differences in the 2-h glucose curve were not detectable, probably attenuated by the carbohydrate content of the breakfasts. On the other hand, in this study different S&SEs exerted different effects on subjective appetite sensations. Despite being similarly accepted as the energy-containing control, the Suc_Ace blend was associated with a weaker satiety impact over 3 h vs sucrose. Specifically, the Suc_Ace blend induced higher prospective intake vs the StA_Tha blend and vs. sucrose, but changes were of a small magnitude and did not translate into energy intake differences over the next 24 h.

Although there were effects of some of the blends on blood cholesterol levels, such effects were of very small magnitude (<3% vs the control condition in all cases). For reference, such changes need to be of 10% or more to be considered clinically relevant in chronic interventions (American Diabetes Association, 2008; Bradley et al., 2009). We believe lipid changes in our study probably reflect spontaneous fluctuations not detectable at baseline. This is confirmed by a recent meta-analysis (Movahedian et al., 2021) and previous studies with S&SEs showing no effects on blood lipids in several diverse populations and when used in different doses over several months (Higgins & Mattes, 2019). LDL-cholesterol increases after consuming StA_Tha in this study (about 3 mg/dL vs. sucrose) were smaller compared with those reported in the literature (>4 mg/dL) (Movahedian et al., 2021). Despite this, the possibility that these effects may be cumulative or depend exclusively on the participant's BMI cannot be ruled out and so further investigation is needed.

In agreement with previous work related to the absence of adverse effects of S&SE on metabolic parameters (Gallagher et al., 2021; Movahedian et al., 2021; Nichol, Holle, & An, 2018), none of the blends tested in the present study induced rebound hunger and all were safe in terms of hepatic impact and side effects. Our findings also confirm previous work related to the lack of adverse effects of S&SE on acute blood glucose control (Greylling, Appleton, Raben, & Mela, 2020; Tucker & Tan, 2017)

The present work revealed improved insulinemic responses for steviol glycosides and mogroside V vs sucrose. Several studies have examined the glycaemic impact of steviol glycosides, mostly stevia RebA (Anton et al., 2010; Stamataki, Crooks, Ahmed, & McLaughlin, 2020; Stamataki, Scott, et al., 2020; Tey, Salleh, Henry, & Forde, 2017a, 2017b); and sucralose, with or without ace-K (Bryant, Wasse, Astbury, Nandra, & McLaughlin, 2014; Pepino, Tiemann, Patterson, Wice, & Klein, 2013; Sylvetsky, Brown, Blau, Walter, & Rother, 2016), with fewer studies evaluating mogroside V (Tey et al., 2017a; 2017b). To the best of our knowledge, no peer-reviewed, comparable randomised clinical trial for thaumatin has been published.

The effects of stevia (as steviol glycosides, mostly RebA) are well documented and tend to agree with our results. Trials using stevia RebA in beverage form have shown improvements in the glycaemic response vs caloric (sucrose or glucose) preloads in acute settings (Stamataki, Scott, et al., 2020; Tey et al., 2017b), but no impact on the long-term, despite reductions in energy intakes (Stamataki, Crooks, et al., 2020; Tey et al., 2017a). In terms of the glycaemic response to a meal, stevia RebA, but not other S&SEs, was found to attenuate the post-prandial blood glucose peak in previous studies (Anton et al., 2010; Stamataki, Scott, et al., 2020). We did not detect changes in the 2-h temporal profile of glucose after consumption of S&SEs or sucrose with a meal, however, all S&SE blends improved the 2- h insulin curve and both insulin and glucose iAUCs, vs. sucrose. The lack of impact of blends on the 2-h glucose curve is probably due to the relatively large carbohydrate load given very close to the meal with all beverages.

The main contrast between the present study and previous ones employing stevia is in the total energy intakes (including preload and ad libitum intake). While in a previous acute study (Stamataki, Scott, et al., 2020) participants ate overall less energy after a stevia RebA vs sucrose preload, in our study the reduction in total intakes for both blends including stevia (RebA and RebM) was more subtle and not significant. The results from Stamataki, Crooks, et al., 2020 also contrast with those from Anton et al., who used solid preloads sweetened with either stevia, aspartame, or sucrose, and found no added energy intake after S&SEs (Anton et al., 2010). Due to the solid nature of the preload, it is possible that the satiating impact of the S&SEs in that study may have been enhanced vs a liquid preload, either via the texture or other food characteristics (Almiron-Roig et al., 2013; Appleton et al., 2021). In line with our results, another study (Tey et al., 2017b), also failed to detect an impact in total energy intakes after a sucrose or stevia RebA beverage preload.

Contrary to preload beverages containing mogroside alone (Tey et al., 2017b), mogroside together with steviol (RebM) in our study did not induce higher appetite ratings, confirmed by comparable total energy intakes vs the sucrose condition. Our findings are still relevant as the dosage of both mogroside and sucrose used in the Tey's study were higher [0.63 g mogroside extract exclusively in Tey's vs 0.13 g in this study (as blend); and 65 g sucrose in Tey's vs 26 g in the present study] (Tey et al., 2017b). Therefore, the impact on glycaemic and appetite responses are still visible at these much lower concentrations.

A beverage containing ace-K with sucralose with and without aspartame marginally increased insulin AUCs (by 22–25%) and glucose-induced GLP-1 secretion in a previous study without impacting on glycaemia (Sylvetsky et al., 2016). Ace-K, but not sucralose, alone was also found to exert a small impact on glycaemia when administered in doses equivalent to habitual consumption (Bryant et al., 2014). Ace-K differs from other S&SEs because it activates bitter taste receptors at lower concentrations (Dotson et al., 2008). Overall, the impact of sucralose on glycaemic response is under debate (Grotz & Jokinen, 2014; Khan &

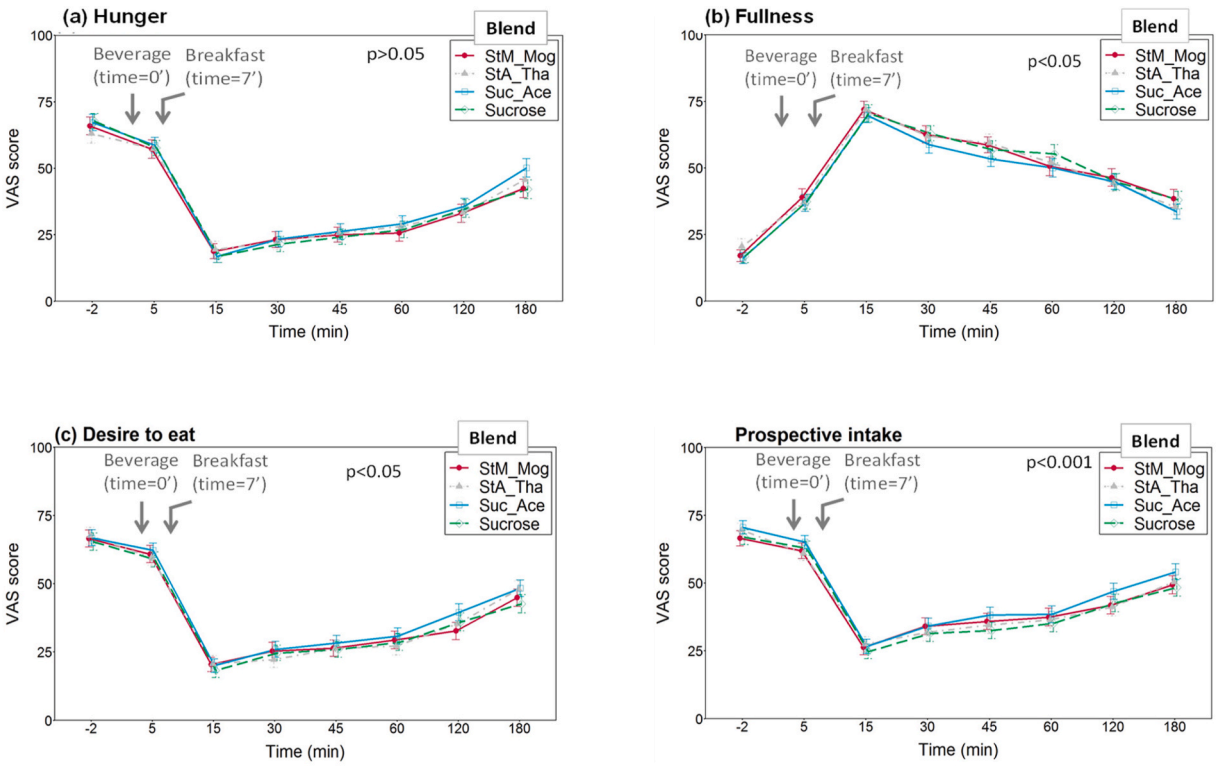

Fig. 4. Temporal profiles for subjective hunger, fullness, desire to eat and prospective intake across blend condition (N = 58–60). Data points are means with SE. Overall impact of blend shown on the right upper corner.

Table 4
Liking and desire scores for the intervention beverages collected at time 5 min (after drink consumption). Values are mean (SD) across all centres. Means with different superscript letters differ at the $p < 0.001$ level (liking) or $p < 0.05$ level (desire).

VAS rating (0–100 mm)	N[a]	StM_Mog	StA_Tha	Suc_Ace	Sucrose	Overall impact of blend
Liking[b]	59–60	59.53 (21.78)[a]	59.51 (23.95)[a]	71.32 (18.12)[b]	73.41 (16.90)[b]	p < 0.001
Desire[c]	58–60	34.75 (23.12)[a]	32.97 (21.53)[a]	43.5 (25.62)[b]	47.07 (23.07)[c]	p < 0.001

[a] One outlier was identified and excluded for sucrose for "Liking"; two missing values for "Desire" and one missing value for "Liking" (both for StA_Tha) were identified and those subjects were excluded.

[b] Linear mixed effects regression adjusted for intervention site, age group, and sex. Intervention site and sex retained a significant impact in the final model.

[c] Linear mixed effects regression adjusted for intervention site, age group and sex. All covariates retained a significant impact in the final model (see Supplementary Material, Additional Results, for details).

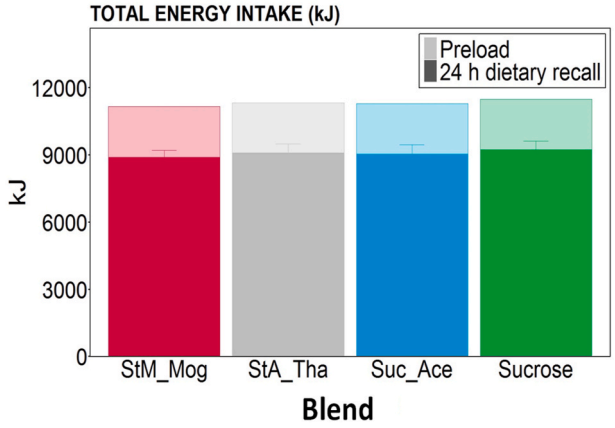

Fig. 5. Total energy intake by blend condition. Data across all centres (N = 59–60). Columns are total mean ± SE energy consumed including preload (beverage plus breakfast) and 24 h ad libitum intake. There were no significant differences across blend in 24 h ad libitum energy intake ($p = 0.278$), or in total energy intakes ($p = 0.825$) in the adjusted models.

Sievenpiper, 2021; Pepino et al., 2013; Sylvetsky et al., 2016; Yunker et al., 2021) and it is unknown by which mechanism sucralose's effects, if real, happen (e.g. by activation of pancreatic or intestinal sweet taste receptors) (Buchanan et al., 2022; Sylvetsky & Rother, 2018). Some of these studies have used beverages containing other ingredients (i.e. cola-based, caffeine-free sodas), which may have confounded the results.

Concerning the appetite response, our findings support the concept that some S&SEs induce higher subjective appetite and lower subjective fullness compared with caloric controls (Tey et al., 2017b). However, we detected no changes in the ni-AUC values for the appetite VAS and no impacts on total energy intakes. While some studies have found related S&SE blends to impact similarly on appetite (e.g. containing sucralose) (Sylvetsky et al., 2016), stevia and aspartame preloads were equally satiating in other studies (Anton et al., 2010; Stamataki, Scott, et al., 2020). In the present work, both blends with steviol glycosides seemed to control appetite better compared with the sucralose blend irrespective of time course, therefore the potential different mechanisms of action are worthy of further investigation.

The Suc_Ace beverage was similarly liked and desired as the energy-containing sucrose control, while the novel stevia blends had a lower acceptance, although still close to 60%. Unpublished data suggest that the Suc_Ace blend was also associated with a lower craving control compared with all other conditions (that is, regardless of energy

content). It has been suggested that sucralose can increase reward responses to specific food cues in women and in persons living with obesity (Yunker et al., 2021), which would initially agree with our observations. It is also known that S&SE can bind to different regions of the sweet taste receptor heterodimer (Kim, Chen, Abrol, Goddard, & Guthrie, 2017) and in gut sensor cells T13R receptors (Buchanan et al., 2022) unchaining distinct patterns of intracellular signals which likely contribute to each S&SE sensory profile, pre-ingestive responses and downstream effects (Higgins & Mattes, 2019).

4.1. Strengths and limitations

This study overcomes a number of limitations identified in a previous systematic review on the impact of S&SE on the glycaemic response (Greylling et al., 2020). First, this was a large cross-European trial involving blends, as opposed to single sweeteners, which allowed for an increase in sweetness and reduction in off-tastes (Feder, 2012; Michail, 2017; Pawar, Krynitsky, & Rader, 2013). As a result, smaller doses of some S&SEs were used compared with some previous studies using single doses. Our findings on the metabolic impact in particular for the stevia blends and for thaumatin (lacking published clinical data), may be useful as part of any ongoing assessments of these S&SEs. The cross-European nature of the trial may help to generalise the results among habitual S&SE consumers.

Second, the present study used of a tightly controlled cross-over design with exclusion of normal-weight participants, which ensured a relatively low inter-individual variability. The study was also double-blinded, which is often not possible in nutritional interventions.

The wide range of endpoints assessed was made feasible by the multidisciplinary approach of this work and the relatively large sample size, compared with similar studies. This was particularly useful in the analysis of covariates for appetite ratings and metabolic markers, allowing detection of subtler differences between S&SE blends, beyond the control condition. Also, treatment order effects were minimal and did not modulate the impact of blend on appetite ratings.

The intervention beverages were delivered very close in time with a standardised breakfast providing about 1/3 of the individual's daily requirements, including 50–80 g of carbohydrate, which likely attenuated the impact of the blends on blood glucose levels and later energy intakes. A different type of meal (e.g. fat or protein-rich) may have induced different glycaemic and lipid responses and could also be affected by the nutritional status of the participants (Movahedian et al., 2021). This design was purposely chosen to simulate normal eating and drinking situations and to maximize the impact of the intervention product providing virtually no energy (for which little or no compensatory behaviour was expected) (Almiron-Roig et al., 2013). Although, such a design makes the interpretation of the true effects of each blend more difficult, the purpose was to see if blends given before a fixed meal resulted in different glycaemic responses, and this was achieved. A retrospective power calculation taking into account multiple comparisons estimated the reached power to be 50–82% for the glucose iAUCs comparisons vs. sucrose, and of 90–92% for the insulin iAUC comparisons.

The beverages were designed to be matched for sweetness intensity, bitterness intensity and other sensory characteristics. Although, sensory analyses failed to show total similarity in sweetness levels in each of the beverages, differences in liking and desire were moderate and did not significantly affect appetite and energy intakes except for minor changes in fullness and desire to eat ratings. As this was an acute postprandial study, the effects of longer and larger doses of S&SEs were not analysed. These effects may differ depending on trial duration and repeated exposure. Finally, participant-specific, individual responses were not fully investigated. For example, insulin sensitivity may be affected by menstrual cycle (Grotz & Jokinen, 2014) and this was not controlled for. However, exposure conditions were randomised and the trial lasted for approximately 4–6 weeks, which hopefully helped counterbalancing the potential effect of menstrual cycle.

5. Conclusions

The results of this investigation confirm the neutral or beneficial impact in acute glycaemic control arising from combining plant-based S&SEs such as stevia RebA, stevia RebM, thaumatin, and mogroside V, compared with a sucrose-yielding beverage. The explored S&SEs in beverage format could be used to improve the glycaemic response to a meal without significant negative effects on acute food intake behaviour or body metabolism, which would support their potential role in the prevention and management of diabetes and for body weight management, as part of a wider lifestyle approach.

Author's contributions

JAH, JCGH, and AR are the SWEET project coordinators. JAM and GF are leader and co-leader for this acute clinical trial work package in SWEET; CS coordinated the S&SEs selection process, design and manufacturing of the beverages and sensory analyses. MMR led the Consumers' Perspectives theme and implemented the Qualtrics survey alongside CEH. EAR, LK, and CAH led the intervention studies at Navarra, Copenhagen, and Liverpool respectively, with support from SNC, JAM, AR, and JAH. GC, MN, LK, and NM led the data collection. ARH is the datahub manager for the acute trials and performed the data analysis for all sites. HM performed the biochemical analyses. EAR wrote the first draft of the paper. All authors provided revisions and have approved the final version of the manuscript.

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Declaration of competing interest

JCGH, JAH, and CAH and are in receipt of research funding from the American Beverage Association; MMR and CEH's research centre provides consultancy to, and has received travel funds to present research results from organisations supported by food and beverage companies. ARA has received honoraria from Nestlé, Unilever and the International Sweeteners Association. CAH has received honoraria from the International Sweeteners Association. CS is an employee of Cargill, Inc. The other authors have nothing to declare.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.appet.2023.106515.

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