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EffectS of non-nutritive sWeetened beverages on appetITe during aCtive weigHt loss (SWITCH): Protocol for a randomized, controlled trial assessing the effects of non-nutritive sweetened beverages compared to water during a 12-week weight loss period and a follow up weight maintenance period

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ABSTRACT

Background: Acute and medium-term intervention studies suggest that non-nutritive sweeteners (NNS) are beneficial for weight loss, however there is limited human data on the long-term effects of consuming NNS on weight loss, maintenance, and appetite. Further research is therefore required to elucidate the prolonged impact of NNS consumption on these outcome measures.

Methods/design: A randomized parallel groups design will be used to assess whether regular NNS beverage intake is equivalent to a water control in promoting weight loss over 12-weeks (weekly weight loss sessions; Phase I), then supporting weight maintenance over 40-weeks (monthly sessions; Phase II) and subsequently independent weight maintenance over 52-weeks (Phase III) in 432 participants. A subset of these participants (n = 116) will complete laboratory-based appetite probe days (15 sessions; 3 sessions each at baseline, at the start of phase I and the end of each phase). A separate subset (n = 50) will complete body composition scans (DXA) at baseline and at the end of each phase. All participants will regularly be weighed and will complete questionnaires and cognitive tasks to assess changes in body weight and appetitive behaviours. Measures of physical activity and biochemical markers will also be taken.

Discussion: The trial will assess the efficacy of NNS beverages compared to water during a behavioural weight loss and maintenance programme. We aim to understand whether the impact of NNS on weight, dietary adherence and well-being are beneficial or transient and effects on prolonged successful weight loss and weight maintenance through sustained changes in appetite and eating behaviour.

Trial registration: Clinical Trials: NCT02591134; registered: 23.10.2015

1. Introduction

The global rise in the prevalence of obesity is a major public health concern [1] attributed to an 'obesogenic environment', characterised by increases in low-cost, energy-dense foods and drinks, amongst other lifestyle factors. Increased consumption of sugar-sweetened beverages (SSBs) has been related to this rise in obesity prevalence [2,3,4], possibly due to the poor satiating value of these beverages [5,6], with individuals not responding to additional calories physiologically [7] or cognitively [8,9]

Non-nutritive sweeteners (NNS) enable the consumption of sweet tasting, yet low energy, foods and beverages. Low energy foods and beverages could help reduce energy intake due to an absence of energy compensation [10-12] driven by changes in appetite regulation and gut hormone release compared to SSB [12]. Consumption of these products has been associated with reductions in body weight and weight-related disease risk [13]. Recently, Peters et al., [14,15] provided participants with either NNS beverages or water as part of a 12-week behavioural weight loss programme to understand the effects of NNS during active weight loss [14], followed by a weight maintenance period [15]. In the longest study to date, the NNS group lost significantly more weight and reported greater reductions in hunger after 12 weeks. This group was also better able to maintain weight loss over the subsequent 40 weeks compared to control. These data indicate potential benefits of including NNS products to help reduce and maintain reduced body weight, although no mechanisms for these effects were examined. Indeed, recent reviews of randomized controlled clinical trials (RCTs) show associations between substituting SSBs for NNS and lower weight, fat mass, waist circumference and body mass index (BMI) in both adults and children [16]; long-term lower energy intake and weight loss

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(when combined with other low energy alternatives) [17] and no relation between NNS and increased energy intake or weight [18]

Despite promising findings, concerns remain about the potential negative impact of NNS beverages on appetite and weight management. Some argue that chronic NNS exposure may undermine energy regulation by impeding the learned association between sweetness and energy [19,20]. Rodent studies suggest that NNS alter blood glucose levels via altered post-prandial glucagon-like peptide 1 (GLP-1) secretion, weakening the impact of sugars on the satiety hormone response [21], whilst clinical studies of insulin sensitivity and GLP-1 release yield mixed results [22,23,24,25]. Some epidemiological evidence suggest an association between the use of NNS and obesity [26,13,27], though findings may be explained by reverse causation [18,27].

The mechanisms by which NNS may affect energy balance and weight maintenance during a long-term intervention still need to be elucidated, including the influence on energy intake, compensation, appetite control, and food choice which has not been quantified thus far. The present research will examine (i) the effect of NNS beverages on weight loss and long-term weight maintenance and (ii) the behavioural and biological mechanisms through which these effects arise as compared to water.

2. Methods and materials

2.1. Outcome measures

2.1.1. Primary outcome measure

The primary outcome measure will be weight change (kg) from baseline to post-weight loss phase (WLP) and weight maintenance phase (WMP; end of year one).

2.1.2. Secondary outcome measures

2.1.2.1. Physiological.
i) Anthropometric (waist and hip circumference) and body composition (percentage fat mass and total fat mass, upper body and lower body fat and fat-free mass measurements using DXA scanning in Subset 2).
ii) Biochemical changes in markers of glycaemic control (fasting insulin, fasting glucose and HbA1c), fasting lipid profiles (total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL) and liver function tests (ALT, AST and GGT)).

2.1.2.2. Psychological.
i) Measurements of appetite expression.
Changes in food preferences, cravings and eating behaviours (through 24-hour recall food diaries, sweet food frequency questionnaires (sFFQ) and associated craving questionnaires) as well as changes in mood and mental wellbeing will also be examined in the study population as a whole. Appetite expression (hunger, satiety, liking and wanting) and calorie intake (food choice, macronutrient intake and energy compensation) will be assessed in a subset containing equal numbers of NNS beverage and water consumers (Subset 1). These between-group (and appropriate within-group) comparisons will determine whether the effects of NNS or water on subjective ratings of appetite and mood are beneficial to successful weight management (over the weight loss and weight maintenance phases). Examination of food choice, changes in attitudes to NNS or water, food preference, cravings and macronutrient intake will investigate potential detrimental or beneficial in preference for sweetness.
ii) Experience and ease of weight loss in WLP and assisted WMP.
To determine the behavioural mechanisms of action when using NNS or water during weight loss and weight loss maintenance in those who regularly consume NNS and/or water beverages, the experience of and perceived ease of weight management will be assessed by the inclusion of psychological cognitive tests and questionnaires.

2.2. Trial design

The study will use a parallel randomized design with two arms: an NNS beverage arm (active) or a water beverage arm (control). The trial will enroll 432 participants. All participants will undergo an initial 12-week weight loss phase (WLP; Phase I) - in which participants will attend weekly behavioural weight loss group sessions and incorporate either NNS or water as their treatment group beverages into their diet throughout the trial. Subsequently, participants will undergo a 40-week assisted weight maintenance phase (WMP; Phase II) and attend monthly group sessions (whilst continuing to consume NNS or water). A third phase will consist of a further 12-month non-assisted WMP (Phase III) in which participants will not receive any further behavioural and nutritional advice, but continue to consume NNS beverages or water and complete monthly retrospective appetite and mood ratings (Fig. 1). Two subgroups will additionally complete appetite probe days (Subset 1; 15 sessions in total; $n = 116$) or undergo DXA scanning (Subset 2; 4 sessions in total; $n = 50$).

2.3. Participants

2.3.1. Inclusion criteria

The following inclusion criteria must be met: healthy overweight and obese adult males and females (BMI: 27–35 kg/m^2; age range: 18–65 y) who are either regular consumers (>3 drinks per week but < 2 l per day) of chilled NNS or are NNS beverage naïve (assessed as no NNS or up to 25% NNS beverage choices made over the last five years). Participants must accept randomization to either a water or NNS beverage condition and must be willing to abstain from consuming NNS beverages (if randomized to the water condition) or willing to consume NNS beverages (if randomized to NNS group) for the duration of the trial. They must not be planning on moving from the Merseyside area for the duration of their participation in the trial and they must provide voluntary written informed consent.

2.3.2. Exclusion criteria

Exclusion criteria include: expressing a significant dislike of NNS beverages (less than moderately likeable on a 7-point Likert scale); first year University students (to avoid the 'freshman 15' phenomenon of weight gain within the first year of attending University and thus increasing variance in the sample; [29,30]); any significant health problems (including a history of cardiovascular diseases); any gastrointestinal problems; type 1 or type 2 diabetes mellitus; taking any medication or supplements known to influence appetite or weight within the past month and/or during the study; stated major psychiatric disorder (made clear by medicines specified); currently suffering from depression (made clear by medicines specified); currently being treated for a psychological condition; pregnancy, planning to become pregnant, breastfeeding or <6 months post-partum; history of anaphylaxis to food; known food allergies or food intolerance; dislike of >25% of the study foods offered on the appetite probe day (Subset 1 only); non-breakfast eaters; smoking or having ceased smoking in the last six months; currently dieting, having ceased a diet in <4 weeks, or having