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NUTRITION

APRIL 2023

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Hansen TT, Andersen SV, Astrup A, Blundell J, Sjödin A. Is reducing appetite beneficial for body weight management in the context of overweight and obesity? A systematic review and meta-analysis from clinical trials assessing body weight management after exposure to satiety enhancing and/or hunger reducing products. Obes Rev. 2019 Jul;20(7):983-997.

What We Know, Think We Know, or Are Starting to Know

In a very recent Deepdive in April we covered the question of whether "metabolic adaptation", defined as decreases in resting metabolic rate, persists following weight loss to an extent that might predispose an individual to weight regain. And while this does not appear to be strongly supported [1], components of energy expenditure are not the only relevant factor that change with weight loss.

One area of interest that is suggested to exert more of an influence on weight loss and regain is that of appetite regulation [2,3]. In a highly cited example, a study by Sumithran *et al*. [2] found that in participants who lost an average of 13.5kg over a 10-week intervention period, after 1yr follow-up their levels of appetite-regulatory hormones, including leptin and ghrelin, and subjective appetite levels, remained higher than before weight loss.

However, while it may be tempting to draw a straight line between increased subjective and objective appetite* [see ***Geek Box** below for more detail on measuring appetite], leading to increased energy intake, leading to weight regain, here is where we must take a pause before filling in evidential gaps with assumptions.

For example, in the Sumithran *et a*l. [2] paper, elevated levels of appetite regulatory hormones and subjective appetite ratings were not correlated with weight regain over 1yr. And subjective measures, while useful to represent changes in subjective levels of appetite and hunger, do not correlate strongly with actual energy intake [4].

A question that arises here is, if increased appetite or hunger may not necessarily predict weight regain based on current evidence, does enhancing appetite and hunger regulation make a difference for weight loss success and maintenance? The evidence for this specific research question is surprisingly sparse. The present study was a systematic review and meta-analysis of the available literature on interventions assessing reductions in appetite and body weight outcomes.

*Geek Box: Measuring Appetite in Nutrition Research

To assess appetite and hunger in research there are three primary methodologies. The first is assessing "ad libitum" energy intake, i.e., allowing participants to consume as much energy from a presented meal as desired, and measuring how much is consumed. This generally requires researcher oversight in a clinical research facility. The second is subjective appetite, hunger, and desire to eat measures using 'visual analogue scales' [VAS]. A VAS is a straight, horizontal line, commonly around 100mm [10cm] in length. The far left will generally represent the lowest end of the variable being measured, i.e., with fullness 0mm could be 'not hungry at all' while 100mm could be 'extremely hungry'. Participants are asked to make a vertical line with a pen/pencil/marker across the horizontal measurement line, at a point which represents for them how they feel in response to that question. VAS can be used in a laboratory setting, but also used in a free-living context. And the third is the measurement of appetite regulatory hormones, e.g., leptin secreted from adipose tissue, ghrelin secreted from the stomach, or GLP-1 secreted from the small intestine. Assessment of these biological markers requires blood sampling from participants. Thus, which method is used will depend on the study design, the precise research question being addressed, and the resources [financial and technical] available to the research team. We discuss these concepts, as well as the concepts of "satiation" and "satiety", in this Research Lecture.

The Study

The researchers conducted a systematic review and meta-analysis of trials investigating the effects of appetite enhancement on body weight. To be included in the analysis, the study had to meet the following criteria:

- **Design**: Randomised controlled intervention trials.
- **Population**: Adults or adolescents with overweight/obesity.
- **Intervention**: Foods/meals, nutrition supplements, or pharmaceutical drugs, that influence appetite.
- **Control**: Any comparator group to the intervention; no conditions specified.
- **Duration**: 8-weeks or greater.
- **Outcomes**:
    - **Appetite**: Differences in either *ad libitum* energy intake or VAS scores between intervention and control group.
    - **Weight**: Differences in weight loss between intervention and control groups.

The review distinguished between acute studies, where appetite assessments were only carried out at baseline, and studies with repeated measures before and after the intervention. It also distinguished between studies where appetite was assessed by measuring *ad libitum* energy intake or measured by subjective VAS evaluations.

Results: 12 studies were included in the final review and analysis. 4 studies assessed acute appetite, while 9 assessed repeated measures of appetite [1 study had both measures]. 3 studies had assessed appetite using both *ad libitum* energy intake and VAS; 2 used *ad libitum* energy intake only; 7 used VAS only.

4 studies were food-based interventions; 6 were nutritional supplement interventions; 2 were pharmaceutical interventions [1 using the GLP-1 agonist semaglutide, and the other using the drug lorcaserin, a 5-HT2C serotonin receptor agonist]. Of either the food-based or nutritional supplement interventions, no two studies used the same intervention.

***Weight Loss Following Acute Ad Libitum Test Meal*:** 3 studies were included under this criterion, of which 2 showed that the intervention groups consumed less *ad libitum* energy intake [both food-based trials; one with a 500ml water preload before testing; the other using an egg-based breakfast] at baseline, and lost more weight during the study, compared to controls.

***Weight Loss Following Acute Subjective VAS*:** 2 studies were included under this criterion, and both showed that the intervention group had greater subjective appetite regulation [i.e., higher satiety scores, lower hunger scores, higher fullness scores], and both intervention groups lost more weight during the study compared to controls. Both interventions were food-based [one with a high-energy, high-protein/carb breakfast; the other with an egg-based breakfast].

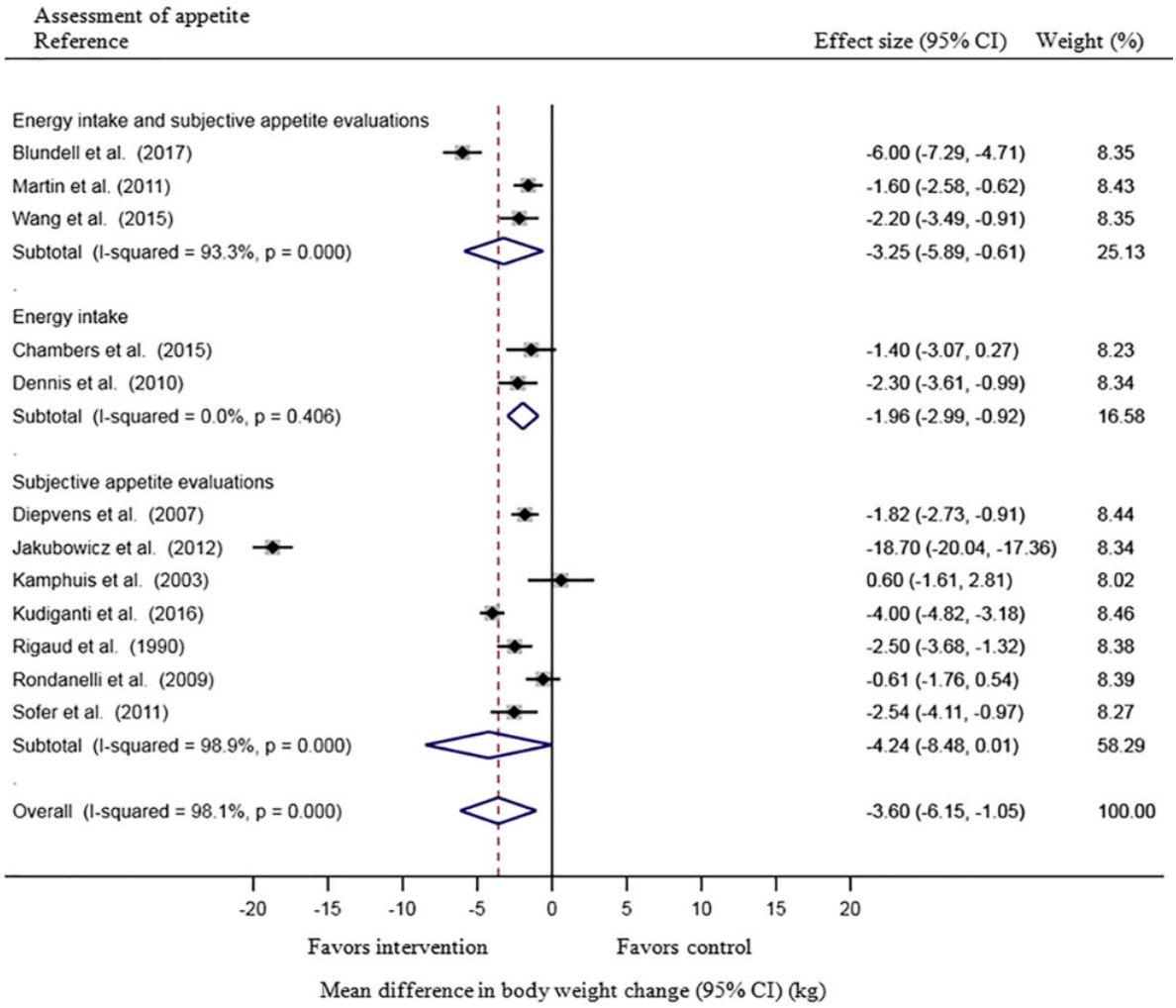
***Weight Loss Following Repeated Measures of Ad Libitum Energy Intake*:** 2 studies were included under this criterion, and both were the pharmaceutical trials included in the review. In both studies, participants in the intervention groups consumed significantly less *ad libitum* energy intake at baseline and after weight loss, and lost significantly more weight compared to controls.

Weight Loss Following Repeated Measures of Subjective VAS*:** 9 studies were included under this criterion, of which 7 found reduced appetite in the intervention groups over repeated measures and greater weight loss in these intervention groups compared to controls. 2 studies found reduced appetite measures, but no differences in weight loss between intervention and control groups [more under ***Interesting Finding, below].

Of the 7 studies finding reduced appetite and weight loss, 2 were the pharmaceutical trials, 2 were food-based interventions, and 3 were nutritional supplement interventions.

***Meta-Analysis of Overall Effects of Appetite Reduction on Weight Loss*:** Included all 12 trials together in a meta-analysis showed that the overall summary estimate of effect of appetite reduction across all studies was a 3.60kg [95% CI, 1.05 to 6.15kg] weight loss compared to controls [see **figure** below].

A sensitivity analysis excluded the 2 studies with the largest effects [Blundell et al., 2017, which was the semaglutide trial; Jakubowicz et al., 2012, where the difference between intervention and control group was driven by a ~12kg weight gain in the control group]. In this analysis, the overall summary estimate of effect was a 1.96kg [95% CI, 1.20 to 2.72kg] weight loss in the intervention groups compared to controls.



The Critical Breakdown

Pros: The review was clear on appetite assessment methodologies and required at least one of either *ad libitum* energy intake or subjective VAS to have been assessed in a study. The review and analysis distinguished between the method of appetite assessment, and whether the measures in the primary included studies were acute or repeated over the course of the study. It was also required that appetite was assessed in a laboratory setting in the primary included studies, improving the robustness of the respective measures.

Cons: There was a real lack of conceptual clarity to the studies aims and objectives [more under ***Key Characteristic***, below]. The literature search was confined to PubMed alone, which may have missed some relevant publications. The review lumped divergent intervention trials together, including pharmaceutical interventions with diet and nutrition supplement studies, however, they refer to all interventions as "foods"; to the unsuspecting reader, they may easily miss that pharmaceutical trials were included. The only studies measuring *ad libitum* energy intake with repeated measures were the drug trials. While the reporting makes it seem as if reduced appetite *caused* weight loss, in reality it appears only two studies analysed whether reductions in appetite were predictive of weight loss outcomes; therefore, this analysis is primarily demonstrating associations, despite including intervention trials.

Key Characteristic

It is a long-standing critique of meta-analysis generally [5,6], and of meta-analysis in nutrition research [7,8], that synthesising evidence requires that the primary included studies be of a similar methodological design, i.e., that they are combinable [recommended further watching: our previous Research Lecture on meta-analysis].

This requires, as it does to any research, that we have a *clearly defined intervention/exposure*. Let's think about this requirement in the context of the present study which included as the intervention: semaglutide; a high-energy/protein-carb breakfast; "Olibra" [a fat emulsion added to yogurt]; conjugated linoleic acid; "Meratrim" [a combination of flower heads and fruit rinds]; or "PhosphoLEAN" [appears to be a green tea catechin extract of sorts].

On one level, it seems the research question being addressed is clear: interventions that reduced appetite and their relationship with weight loss. And, overall, we could take the finding from the meta-analysis and infer that there is a modest effect on weight loss of ~3.60kg in interventions that targeted enhancing appetite and satiety.

And we would also see that this was attenuated to a much humbler summary effect estimate of 1.96kg on removal of two trials that influenced that larger overall finding; one a drug study, the other a diet trial where the magnitude of difference in weight loss was inflated by the significant weight gain in the control group.

But where do we go from there? Because this analysis compared apples and pears, we have nothing of substance to infer *what* intervention exactly may have the most beneficial impact on appetite reduction in the context of weight loss. And this is important, for reasons we'll discuss in the next section...

Interesting Finding

The reason the lack of conceptual clarity in this analysis, of the lack of a clearly defined intervention being assessed, is so important is because it remains relatively unclear if enhancing appetite *leads* to weight loss. Notice the more causal language here.

In the present study, in the analysis of studies assessing appetite using VAS with repeated measures, 3 studies showed that appetite was decreased in the intervention groups after the intervention compared to baseline, despite weight loss occurring in these participants. Conversely, 2 studies showed that appetite was decreased in the intervention groups but there was no difference in weight loss between intervention and control groups.

This highlights the disconnect in the chain of causation. The proposed chain is that reduced appetite leads to reduced energy intake, which leads to improved bodyweight regulation. But we have some gaps in this chain. The first is that subjective measures of appetite are, perhaps surprisingly, a poor predictor of subsequent energy intake [4]. The second is that the available evidence suggests that elevated subjective appetite and hunger hormones do not appear to correlate to weight regain [2,9].

But the latter is a slightly different question to whether relatively improved appetite and satiety may *predict* the likelihood of weight loss and maintenance. And the present review and meta-analysis leaves us with a broad conclusion that it may, with little clarity on what specific interventions may best achieve this.

Relevance

The present study at least suggests that reduced appetite levels, either acutely before an intervention, or repeated before and after an intervention, are associated with weight loss [note the use of associative language here]. However, where does this leave the inference of whether enhanced appetite *leads* to weight loss?

In a previous Deepdive, we covered an analysis which compared "satiety phenotypes", i.e., individuals with low or high satiety responsiveness. This analysis had weekly assessments of subjective appetite, and found that appetite control was greater in the "high-satiety phenotype", while the "low-satiety phenotype" struggled; this was reflected in the 5.28kg weight loss in the former group compared to the 2.97kg weight loss in the latter group.

In the recent SATIN trial, which was not included in the present meta-analysis, which used repeated measures of VAS in addition to *ad libitum* energy intake test meals, there were moderate correlations between appetite suppression scores and weight loss maintenance [10].

And another recent study showed that while both *fasting* and postprandial levels of hunger and fullness were higher immediately after weight loss, after 1yr fasting hunger remained higher than baseline, but *postprandial* fullness ratings were also higher [3]. Thus, it may be that increased postprandial fullness levels offset higher subjective fasting hunger after a period of weight loss maintenance [3].

Cumulatively, the needle tips towards a relationship between appetite measures and weight loss, but there does need to be more interventions testing this relationship as an a *priori* hypothesis. The current evidence does not quite permit us to conclude that enhanced appetite is a causal mediator of energy reductions and weight loss.

Application to Practice

While interesting, the present study ultimately doesn't fully answer the question, because of the lack of a clearly defined intervention. One aspect of the previous research that is interesting is the suggestion that if an intervention has an acute effect on appetite, that effect is likely to be persistent even after weight loss [11].

Perhaps the factor with the strongest influence on satiety is dietary energy density, with low energy density foods enhancing satiety [12], and mediating weight loss relative to satiety responsiveness [10,13]. In addition, protein and fibre appear to exert effects on satiation and satiety secondary to energy density [10].

And in the recent "Big Breakfast Study", appetite was enhanced with high morning energy intake compared to evening energy intake, however, these diets were fully controlled and isocaloric, so any effect of appetite on enhancing weight loss could not be demonstrated [14]. As we covered in this recent Research Lecture, this effect of time-of-day energy intake on appetite appears to be robust.

These are all factors which may be considered tools in the toolbox of appetite regulation and satiety in the context of weight loss and maintenance.

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