Title

Non-nutritive sweeteners and body weight management: another brick in the wall of evidence

Running title

Non-nutritive sweeteners and body weight

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In this issue, Harrold et al. [1] report outcomes at 52-weeks of their randomised controlled trial (RCT), called SWITCH, which compared consumption of beverages sweetened with non-nutritive sweeteners (NNS), with consumption of water. The authors deserve to be congratulated on performing a well-powered, long-term RCT with significant relevance to public health – in part they did this under restrictions necessitated by the COVID-19 pandemic. Participants in the trial were women and men with overweight or obesity, enrolled in a weight management programme, comprising 12 weeks active weight loss and 40 weeks weight maintenance support (with a planned follow-up after a further 52 weeks of unassisted weight maintenance, which is ongoing). Outcomes at 12 weeks were published earlier this year [2]. There was weight loss of 6.3% at 12 weeks, which was maintained at 52 weeks (7.5%) (complete cases datasets). At 52 weeks, the weight loss was statistically significantly greater for the participants randomised to NNS beverages versus those randomised to water (7.5 kg versus 6.1 kg). So, as well as achieving and maintaining successful weight loss, this new RCT provides evidence of a small advantage for weight management of consuming NNS beverages over water.

Why do this research?

Potentially, NNS offer an opportunity to reduce energy intake, especially from beverages. This depends on the reduced added sugars intake achieved by the substitution of NNS for sugars not being fully compensated for by increased energy intake elsewhere in the diet. The evidence on this is clear: such substitution does reduce energy intake, and body weight [3-5], and this evidence forms part of the rationale for public health policies advocating reduced added sugars intake. A concern, though, is that sweetness in the diet ('sweet-tooth hypothesis'), and/or de-coupling sweetness and energy intake ('sweet-taste-confusion hypothesis'), might undermine the effectiveness of NNS use (reviewed in [6]). If so, a better strategy might be to substitute sugar-sweetened beverages (SSBs) with consumption of water, rather than NNS beverages.

What does the SWITCH trial tell us?

The headline result of SWITCH is that consumption of NNS versus water was, at the very least, not disadvantageous to weight management. To understand how this result relates to hypothesised effects of NNS, it is necessary to unpick more details of the trial. To be eligible for inclusion, participants had to be consuming 'regularly more than three cold beverages per week (water, NNS, or sugar-sweetened; NNS and sugar sweetened beverages had to be <2 L per day)' [2]. For the 52 weeks, participants were asked to consume at least two 300 ml servings per day of their assigned beverage (NNS beverages or water, which could be carbonated or uncarbonated, and which were delivered, free-of-charge, to the participants' homes). Participants randomised to the water group were asked to abstain from all NNS beverages (including adding NNS to e.g., tea and coffee). All participants were permitted to consume SSBs, and water, but the weight-loss programme included a recommendation to limit consumption of SSBs. In sum, therefore, depending on their assignment, individually, participants could have increased, decreased, or maintained their consumption of sweet-tasting, flavoured beverages. In actuality, the water and NNS beverages participant groups reduced (from similar baselines) their sugars consumption to a similar, substantial extent

(39%). At the same time, 'sweetener consumption', and therefore presumably sweetness exposure, was reduced in the water group, but not changed in the NNS beverages group. That is, contrary to the sweet-tooth hypothesis, there, was not a greater reduction in sugars intake in the water group commensurate with their reduced sweetness exposure.

A further feature SWITCH is that a quarter of the participants were NNS beverage 'naïve'; that is, in the 5-years prior to the trial, they had, at most, consumed NNS beverages infrequently. Analyses presented in Harrold and colleagues' article [1] indicate that weight loss for participants assigned to NNS beverages in the trial did not differ in respect of NNS naïveté. This is contrary to the sweet-taste confusion hypothesis, because it predicts that increased exposure to sweetness mis-matched with energy intake should acutely undermine appetite control in this group (i.e., place an additional burden on them), compared with the NNS beverage non-naïve participants who had pre-existing experience of this potential disadvantage.

The sweet-tooth and the sweet-taste-confusion hypotheses are hard to test experimentally, though the evidence against them, including these results from SWITCH, is growing [e.g., 6-8].

How does this research fit with previous evidence?

On the main question for SWITCH, which is how NNS beverage versus water consumption compares for weight management, the answer is, not quite equally: with a small benefit in favour of NNS beverages in the long-term. This result sits comfortably within the range of results identified in meta-analyses [4, 5] of previous RCTs making this comparison, which collectively show no difference for body weight between NNS beverages and water. The wall of evidence, however, is rather uneven. For example, an earlier RCT, on which SWITCH was largely modelled, found a greater effect in favour of NNS [9]. By contrast, another long-term RCT, also within the context of a weight-management programme, found a substantial effect in favour of water [10]. We [5] were surprised by this latter result, given the nature of the NNS versus water intervention, which was one NNS beverage or water (250 ml) after lunch 5 days per week; and we were surprised by the small variance in body weight change in this trial ([5] Supplementary Information p 6).

It is also worth noting here, that it is unlikely that a postingestive physiological action of NNS on appetite and/or metabolism can account for effects of NNS consumption on body weight, as meta-analyses show no effect on body weight of NNS consumed in capsules versus placebo capsules [4, 5]. (In these capsule studies, there is no difference between the treatments in either sweetness in the mouth, or in energy content.) On the other hand, substitution of NNS for sugars is not neutral with respect to individual differences in physiological and/or psychological traits. For example, a large RCT found evidence that children with higher initial BMI compensated less for covert reduction in energy intake achieved with NNS for sugars substitution, than did children with lower initial BMI [11].

Finally, I should disclose that my research on NNS has spanned four decades. Initially, I was sceptical about their usefulness – thinking that potential savings in energy intake might be compensated for, consciously and/or unconsciously; and that, furthermore, sweetness might increase appetite. Both these hypotheses have been disproved, and it is now clear that the totality of causal evidence (irrespective of funding source, i.e., industry versus non-

industry [5]), and including results from appropriately analysed prospective cohort studies [12], supports the use of NNS in weight management. The SWITCH trial further reinforces this body of evidence.

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Author contributions

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Conflict of interest statement

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