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Reprint of "Beverages containing low energy sweeteners do not differ from water in their effects on appetite, energy intake and food choices in healthy, non-obese French adults"☆,☆☆

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ABSTRACT

The usefulness of replacement of caloric sugars by low-calorie sweeteners (LCS) for weight management has been questioned on the grounds that the uncoupling of LCS sweet taste and dietary energy may confuse physiological mechanisms, leading potentially to higher energy and sugar intake. The aim of the present study was to determine whether LCS beverages compared to water, when consumed with meals, differ in their effects on energy and food intake in acute trials and after long-term habituation. *Ad libitum* food intake of 166 (80 women; 86 men) healthy non-obese adults (BMI between 19 and 28 kg/m^2), infrequent consumers of LCS was measured in four 2-consecutive-day testing sessions (Day 1 in the laboratory, Day 2 free-living). During the first 3 sessions, held one-week apart, participants were required to drink either water or commercial non-carbonated LCS lemonade (330 ml) with their main meals (randomised cross-over design). On Day 1, motivational ratings were obtained using visual analogue scales and *ad libitum* food intakes (amounts and types of foods selected) were measured using the plate waste method. On Day 2, participants reported their *ad libitum* intakes using a food diary. After Session 3, participants were randomly assigned to the LCS habituation group or to the water control group. The habituation (660 ml LCS lemonade daily vs 660 ml water) lasted 5 weeks. The fourth and final test session measured food intakes and motivational ratings after habituation. Water and LCS beverage did not differ in their effects on total energy intake, macronutrient intakes or the selection of sweet foods and on motivational ratings. Similar results were obtained in both LCS-naïve and LCS-habituated individuals.

1. Introduction

Strategies for reducing the sugar content of beverages and foods are viewed as critical to global public health. Observational studies (Bundrick, Thearle, Venti, Krakoff, & Votruba, 2014; Dubois, Farmer, Girard, & Peterson, 2007; Liebman et al., 2003; Schulze et al., 2004; Troiano, Briefel, Carroll, & Bialostosky, 2000), intervention trials (Chen et al., 2009; Tordoff & Alleva, 1990), and systematic reviews and meta-analyses (Malik, Schulze, & Hu, 2006; Vartanian, Schwartz, & Brownell, 2007; Pan & Hu, 2011; Te Morenga, Mallard, & Mann, 2012) have all linked excessive sugar consumption to higher energy intakes and to weight gain. The World Health Organization has recommended reducing the percentage of daily energy from free sugars to 10% ("strong recommendation"), or even 5% ("conditional recommendation") (WHO Guideline, 2015).

Low-calorie sweeteners (LCS) have long been used to reduce sugar calories while maintaining the palatability of beverages and foods. However, two types of reservations have been raised regarding the use of LCS for the reduction of sugar calories and for weight management. The first argument, first raised by Blundell & Hill, 1986 (Blundell & Hill, 1986), had to do with the supposed paradoxical stimulation of appetite by LCS that provide sweet taste without calories. That objection was addressed directly in subsequent experimental studies showing no short-term effects of LCS on hunger, appetite, or energy intakes

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Abbreviations

BMI	Body Mass Index
LCS	Low calorie sweeteners
TEI	Total energy intake
VAS	Visual analogue scale
AUC	Area under the curve
LCS-bev	experimental beverage sweetened with LCS

(Drewnowski, 1995). The second argument had to do with the long term efficacy of diet beverages in weight management. It has been suggested in a recent review that prolonged ingestion of LCS may disrupt the learned responses that normally contribute to energy homeostasis and body weight control (Burke & Small, 2015). Potential mechanisms could involve the disruption of cephalic-phase insulin secretion, incretin mobilization by sweet taste receptors in the gut, cognitive influences, alteration of gut microbiota, and direct neurotoxicity (Berthoud, Bereiter, Trimble, Siegel, & Jeanrenaud, 1981; Jang et al., 2007; Suez et al., 2014; Curry & Roberts, 2008).

The impact of LCS on body weight change over time has been addressed previously (de la Hunty, Gibson, & Ashwell, 2006; Bellisle & Drewnowski, 2007; Mattes & Popkin, 2009; Miller & Perez, 2014; Bellisle, 2015; Peters & Beck, 2016). The recent systematic review of Rogers et al. (Rogers et al., 2016) covered 90 animal studies, 12 prospective cohort studies, 129 short-term randomized controlled comparisons, and 10 randomized controlled trials of the effects of LCS as compared to sugar sweetened beverages or to plain water. They concluded that there was considerable evidence to suggest that LCS consumed in place of sugar were helpful in reducing relative energy intake and, importantly, went on to note that "the effects of LCS beverages also appeared neutral relative to water, or even beneficial". One possible mechanism suggested by current research is that LCS satiate rather than enhance the appetite for sweetness (Piernas, Tate, Wang, & Popkin, 2013).

While the research focus has been on comparing LCS beverages to sugar sweetened beverages, relatively few experimental studies have compared the long term effects of LCS beverages with those of plain drinking water (Rogers et al., 2016). Yet many of the current recommendations favor plain drinking water rather than LCS beverages as substitutes for sugar-containing beverages (Borges et al., 2017). The present study, a two-arm randomized clinical trial (RCT), tested the impact of LCS beverages versus plain water on energy intake in healthy French adults. Importantly, the present cohort was composed of LCS-"naïve" men and women who did not consume LCS on a regular basis and tests were performed before and after a 5 week habituation period to LCS.

The main hypothesis was that LCS beverages would not differ from plain water in their impact on mean energy intake, either before or after LCS habituation, in the laboratory or at home. A non-inferiority statistical analysis was used to test this hypothesis. A secondary hypothesis was that LCS beverages, compared with plain water, would not modify appetite, macronutrient intakes, choices of sweet or savory foods, and would not lead to an increase in sugar consumption in LCS-naïve and LCS-habituated participants, as measured both under laboratory and free-living conditions.

2. MATERIAL and METHODS

2.1. Participant screening, recruitment, and enrollment

Male and female volunteers (18-45 years-old) were recruited through advertising in the local community. Power calculations, based on Julious (Julious, 2004), established that the planned equivalence/non-inferiority statistical tests required 80 women and 86 men. Initially 2214 potential candidates were screened by telephone. Inclusion criteria required that participants be healthy, non-obese (body mass index between 19 and 28 kg/m^2), and infrequent, non-regular users of LCS. Potential participants who consumed LCS (in the form of beverages, tabletop LCS, or diet foods) more often than once every 2 weeks were excluded. Potentially eligible participants (n = 667) were invited to an in-person interview with the research staff. Following medical screening, 174 participants were found eligible for the study; however 8 did not return for the first experimental session. The final per protocol (PP) study sample was 80 women and 86 men (N = 166). Fig. S1 in supplementary data, gives the flow diagram of the recruitment and participation through the phases of the study. All participants signed an informed consent form and were informed of their right to withdraw from the study at any time.

The protocol was approved by the Institutional review Board (CPP of Lyon Sud-Est III, September 16, 2014), registered and authorized by the French competent health authorities (ANSM, June 19, 2014, N° ID RCB: 2014-A01024-43). The study was registered in the *Protocol Results registration System* (PRS) at ClinicalTrial.gov (Identifier: NCT02297880). The first participant was enrolled on October 14, 2014 and the experimental procedure ended on March 14, 2016.

2.2. Design and time course of the study

The RCT was designed as a two-arm study comparing plain water versus LCS lemonade. Study duration was 9 weeks for each participant, with 4 experimental 2-day sessions. In each of these weekly sessions, food intake and appetite were followed first under laboratory conditions (day 1) and then under free-living conditions (day 2). During session 1 (week 1), all participants consumed plain water with meals eaten in the laboratory (day 1) and under free-living conditions (day 2). Participants were required to consume at least 330 mL mineral water (one bottle) at each main meal (breakfast, lunch, and dinner).

During sessions 2 and 3 (weeks 2 and 3) the participants were required to drink either 330 mL LCS lemonade or 330 mL plain water in counterbalanced order. Half of the sample received water (week 2) then lemonade (week 3); the other half received lemonade first, then water. Participants were required to consume 330 mL lemonade or mineral water (one bottle) at each main meal (breakfast, lunch, and dinner) on both laboratory (day 1) and free-living days (day 2).

After week 3, the participants were randomized into two study arms. The Experimental group was habituated to drinking two cans of the LCS lemonade each day, preferably with the main meals, during the next 5 weeks (weeks 4–8). We estimated that 3 cans per day for 35 days would have been excessive, resulting in a high risk of noncompliance. The Control group consumed the same amounts of mineral water and was instructed to avoid LCS sweetened beverages or foods. Randomization was stratified by sex and energy intake at baseline. Men and women with comparable energy intakes at baseline were randomly assigned to the Experimental or Control groups. Energy intakes were assessed using a 3-d food diary completed at study enrollment at the time of the medical visit.

During the habituation period (weeks 4–8), according to their group, participants were instructed to consume 660 mL/day LCS lemonade or mineral water (2 bottles or cans/day). During week 9, the Experimental LCS group was tested with LCS lemonade and the Control group was tested with water, under the same conditions as in weeks 1–3. No cross-over was used after the habituation period since all the participants in the experimental group then received the LCS beverage associate to the meals, and all the control received water. This design allowed detailed comparisons of the effects of LCS versus water both at the time of the first exposure to LCS (weeks 2 or 3) and following the 5-week LCS habituation period (week 9). Fig. S2 in supplementary data summarizes the research design.