Predicted Function, Not Proven Benefit

A Critical Appraisal of the SWEET Study on Sweeteners and the Gut Microbiome

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The pan-European SWEET study is the longest randomised human exposure to sweeteners and sweetness enhancers (S&SEs) currently available. Over one year, adults with overweight or obesity assigned to a healthy diet permitting S&SEs maintained 1.6 ± 0.7 kg greater weight loss than those restricting them (P = 0.029), with no adverse cardiometabolic changes and increased relative abundance of several SCFA-associated taxa (Pang et al., 2025). The weight-maintenance result is directly supported and constrains any claim that habitual sweetener use predictably promotes weight gain. This commentary addresses a narrower question: what the design permits the trial to establish, and what it leaves open.

1. Attrition exceeded plan, and the reported power applies to the weight outcome only

Directly supported. The trial specified two primary outcomes: "The primary outcomes were 1-year changes in body weight and gut microbiota composition in adults" (Pang et al., 2025). The authors report that "the dropout rate was higher than expected (40% versus 30%), which resulted in a lower number of completers than required for 90% power," while noting that 203 completers provided 86% power for one-year weight change, "which can be deemed satisfactory." That reassurance addresses the weight outcome. Gut microbiota composition was assessed in a predefined subgroup of 137 adults (Copenhagen n = 26; Pamplona n = 26; Harokopio n = 25; Maastricht n = 60), and no separate power calculation is reported for it. The microbiota findings therefore rest on a smaller predefined subgroup, without an accompanying power estimate, despite carrying co-primary status.

2. The compositional shift was measured; metabolic function was inferred

Directly supported. The compositional finding is real. The S&SE group showed increased relative abundance of several SCFA-associated taxa, including *Butyricimonas* (β = 0.69, s.e. = 0.20, P = 0.0094). However, taxonomic abundance does not directly measure metabolite production. Functional pathways were inferred from 16S data using PICRUSt2, and SCFAs were not quantified, a limitation the authors state directly: "the absence of direct measurements of SCFAs may have limited our ability to fully interpret the metabolic implications of the observed microbial shifts." The study therefore supports a change in microbial composition and predicted functional potential, but it does not demonstrate increased SCFA, or specifically butyrate output.

3. Direct SCFA measurement would not, by itself, have resolved the question

Reasonably supported. Quantified butyrate would remain difficult to interpret without a corresponding measure of utilisation. Butyrate supplies approximately 70% of colonocyte energy through mitochondrial β-oxidation (Roediger, 1980; reviewed in O'Riordan et al., 2022). That oxidation consumes oxygen and maintains the epithelial hypoxia and PPAR-γ signalling associated with barrier integrity and luminal anaerobiosis (Byndloss et al., 2017; Kelly et al., 2015). Most colonic butyrate is

consumed at the epithelium, and comparatively little reaches systemic circulation (Bloemen et al., 2009; Boets et al., 2017). Luminal or faecal butyrate concentration therefore reflects production minus colonocyte uptake rather than production alone.

Mechanistically plausible; not tested in this trial. Where colonocyte β-oxidation is impaired, epithelial metabolism shifts toward anaerobic glycolysis, luminal oxygen tension rises, and butyrate utilisation falls, and conditions associated with dysbiotic Enterobacteriaceae expansion (Byndloss et al., 2017; Litvak et al., 2018). In that state, unused butyrate would accumulate rather than decline. SWEET measured neither butyrate nor any index of its utilisation, so the trial provides no evidence on this point in either direction. The relevance is methodological, a production marker without a utilization marker cannot distinguish efficient from impaired epithelial metabolism.

4. The intervention tested a category, not a compound

Directly supported. The S&SE arm was not restricted to non-nutritive sweeteners. It permitted high-potency sweeteners (aspartame, acesulfame-K, saccharin, thaumatin, neotame, steviol glycosides), polyols (erythritol, sorbitol, mannitol, isomalt, maltitol, lactitol, xylitol), slowly digestible carbohydrates (sucromalt, isomaltulose), and sweet fibres including inulin-type oligosaccharides. Inulin-type oligosaccharides are established prebiotics, and polyols are incompletely absorbed fermentable substrates; both alter microbial composition independently of non-nutritive sweeteners. The observed shift toward SCFA-associated taxa cannot be attributed to any single sweetener, and the design cannot separate a sweetener effect from a fermentable-substrate effect. That the category is heterogeneous is established: Suez et al. (2022) reported that saccharin and sucralose impaired glucose tolerance while aspartame and stevia did not, with distinct microbiome effects across all four.

5. Endpoints relevant to microbiome-mediated safety were not assessed

Directly supported by omission. SWEET did not measure intestinal permeability, endotoxin (LPS) exposure, mucosal inflammation, or neuroimmune and mitochondrial-functional indices such as PGC-1α and TFAM expression, plasma TCA-cycle intermediates, or kynurenine-pathway activity. These are the pathways through which additive-associated microbiome change is hypothesised to affect the host. Their absence is not a design flaw, the trial was powered for weight management, but it bounds the conclusions the trial can support.

6. Design features that limit generalisability

Directly supported. Following the weight-loss phase, both arms consumed a structured healthy ad libitum diet providing under 10% of energy from sugars, differing only in whether S&SE products were permitted. The comparison is therefore between two managed dietary patterns in recently weight-reduced adults, not between sweetener use and its absence in the free-living food supply. Reported energy intake was approximately 25% below estimated requirement. One year is a substantial randomised exposure and a short latency for cardiometabolic or neurodegenerative endpoints.

Conclusion

Within one structured weight-management context over one year, S&SEs did not adversely affect the outcomes measured and modestly supported weight maintenance. This constitutes meaningful evidence against acute-to-medium-term metabolic harm in that setting. It does not constitute evidence regarding barrier integrity, SCFA utilization, mucosal inflammation, or long-term neurometabolic safety, none of

which were measured. The authors' own interpretation is appropriately bounded; the overstatement lies in secondary readings that treat predicted functional potential as demonstrated metabolic benefit. A precautionary formulation position, excluding these ingredients pending stronger long-term human data, remains consistent with this trial rather than contradicted by it.

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Disclosure. TLC NeuroMicrobiome Labs Inc. formulates protein products that do not contain non-nutritive sweeteners. This commercial interest is disclosed so that readers may weigh it. The trial's favourable findings are reported here as the authors stated them.

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