Effects of non-nutritive sweetened beverages versus water after a 12-week weight loss program: a randomized controlled trial

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Conflicts of interest

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Author contributions

Joanne A. Harrold and Jason C.G. Halford were both principal investigators. The study was designed by Joanne A. Harrold and Jason C.G. Halford, with contributions from Charlotte A. Hardman. Joanne A. Harrold provided day-to-day project management. Scott Hill, Cristina Radu, Paul Thomas, and Paula Thorp collected and cleaned the data. Paul Christiansen analyzed the data. All authors contributed to the interpretation of the results and the development of the manuscript.

Study importance

What is already known about this subject?

- Weight loss has been observed following consumption of both non-nutritive sweetened (NNS) beverages and water in the context of behavioral weight management programs in randomized controlled trials.
- However, most of these trials have been of short duration (less than 6 months), whereas large-scale, longer-term trials (of 1 year or more) on this topic are limited.

What are the new findings in your manuscript?

- This is an ongoing 2-year randomized controlled trial (1 year of assisted weight management plus a voluntary, unassisted 1-year extension); at week 12, after a weekly behavioral weight management program, weight loss was equivalent in participants who consumed NNS beverages and those who consumed water.
- The design of this UK-based trial was modeled on a previous US-based trial, but with the inclusion of participants who do not normally drink NNS beverages (i.e., NNS beverage-naïve) as well as those who do; the results provide insights into the generalizability of the effects observed by testing them in a different geographic population (previously in the US, now in the UK).

How might your results change the direction of research or the focus of clinical practice?

- The results of this trial provide further evidence that NNS beverages have similar effects as water on weight loss during a 12-week behavioral weight management program, even in people who would not normally drink NNS beverages.
- These reproducible findings should therefore help reassure healthcare professionals that NNS beverages can be used during weight loss without deleterious effects.

Abstract

Objective: Compare non-nutritive sweetened (NNS) beverages versus water for weight loss after a 12-week behavioral weight management program.

Methods: This is an ongoing 2-year parallel-group, open-label, controlled equivalence trial; week 12 data are reported. Adults with body mass index 27–35 kg/m^2 who regularly drank cold beverages were randomized 1:1 to intention-to-treat water or NNS beverages while undergoing a weekly 12-week group behavioral weight management program. Weight change to week 12 was the primary endpoint (equivalence: two-sided p>0.05); changes in waist and hip circumference, blood pressure, glycemic control markers, fasting lipid profiles, liver function tests, hunger (visual analog scale), sugar and sweetener consumption, and activity levels were secondary endpoints.

Results: Overall, 493 participants were randomized (water: n=246; NNS beverages: n=247); 24.1% were NNS-naïve. Weight change was equivalent with water versus NNS beverages (–5.6 vs. –5.8 kg; difference [90% confidence interval]: –0.2 kg [–0.7 to 0.4]). There were no significant differences between groups for secondary endpoints except reductions in waist circumference (greater with NNS beverages vs. water), HbA_{1c}, and consumption of any type of sweetener (both greater with water vs. NNS beverages).

Conclusions: Weight loss was equivalent with NNS beverages and water following a 12-week behavioral weight management program.

INTRODUCTION

Obesity is a growing global health challenge; there are predicted to be over one billion adults living with obesity worldwide by 2030 (1). Overweight and obesity are associated with a plethora of weight-related complications such as type 2 diabetes and cardiovascular disease (2,3), as well as poor mental health and quality of life (4,5). In addition, obesity and related complications have direct and indirect economic effects by increasing healthcare resource utilization and lowering productivity (6-8).

Sugar-sweetened beverages are a major source of sugar in the diet that, with excess consumption, contribute to weight gain (9). Dietary guidelines therefore often recommend reducing use of such beverages in favor of lower-calorie options such as water or those sweetened with non-nutritive sweeteners (NNS) in order to reduce sugar consumption (10,11). NNS have sweetness potencies many times greater than that of sugar, enabling them to evoke pleasant sweetness sensations at much lower concentrations than sugar while providing few, if any, calories (12). In theory, their use can assist with weight management by reducing energy intake while allowing people to continue consuming favored beverages.

In practice, the use of NNS as part of a weight management strategy remains under debate (12-14). Some studies in rodents and small mechanistic studies in humans suggest NNS potentially promote overweight and obesity through a variety of mechanisms such as changing eating behavior (15) or altering gut microbiota (16). However, these findings have not been replicated in randomized controlled trials (15,16). For observational studies, meta-analyses suggest an association between NNS use and an increase in body mass index (BMI), risk of obesity, and weight-related complications (17,18), though these findings may be affected by reverse causality (17,19). In contrast, randomized controlled trials indicate either positive or neutral effects on body weight and cardiometabolic risk factors with their consumption (17,20). Similarly, a meta-analysis of intervention studies found neutral effects of low-calorie sweetener consumption on body weight when compared with water/nothing

and beneficial effects when compared with sugar (21). For beverages specifically, which have been the subject of most of the studies conducted to date, findings suggest weight loss outcomes with NNS beverages are similar to those with water, and are greater with NNS beverages compared with sugar-sweetened beverages (17).

Given the debate in the literature, there remains a need for randomized controlled trials investigating the effects of NNS beverages on body weight and associated weight-related outcomes. Most trials in this area have been of short duration (less than 6 months) (17). Thus, trials that are large enough and long enough to provide robust results in particular are required. The effectS of non-nutritive sWeetened beverages on appetITe during aCtive weigHt loss (SWITCH) trial was conducted to address this need (22). It was designed based on a previous trial by Peters and colleagues at the University of Colorado and Temple University (23), which was a 1-year randomized controlled trial comparing effects of NNS beverages and water on weight loss and overall weight management. The Colorado/Temple trial consisted of 12 weeks of active weight loss (using a weekly behavioral weight management program), followed by 40 weeks of assisted weight maintenance (monthly lifestyle intervention sessions) (23). The SWITCH trial built on this by including an additional voluntary 1-year extension to assess effects during unassisted weight maintenance, as well as including both NNS beverage-naïve and non-naïve participants.

In alignment with the Colorado/Temple trial (24), this manuscript reports the results after the 12-week active weight loss phase of the SWITCH trial. The aim of this analysis was to evaluate the effects of consuming NNS beverages on weight loss compared with consuming water after a 12-week behavioral weight management program. These data will also allow for assessment of weight regain during the weight maintenance phases of the trial.

A plain language summary of this article (as text and as a shareable infographic) are available in Appendices S1 and S2.

METHODS

The design of the SWITCH trial has previously been reported (22) and is briefly described here.

Population

Participants were recruited from a 50-mile radius in and around the county of Merseyside, England. Eligible participants were healthy males and females with overweight or obesity (BMI: 27–35 kg/m^2) aged 18–65 years who regularly drank >3 cold beverages per week (water, NNS, or sugar-sweetened; NNS and sugar-sweetened beverages had to be <2 L per day). Individuals who did not regularly consume >3 chilled beverages of any type per week, who were smokers (within 6 months of screening), had gastrointestinal-related conditions, food allergies, excessive alcohol consumption, diabetes or other serious health challenges (including a history of cardiovascular disease), had taken medication or supplements known to affect weight in the 1 month to screening, engaged in regular intense exercise, were dieting or had significant weight loss in the 1 year to screening, or who had undergone bariatric surgery were excluded. All participants were required to be willing to consume NNS beverages or water for the duration of the trial, and discontinue drinking NNS beverages if they were assigned to the water group; participants in both groups could continue to drink sugar-sweetened beverages. Full eligibility criteria are provided in Appendix S3.

Trial design

The SWITCH trial is an ongoing 2-year, parallel-group, open-label, randomized, controlled trial composed of three phases: a 12-week active weight loss phase, a 40-week assisted maintenance phase, and a voluntary 52-week non-assisted maintenance extension phase (Figure 1). The first two phases were included to align with the previous trial by the Colorado/Temple group (23), with the addition of the non-assisted maintenance extension phase; the extension phase was made voluntary as an amendment to the original protocol.

The trial was conducted at the University of Liverpool, England. The protocol and amendments were reviewed and approved by the University of Liverpool. The National Research Ethics Service Ethics Committee North West – Liverpool East provided ethical approval (reference 16/NW/0347). All participants provided written informed consent.

All participants who remained in the trial and completed the first 52 weeks were reimbursed £300, with an additional £100 if they also completed the voluntary 52-week extension (i.e., a total of £400 for participants who completed the full 2 years). Further reimbursement was provided at the end of the 2 years for participants involved in two additional assessments: appetite probe days (data not reported here), for which participants received £130; and dual-energy X-ray absorptiometry (DXA), for which participants received £200.

Interventions

Participants were assigned (1:1) to either water or NNS beverages by block randomization (block sizes of 4 and 6) using a computer-generated randomization sequence. To ensure groups were balanced on key characteristics, randomization was stratified by sex (male and female), age (18–35, 36–50, and 51–65 years), BMI (<30 and ≥30 kg/m^2), and NNS naïveté (naïve and non-naïve consumers [NNS beverages comprising 0–≤25% and >26–100% of drink choices, respectively, in the 5 years to screening]).

Participants were asked to consume at least two servings (330 mL per serving) per day of their intention-to-treat NNS beverages or water (depending on randomized assignment) for the duration of the trial. Both NNS beverages and water could be still or carbonated. There was a mix of carbonated and still options among the most popular beverage choices. For the water group, at least two of the daily 330 mL servings were to be of bottled water; additional servings could be of municipal tap water. Participants in the water group were also asked to refrain from drinking NNS beverages for the duration of the trial. Funding for the trial beverages was provided by the trial sponsor to investigators, who

managed direct delivery to participants' homes. Participants could select from a range of 20 different types of branded beverage options from various manufacturers that were available in individual 330 mL servings; to be classed as non-nutritive, the beverages selected for inclusion had to contain fewer than 5 kcal per 8 oz, equivalent to 2.11 kcal per 100 mL. Participants' adherence to these requirements was assessed through online daily beverage logs, return of empty packaging, and periodic 24-hour dietary recall assessments.

The 12-week active weight loss phase was based on the comprehensive cognitive-behavioral intervention, 'The Colorado Weigh' (25), used by the Colorado/Temple group (23). The program consisted of weekly one-hour group meetings (5–20 participants) led by a qualified nutritionist who provided guidance on nutrition, behavioral changes, and structured physical activity, as well as homework for participants to complete prior to their next session (22). Further details are available in Appendix S4.

Outcomes and assessments

The primary endpoint was the change in body weight (in kg) from baseline at three timepoints: week 12 (after the weight loss phase), week 52 (after the weight loss and assisted maintenance phases), and week 104 (after the weight loss, assisted, and voluntary non-assisted maintenance phases); data at weeks 52 and 104 are not reported here. Secondary endpoints assessed at week 12 included changes from baseline in: waist and hip circumference, glycemic control markers, fasting lipid profiles, liver function tests, hunger (measured at baseline and once a month as changes on a 0–100 mm visual analog scale [VAS] anchored at "not at all hungry" and "extremely hungry"), sugar and sweetener consumption (assessed using a Sugar and Sweetener Food Frequency Questionnaire [SSFFQ] at baseline and once a month (22)), and activity level (based on steps measured using activity trackers). The SSFFQ assessed the previous month's consumption of sugar or sweetener in foods and drinks based on frequency and portion estimates, with higher scores indicating higher consumption; participants did not need to specify if sweeteners were caloric or non-caloric. The SSFFQ thus provided an estimate of consumption of added sugar and

broadly all sweeteners from any sources (i.e., those added to foods and beverages either by manufacturers or by participants themselves). In addition, change from baseline to week 12 in body composition was assessed in a subset of participants using full-body DXA.

Body weight, and waist and hip circumference were measured by trial staff; these measurements were self-reported during the coronavirus disease 2019 (COVID-19) pandemic, as noted elsewhere. Body weight measurements were taken at baseline and weekly thereafter, and waist and hip circumference, hunger VAS, and SSFFQ were measured at baseline and every 4 weeks thereafter. Fasting blood samples (consenting participants only) and DXA (after an overnight fast; DXA subset only) were taken at baseline and week 12; during the pandemic, blood samples were only taken when COVID-19 restrictions permitted. Physical activity was monitored for 1 week at baseline and week 12 using electronic activity tracker wristbands.

Protocol deviations in response to the COVID-19 pandemic

England's COVID-19 restrictions in 2020 and 2021 necessitated deviations from the planned protocol, as outlined below.

Provision of and adherence to trial beverages

The frequency of beverage deliveries was reduced in order to minimize social contact, but there were no breaks in supply. Participants were asked to submit photos of their empty packaging to measure adherence.

Group meetings and activity monitoring

Group sessions were conducted via the online Zoom platform. The planned curriculum of the sessions was strictly adhered to with adjustments made to the interactive aspects so that they could be included. The distribution of activity tracker wristbands to participants was suspended during this time period.

Assessments

Some scheduled body weight and waist and hip circumference measurements were self-reported by participants using a secure online questionnaire. To collect these data, all affected participants were provided with the same make and model of electronic scale and tape measure, sent directly to their homes, along with detailed instructions. Measurements were taken by trial staff when restrictions permitted. A comparison of self-reported and clinic-collected body weight measurements was performed to assess the potential impact on the primary endpoint. In addition, some individual trial visits during this time were conducted online using a questionnaire developed on the Qualtrics platform. This prevented the collection of blood pressure and blood samples from some participants.

Statistical analysis

The trial was designed to test the equivalence of NNS beverages to water in terms of weight loss at week 52. Equivalence was defined as a two-sided p value > 0.05 at week 52. Assuming an attrition rate of 27% (based on a previous, similar trial (23)), a sample of 316 participants (n = 158 per group) provided 90% power to detect a difference of ±1.5 kg weight change between groups at week 52.

Statistical analyses were performed blind to assigned trial group (NNS beverage or water). The endpoints were assessed using an analysis of covariance (ANCOVA), with blinded trial group as a predictor and baseline value of the outcome of interest as a covariate (e.g., baseline body weight for the analysis predicting week-12 body weight). A sensitivity analysis was performed for week-12 body weight and waist and hip circumference using the same ANCOVA, but with the inclusion of additional covariates (age, sex, location of weight measurement [self-collected vs. clinic-collected], and NNS beverage naïveté [non-naïve vs. naïve]).

The primary analysis used data from participants who completed the week-12 timepoint (the complete cases analysis). Analyses were repeated on two alternative data

296 sets: an imputed multiple imputation data analysis, in which missing data were imputed
297 using predictive mean matching (50 imputations), and a last observation carried forward
298 analysis.

RESULTS

Participants

Between July 2016 and December 2021, a total of 493 participants were randomized and started trial treatment (water: *n* = 246; NNS beverages: *n* = 247) (Figure 2). The 12-week timepoint was completed by 383 participants (77.7% of the starting population), who were included in the primary analysis.

Participants' baseline characteristics were generally similar between the groups (Tables 1–3). However, there were imbalances between the groups in mean concentrations of fasting serum insulin and gamma-glutamyl transferase, which were likely due to outliers (Table 3). In total, 24.1% of randomized participants were NNS beverage-naïve.

Anthropometrics

Of the 383 participants who contributed to the primary outcome, 219 had clinic-collected data, 137 had self-collected data, and 27 had clinic-collected baseline data and self-collected week-12 data. At week 12, the mean weight change from baseline was –5.6 kg with water versus –5.8 kg with NNS beverages for the complete cases analysis; the difference between the groups was not statistically significant for the test of equivalence (Figure 3, Table 2). A Bayesian analysis provided further support for the null hypothesis of there being no difference in weight change between the two groups (Appendix S5). Body weight measurements were not affected by collection location (self-collected vs clinic-collected) (Figure S1).

Baseline weight had a significant effect on weight at week 12; when controlling for this, there were no significant differences in week-12 weight between groups (effect of beverage group [95% confidence interval (CI)]: –0.2 kg [–0.8 to 0.4]; $p = 0.477$). In the sensitivity analysis, baseline weight and age had significant effects on week-12 weight; sex, location of weight measurement, and NNS naïveté had no effect (Tables S1 and S2). When

controlling for all these covariates, there were no significant differences in week-12 weight between groups (effect of beverage group [95% CI]: –0.3 kg [–0.9 to 0.3]; $p = 0.267$). Findings were similar for the imputed data and last observation carried forward analyses (Tables S3 and S4).

Waist and hip circumference were reduced from baseline in both groups (Figures 4 and 5, Table 3). Baseline waist and hip circumference both significantly affected the respective week-12 value; when controlling for this, the beverage group was found to have a significant effect on week-12 waist circumference, but not hip circumference (Tables S5 and S6). When controlling for additional covariates in the sensitivity analysis, the beverage group had no significant effect on week-12 value on hip circumference, but the effect on waist circumference was maintained.

Furthermore, in the DXA subset, fat and fat-free mass, and android and gynoid fat distribution decreased from baseline to week 12 in both groups (Table 3). There were no significant differences in body composition endpoints between water and NNS beverages.

Biomarkers

There were reductions in nearly all biomarkers assessed at week 12 in both groups (Table 3). The exception was aspartate aminotransferase, which slightly increased with water, but decreased with NNS beverages; values for both groups remained within normal limits. The reduction in HbA_{1c} was statistically significantly greater with water (0.9 mmol/mol) compared with NNS beverages (0.3 mmol/mol), but the difference was not considered clinically meaningful. There were no statistically significant differences between groups for the other biomarkers.

Appetite

Hunger and sugar consumption were reduced in both groups at week 12, whereas sweetener consumption was only reduced with water. The differences between groups were

not statistically significant for hunger and sugar consumption, but the reduction in sweetener consumption was significantly greater with water versus NNS beverages (Table 3).

Activity

Activity levels (measured as the number of steps) had increased in both groups at week 12, with no statistically significant difference between them (Table 3).

DISCUSSION

At week 12, following the active weight loss phase of the 2-year SWITCH trial, NNS beverages and water were equivalent in terms of weight loss, with participants in both groups losing on average just under 6 kg of body weight. This weight loss was accompanied by reductions in anthropometric measures, glycemic control markers, fasting lipid profiles, most liver function tests, hunger, sugar and sweetener consumption, and increased activity levels in both groups. There were no statistically significant changes between groups for these endpoints except waist circumference, HbA_{1c}, and, as may be expected, sweetener consumption (either caloric or non-caloric). For waist circumference, the effect of beverage group remained significant when both baseline value and sex were controlled for in a sensitivity analysis. The difference in HbA_{1c} between groups was not clinically significant as values in both groups remained within the normal range.

The results of this week-12 analysis were not unexpected considering the participants in both groups were highly motivated to lose weight and underwent the same behavioral weight management program. The program used in this trial was partly based on the model developed by Wyatt and colleagues (25) and used in the similar weight management trial by the Colorado/Temple group (23,24). Like the SWITCH trial, the Colorado/Temple group reported body weight reductions with both water (4.6 kg) and NNS beverages (6.5 kg) after 12 weeks of a weekly behavioral weight management program (24). This is consistent with the conclusion of the SWITCH trial that participants can lose weight during a behavioral weight management program with either water or NNS beverages.

Despite the similarity in overall conclusions between the trials, the weight loss in participants consuming NNS beverages in the Colorado/Temple group trial was significantly greater compared with those consuming water ($p < 0.0001$) (24), whereas this was equivalent in the SWITCH trial. A potential reason for this difference is that the Colorado/Temple group only recruited regular drinkers of NNS beverages; the authors proposed the greater behavior change required for participants in the water group (who had

to abstain from NNS beverages completely) might have affected adherence compared with the NNS beverage group (24). In contrast, SWITCH included both NNS beverage-naïve and non-naïve participants to address the potential impact of the required change in behavior. Sensitivity analyses showed that NNS naïveté did not affect body weight at week 12, indicating that naïve and non-naïve participants had similar levels of weight loss. For comparison, a separate trial asked regular drinkers of sugar-sweetened beverages to switch to either water or NNS beverages (26). While weight change between the two groups was not directly compared in that trial, the authors noted that the NNS group had a lower beverage calorie intake than the water group, and the water group may have experienced slower weight loss over the 6-month trial period. They concluded this may be due to participants assigned to the NNS group finding the switch from sugar-sweetened beverages easier than those assigned to the water group, which could have helped them maintain adherence (26).

Unlike the randomized controlled trials described here and elsewhere (23,24,26-29), meta-analyses of observational studies have suggested adverse effects of NNS beverages on body weight and related health outcomes (17,18). When interpreting these conflicting findings, it is important to be cognizant of the lower position of observational studies in the hierarchy of evidence relative to randomized controlled trials (30). Furthermore, it has been suggested that the findings of such observational studies may be a result of reverse causation (17,31,32); i.e., participants who are predisposed to weight gain or development of weight-related complications (e.g., because they have recently gained weight or have elevated risk factors) switch to or increase use of NNS beverages. This could lead researchers to incorrectly believe the NNS use itself led to the increased body weight and development of complications. While randomized controlled trials have not replicated these effects, many of the trials in adults conducted to date have been small ($n < 100$ per group) and/or of short duration (27-29,31), which could limit the validity of their results and make identifying differences between groups difficult. However, the data reported here from

week 12 of the large SWITCH trial reinforces the earlier findings of these existing randomized controlled trials, as well as the conclusions of a large meta-analysis of intervention studies (21), namely that NNS beverages have similar effects as water on weight loss (17,20). Moreover, data from the SSFFQ in SWITCH show that participants in both the NNS and water groups significantly reduced their consumption of added sugar over the 12 weeks compared with baseline. The degree of reduction was similar in the two groups, indicating that consuming NNS beverages does not promote increased consumption of sugar-sweetened foods. In turn, this suggests that NNS beverages could be used as an aid to manage calorie and sugar intake, and thus serve as a viable alternative to sugar-sweetened beverages, including for individuals trying to lose weight.

Strengths of the 12-week analysis of the SWITCH trial include the randomized controlled design and large population, which provided robust, high-quality data on the effect of NNS beverages on active weight loss. Beyond this timepoint, SWITCH will assess the effects of NNS beverages at 1 year, after both assisted weight loss and maintenance, and again after an additional, voluntary 1-year period of unassisted weight maintenance. These three different timepoints will provide greater insight into the longer-term effects of NNS beverages during different periods of weight management. In addition, the inclusion of both NNS beverage-naïve and non-naïve participants helped address any potential impact of prior experience of consuming NNS beverages and thus increased confidence in body weight outcome.

In terms of limitations, the SWITCH trial was conducted at one site in England and did not collect racial or ethnicity data. This meant the potential impact of race or ethnicity on the results could not be considered. It could also have limited the generalizability of the results to other countries, or to racial and ethnic groups not represented in the trial population. In addition, while participants who were NNS beverage-naïve were included in the trial, subgroup analyses by NNS naïveté could not be performed as the number of these participants enrolled was too small (descriptive statistics for these groups are in Table S2).

Despite the small number, the overall proportion of these participants included in the trial (24.1%) was consistent with the proportion of participants who reported not consuming NNS-containing foods or beverages in another UK-based study (25.3%) (33). Instead, NNS naïveté was included as an additional covariate in the sensitivity analysis, which found it had no significant effect on week-12 body weight. The sensitivity analysis also had to include location of weight measurement as a covariate, as the COVID-19 pandemic meant some measurements had to be taken by participants in their homes and self-reported. However, the sensitivity analysis, as well as a comparison of clinic-collected versus self-reported body weight, showed that this had no effect on weight at week 12, increasing confidence in the outcomes observed.

CONCLUSION

After a 12-week active behavioral weight management program, weight loss was not affected by consuming NNS beverages compared with water. Whether the use of NNS beverages affected the maintenance of this weight loss over the following 40 weeks of the trial is currently being assessed.

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DATA SHARING

Participant data are not publicly available but can be requested from the corresponding author after study completion. Requests should be reasonable and accompanied with research proposals that have received appropriate ethical approval. Data will be made available in an anonymized format in compliance with applicable privacy and data protection laws.

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FIGURE LEGENDS

FIGURE 1 Trial design

NNS, non-nutritive sweetened.

FIGURE 2 Participant disposition

[a]Week 12 data were missing for 11 participants (*n* = 6 for water; *n* = 5 for NNS beverages) who remained in the trial. These individuals were therefore not included in the analyses using the complete cases dataset for the week-12 timepoint, but were included in the analyses using the imputed and last observation carried forward datasets. They may also contribute to analyses at future timepoints.

BMI, body mass index; NNS, non-nutritive sweetened.

FIGURE 3 Effects of trial beverage on body weight

Primary analysis of the complete cases dataset, which included all participants with data at baseline and week 12. The shaded areas refer to the kernel density, boxes refer to the interquartile range, the horizontal lines in the center of the boxes refer to the median, and the whiskers refer to 1.5x the interquartile range.

NNS, non-nutritive sweetened.

FIGURE 4 Effects of trial beverage on waist circumference

Primary analysis of the complete cases dataset, which included all participants with data at baseline and week 12. The shaded areas refer to the kernel density, boxes refer to the interquartile range, the horizontal lines in the center of the boxes refer to the median, and the whiskers refer to 1.5x the interquartile range.

NNS, non-nutritive sweetened.

FIGURE 5 Effects of trial beverage on hip circumference

Primary analysis of the complete cases dataset, which included all participants with data at baseline and week 12. The shaded areas refer to the kernel density, boxes refer to the interquartile range, the horizontal lines in the center of the boxes refer to the median, and the whiskers refer to 1.5x the interquartile range.

NNS, non-nutritive sweetened.

TABLE 1 Baseline characteristics

Variable	Water (*n* = 246)	NNS beverages (*n* = 247)
Age, years	46.0 ±11.2	44.7 ±12.0
Female sex, *n* (%)	165 (67.1)	180 (72.9)
BMI, kg/m^{2}[a]	31.3 ±2.3	31.3 ±2.2
NNS beverage naïveté[b]		
Non-naïve, *n* (%)	186 (75.6)	188 (76.1)
Naïve, *n* (%)	60 (24.4)	59 (23.9)

Note: Data are mean ±SD or *n* (%).

Abbreviations: BMI, body mass index; NNS, non-nutritive sweetened; SD, standard deviation.

[a]BMI was measured at screening as part of trial eligibility assessments.

[b]Naïve was defined as NNS beverages comprising 0–≤25% of drink choices in the 5 years to screening; these individuals could be regular consumers of water or sugar-sweetened beverages. Non-naïve was defined as NNS beverages comprising >26–100% of drink choices in the 5 years to screening.

TABLE 2 Effects of trial beverage on the primary endpoint

Group	Baseline	Week 12	Change	90% CI for change[a]
Body weight, kg				
Water (*n* = 191)	90.4 ±11.4	84.8 ±10.8	–5.6 ±3.0**	5.3 to 6.0
NNS beverages (*n* = 192)	89.7 ±11.4	83.9 ±11.1	–5.8 ±3.0**	5.5 to 6.2
Between-group difference	0.7 ±22.9	0.9 ±21.9	0.2 ±6.0	–0.7 to 0.4

Note: Primary analysis of the complete cases dataset, which included all participants with data at baseline and week 12. Data are mean ±SD unless otherwise specified.

Abbreviations: CI, confidence interval; NNS, non-nutritive sweetened; SD, standard deviation.

[a]For the test of equivalence with two-sided p value > 0.05.

**$p < 0.001$.

607 **TABLE 3** Effects of trial beverage on the secondary endpoints

Group	Baseline	Week 12	Change
Waist circumference, cm			
Water (*n* = 188)	104.2 ±9.3	98.3 ±9.1	–5.9 ±5.2**
NNS beverages (*n* = 188)	104.2 ±8.9	96.9 ±8.3	–7.2 ±5.2**
Between-group difference	0.0 ±18.2	1.4 ±17.4	1.4 ±10.3*
Hip circumference, cm			
Water (*n* = 188)	111.9 ±6.8	107.6 ±6.3	–4.3 ±4.1**
NNS beverages (*n* = 188)	112.6 ±7.0	107.7 ±6.8	–4.9 ±4.2**
Between-group difference	–0.7 ±13.8	–0.1 ±13.1	0.6 ±8.3
Systolic blood pressure, mmHg			
Water (*n* = 164)	134.3 ±15.6	130.3 ±14.5	–4.1 ±12.6**
NNS beverages (*n* = 162)	134.4 ±14.1	129.9 ±15.0	–4.4 ±13.9**
Between-group difference	–0.1 ±29.7	0.3 ±29.5	0.4 ±26.6
Diastolic blood pressure, mmHg			
Water (*n* = 164)	82.6 ±9.1	78.2 ±10.2	–4.3 ±9.9**
NNS beverages (*n* = 162)	82.7 ±9.6	80.0 ±9.7	–2.6 ±8.8**
Between-group difference	–0.1 ±18.7	–1.8 ±19.9	–1.7 ±18.7
Total cholesterol, mmol/L			
Water (*n* = 103)	5.4 ±1.1	4.9 ±1.0	–0.5 ±0.7**
NNS beverages (*n* = 98)	5.2 ±0.8	4.8 ±0.8	–0.4 ±0.5**
Between-group difference	0.1 ±2.0	0.1 ±1.8	–0.1 ±1.2
HDL cholesterol, mmol/L			
Water (*n* = 103)	1.5 ±0.4	1.3 ±0.3	–0.1 ±0.2**
NNS beverages (*n* = 98)	1.5 ±0.4	1.4 ±0.3	–0.1 ±0.2**
Between-group difference	–0.1 ±0.8	–0.1 ±0.6	0.0 ±0.4
LDL cholesterol, mmol/L			
Water (*n* = 102)	3.2 ±1.0	2.9 ±0.9	–0.3 ±0.5**
NNS beverages (*n* = 98)	3.1 ±0.7	2.9 ±0.7	–0.3 ±0.5**
Between-group difference	0.1 ±1.7	0.1 ±1.6	0.0 ±1.0
Non-HDL cholesterol, mmol/L			
Water (*n* = 103)	3.9 ±1.1	3.6 ±1.0	–0.3 ±0.6**
NNS beverages (*n* = 98)	3.7 ±0.9	3.4 ±0.8	–0.3 ±0.5**
Between-group difference	0.2 ±2.0	0.2 ±1.8	0.0 ±1.1
Triglycerides, mmol/L			
Water (*n* = 103)	1.5 ±0.8	1.3 ±0.7	–0.2 ±0.6*

NNS beverages (*n* = 98)	1.3 ±0.5	1.2 ±0.5	–0.1 ±0.5*
Between-group difference	0.2 ±1.3	0.2 ±1.2	0.0 ±1.2
Total cholesterol:triglyceride ratio			
Water (*n* = 103)	3.9 ±1.2	3.8 ±1.1	–0.1 ±0.7
NNS beverages (*n* = 98)	3.6 ±1.1	3.6 ±1.0	–0.0 ±0.6
Between-group difference	0.3 ±2.3	0.3 ±2.1	–0.1 ±1.2
HbA_{1c}, mmol/mol			
Water (*n* = 101)	36.7 ±3.8	35.8 ±3.4	–0.9 ±2.0**
NNS beverages (*n* = 95)	36.7 ±4.6	36.5 ±3.5	–0.3 ±2.8
Between-group difference	0.0 ±8.4	–0.7 ±6.8	–0.7 ±4.8*
Fasting plasma glucose, mmol/L			
Water (*n* = 100)	5.1 ±0.5	5.0 ±0.4	–0.1 ±0.4*
NNS beverages (*n* = 95)	5.0 ±0.5	5.0 ±0.5	–0.1 ±0.4
Between-group difference	0.1 ±1.0	0.0 ±0.9	0.0 ±0.8
Fasting serum insulin (SI units), pmol/L			
Water (*n* = 94)	87.9 ±75.9	67.0 ±34.8	–20.9 ±67.9*
NNS beverages (*n* = 95)	79.2 ±47.6	67.0 ±48.0	–12.2 ±42.2*
Between-group difference	8.7 ±126.8	0.0 ±83.8	–8.7 ±113.3
AST, U/L			
Water (*n* = 93)	21.9 ±5.8	22.3 ±16.8	0.4 ±17.2
NNS beverages (*n* = 93)	23.5 ±12.0	21.9 ±12.7	–1.6 ±11.7
Between-group difference	–1.6 ±18.9	0.4 ±29.8	2.0 ±29.4
ALT, U/L			
Water (*n* = 100)	25.4 ±14.6	23.1 ±17.1	–2.3 ±16.7
NNS beverages (*n* = 92)	25.5 ±19.2	22.7 ±21.2	–2.8 ±14.8
Between-group difference	–0.1 ±34.3	0.4 ±38.8	0.4 ±31.5
GGT, U/L			
Water (*n* = 76)	26.9 ±19.5	23.4 ±19.7	–3.5 ±6.9**
NNS beverages (*n* = 66)	48.4 ±129.5	45.3 ±157.4	–3.1 ±39.7
Between-group difference	–21.6 ±191.9	–21.9 ±232.5	–0.3 ±59.1
Hunger VAS[a], mm			
Water (*n* = 186)	43.1 ±27.6	40.4 ±27.2	–2.7 ±33.1
NNS beverages (*n* = 183)	44.3 ±28.9	38.1 ±27.4	–6.2 ±34.7*
Between-group difference	–1.2 ±56.6	2.3 ±54.6	3.5 ±67.9
Sugar consumption[b], score points			
Water (*n* = 177)	111.0 ±45.9	57.3 ±29.3	–53.7 ±43.5**
NNS beverages (*n* = 180)	113.2 ±49.2	51.2 ±27.5	–62.1 ±44.4**

Between-group difference	–2.2 ±95.1	6.2 ±56.8	8.4 ±87.8
Sweetener consumption[b], score points			
Water (*n* = 177)	16.4 ±12.8	2.8 ±5.7	–13.5 ±12.5**
NNS beverages (*n* = 180)	15.6 ±12.3	15.0 ±10.3	–0.7 ±10.0
Between-group difference	0.7 ±25.1	–12.1 ±16.6	–12.8 ±22.6**
Activity level, steps			
Water (*n* = 141)	8,371.1 ±3,120.1	9,479.7 ±3,654.0	1,108.5 ±3,584.6**
NNS beverages (*n* = 140)	8,128.6 ±3,354.7	9,307.8 ±3,758.7	1,179.2 ±3,462.7**
Between-group difference	242.5 ±6,479.9	171.8 ±7,413.8	–70.7 ±7,048.0
DXA subset			
Fat mass, kg			
Water (*n* = 46)	35.8 ±5.1	32.0 ±5.4	–3.8 ±3.4**
NNS beverages (*n* = 48)	36.6 ±5.9	32.2 ±7.0	–4.4 ±2.9**
Between-group difference	–0.8 ±11.0	–0.2 ±12.5	0.6 ±6.3
Fat-free mass, kg			
Water (*n* = 46)	52.4 ±10.3	51.7 ±10.3	–0.7 ±1.4**
NNS beverages (*n* = 48)	53.1 ±11.5	52.3 ±11.6	–0.8 ±1.5**
Between-group difference	–0.7 ±21.8	–0.5 ±22.0	0.2 ±2.9
Android fat distribution, %			
Water (*n* = 46)	48.9 ±5.1	45.2 ±6.2	–3.7 ±3.9**
NNS beverages (*n* = 48)	49.5 ±6.7	45.4 ±8.9	–4.1 ±4.0**
Between-group difference	–0.6 ±11.8	–0.2 ±15.2	0.4 ±7.8
Gynoid fat distribution, %			
Water (*n* = 46)	42.9 ±9.1	40.7 ±9.4	–2.3 ±2.1**
NNS beverages (*n* = 48)	42.9 ±8.7	40.3 ±9.6	–2.6 ±2.0**
Between-group difference	0.0 ±17.8	0.4 ±18.9	0.4 ±4.1

608 *Note:* Primary analysis of the complete cases dataset, which included all participants with data at
609 baseline and week 12. Data are mean ±SD unless otherwise specified; *n*, number of participants with
610 data available.

611 Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; DXA, dual-energy X-ray
612 absorptiometry; GGT, gamma-glutamyl transferase; HbA_{1c}, glycated hemoglobin; NNS, non-nutritive
613 sweetened; SD, standard deviation; SSFFQ, Sugar and Sweetener Food Frequency Questionnaire;
614 VAS, visual analog scale.

615 [a]Assessed using a 0–100 mm VAS anchored at “not at all hungry” and “extremely hungry”.

[b]Assessed using the SSFFQ (22). The SSFFQ assessed the previous month's consumption of sugar or sweetener in foods and drinks based on frequency and portion estimates, with higher scores indicating higher consumption.

*$p < 0.05$.

**$p < 0.001$.