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Singh N, Stewart RAH, Benatar JR. Intensity and duration of lifestyle interventions for long-term weight loss and association with mortality: a meta-analysis of randomised trials. *BMJ Open*. 2019;9(8):e029966.

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

Weight loss research is one of the most contentious areas in health sciences, and a debate that has become increasingly vitriolic and entrenched. Unfortunately, this takes us away from first principles in deducing the role of weight loss as an intervention based on the best available evidence. In this regard, it is important to acknowledge that no health intervention is benign; each, whether dietary, pharmacological, or surgical, must be appraised through our first principles: efficacy, effectiveness, and safety.

Efficacy can be defined as the capacity to produce an effect; does intervention A lead to outcome B under ideal conditions?

When it comes to body composition changes in humans – weight loss or weight gain – we have established and incontrovertible evidence of efficacy related to energy balance. Underfeeding or overfeeding humans produces loss of body mass or gain of body mass, respectively, largely independent of macronutrient composition ^(1–4). There remain some sophists who argue this point, almost entirely housed within the low-carb research community ^(5–7).

Effectiveness, however, can be defined as whether an intervention works in the "real world"; does intervention A lead to outcome B considering other additional relevant factors in a real living context?

And it is effectiveness where most of the debate around weight loss lies. While we can house people in a laboratory and control their feeding to demonstrate *efficacy* (i.e., that energy restriction will lead to loss of body mass), when people are asked to create conditions of energy restriction in their own lives, this intervention lacks *effectiveness* overall ^(8–10).

Finally, we have the important additional criterion of *safety*; does the intervention produce any adverse effects, and what is the likelihood of that adverse effect occurring? Other than the debate around effectiveness of weight loss diets, safety is where the remainder of the debate is often focused.

This aspect of the conversation has primarily revolved around associations between weight loss and increased mortality risk ^(11,12), while also considering non-mortality adverse effects such as weight stigma and related stress responses ^(13,14), and weight regain and negative psychological correlates [e.g., "black and white" thinking about food] ⁽¹⁵⁻¹⁷⁾.

In fact, weight loss research provides an excellent example of the delineation between efficacy, effectiveness, and safety, in a research context. The reason for this discord is that maintaining energy restriction and sustaining loss of body mass is ultimately a behavioural challenge, and is as much psychosocial as physiological.

One factor that has emerged as potentially crucial to increasing the effectiveness of weight loss interventions is intensity of follow-up, i.e., how many contacts does a participant have with a practitioner, be that dietitian or otherwise ^(9,18).

The present brought together several of these questions in a meta-analysis, namely what is the effect of weight loss interventions relative to intensity of follow-up, and does weight loss associate with lower risk of mortality?

The Study

The investigators conducted a systematic review and meta-analysis of weight loss intervention trials, using the following inclusion criteria:

- **Design**: Randomised controlled trials [RCTs] with a minimum of 100 participants
- Intervention/Exposure: Intentional weight loss from lifestyle interventions
- **Control**: Routine care with no specific advice to achieve weight loss
- **Duration**: Trials were required to be over 1yr between the intervention and followup periods
- **Outcome**: Primary outcome was weight loss at 1yr; other outcomes included intensity of intervention required to achieve weight loss, and odds of mortality associated with weight loss

For the primary outcome and the mortality outcome, the analysis was stratified according to baseline body mass index [BMI] of participants, number of practitioner contacts [termed 'interventions' by the authors; comparing either \geq 28 or \leq 28, which was the median of the included studies, in year 1], and whether \geq 75% of contacts occurred in the first six months of the intervention.

The weight loss outcomes were reported as mean kilograms [kg] and 95% confidence intervals [95% CI; <u>watch this Research Lecture</u> for more in-depth discussion]; for the mortality outcome the results were reported as odds ratio [OR] and 95% CI. The research also conducted a regression analysis to determine how much weight loss was associated with each 10 contacts.

Results: A total of 31 RCTs were included in the analysis, encompassing 20,563 total participants, of which 56% were female.

The average study size was 615 participants [range: 100–5,145]; average BMI was 32.5kg/m² [range: 25.8–39.3kg/m²]; average age was 53.8yrs [range: 42.8–69.7yrs]. The average study duration was 2.39yrs [range from 6 months to 9.6yrs].

The average number of practitioner contacts during year 1 was 28 [range: 4–110].

Primary Outcome – Bodyweight Loss at 1yr: Compared to controls after 1yr, lifestyle interventions resulted in 3.63kg weight loss [95% CI 2.58 to 4.67kg].

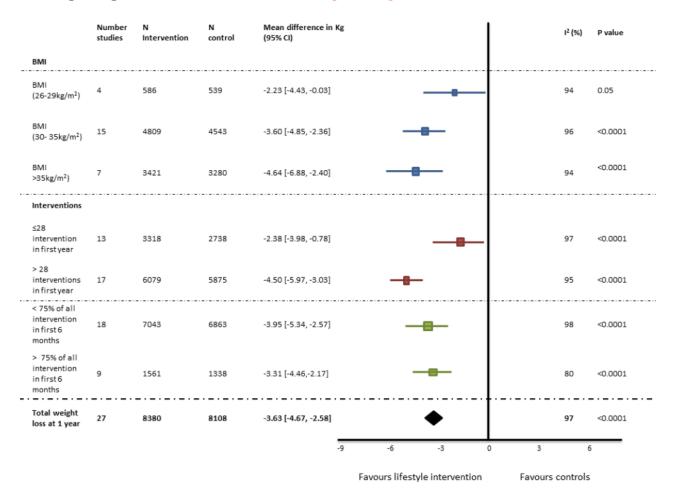
Overall, this amounted to 0.13kg [95% CI 0.07 to 0.19kg] weight loss per average practitioner contacts [i.e., 28].

Regression analysis indicated that each additional 10 contacts was associated with 0.6kg [95% CI 0.23 to 1.4kg] weight loss.

Primary Outcome – Bodyweight Relative to Baseline BMI at 1yr: Compared to controls, weight loss after 1yr in each BMI category was as follows:

- BMI 25-29kg/m²: 1.37kg [95% CI -0.09 to 2.82kg]
- BMI 30-35kg/m²: 3.09kg [95% CI 2.11 to 4.06kg]
- BMI >35kg/m²: 4.04kg [95% CI 2.47 to 5.61kg]

Primary Outcome – Bodyweight Relative to Intervention Intensity at 1yr: Compared to controls, in interventions with <28 contacts over 1yr weight loss was 2.38kg [95% CI 0.78 to 3.98kg], while interventions with >28 contacts resulted in 4.50kg [95% CI 3.03 to 5.97kg] weight loss [more under **Interesting Finding**, below].



Forest plot from the paper illustrating the overall effect of lifestyle interventions vs. controls on weight loss after 1yr [*summarised in black triangle*], and also illustrating the individual stratifications of weight loss according to categories of BMI [*blue symbols, top*], intensity of intervention, i.e., number of contacts [*red symbols, middle*], and whether >75% or <75% of contacts occurred within the first six months of the intervention [*green symbols, middle*].

Secondary Outcomes – Bodyweight Loss at 3yrs: Compared to controls after 3yrs, lifestyle interventions resulted in 2.45kg [95% CI 1.17 to 3.73kg] weight loss.

Secondary Outcomes – Effect of Weight Loss on Mortality: A total of 593 deaths occurred in all studies. Over an average of 9.2yrs, compared to controls the odds of mortality in the intervention groups were 14% lower [OR 0.86, 95% CI 0.73 to 1.02]. As you can see from the confidence intervals, the upper bound crossed 1.0 and the finding was not 'statistically significant', but the direction of effect is clear.

The Critical Breakdown

Pros: The study had clearly stated aim and outcome measures, which included both weight loss outcomes and mortality outcomes. The inclusion criteria was strong overall, with stipulations for trial durations of 1yr minimum, sample sizes of over 100 participants, and an emphasis on intentional weight loss [more under *Key Characteristic*, below]. The overall sample size of ~21,000 for the meta-analysis was substantial for these types of interventions. The statistical analysis was thorough and included informative stratifications for the primary outcome, subgroup analyses by BMI, age, and contacts, and additional regression analysis of the associations between contacts and weight loss. The results were clearly presented.

Cons: The study was designed as a systematic review, but this aspect of the paper [not the meta-analysis] was poorly executed and there are crucial elements of the included studies that are not described in detail, such as the precise nature of the interventions. The definition of "lifestyle intervention" is never expanded, thus the exposure is poorly defined and may encompass anything from diet, to diet and exercise, to diet and exercise and counselling, etc. The study also excluded "specific diets" [e.g., high-protein], and the rationale for this exclusion is unclear, and one is left to wonder what types of diets the intervention groups consumed or whether basic energy restriction was all that was prescribed. Because individual participant data was not available, the analysis was conducted only using the average from each individual study; this meant the effects of different magnitudes of weight loss across individual participants in the study could not be evaluated [to the authors credit this is the first limitation they identify for their paper].

Key Characteristic

The key characteristic of the present study is the concomitant consideration of both weight loss outcome data *and* mortality risk from the same body of evidence. This provides some crucial insights into a major question that we outlined in the *What We Know* section, above, namely the relationship between weight loss effectiveness and safety.

As noted, some research has suggested that weight loss may be associated with increased mortality risk ^(11,12). However, one crucial distinction to make for any such associations is whether weight loss is *intentional* [i.e., deliberate intervention using diet, lifestyle, etc.] or *unintentional* [i.e., weight loss related to illness or other lifestyle behaviours] ^(19,20).

Unintentional weight loss is usually related to serious illness, often itself related to other lifestyle behaviours such as smoking, which may not be adequately adjusted for in observational studies ^(19,21,22). Prior evidence on intentional weight loss from RCTs indicated a 15% lower risk of overall mortality [RR 0.85, 95% CI 0.73 to 1.00] in trials with an average weight loss of ~5.5kg [\pm 4.0kg] ⁽²³⁾.

The present study also emphasised intentional weight loss from lifestyle interventions, and the odds of mortality were 14% lower [OR 0.86, 95% CI 0.73 to 1.02]. Note that relative risk [RR] is different to odds ratio [OR], however, when risk or odds estimates are less than 20%, both estimates roughly approximate to each other.

Thus, we can say that the mortality estimates in the overall evidence are relatively consistent, and indicate that intentional weight loss is not associated with higher mortality risk, and may be associated with modestly lower mortality risk.

Interesting Finding

Let's talk about the effect of intensity of intervention, i.e., number of contacts participants in a study had with study practitioners [e.g., dietitian, behavioural counsellor, medical doctor, etc.]. The present study demonstrated that the greatest magnitude of weight loss [4.50kg, 95% CI 3.03 to 5.97kg] was achieved in trials with an average of 28 contacts with healthcare professionals in the first year of the intervention.

This finding adds yet another strong piece of evidence to the crucial role that practitioner contacts play to intervention success. This finding is not in any way unique to nutrition or lifestyle interventions. For example, a systematic review of psychology interventions found that increased number of sessions [cognitive behavioural therapy (CBT)] and a good therapeutic relationship with the therapist were among the strongest predictors of patient recovery, particularly if social support was present ⁽²⁴⁾.

In the Look AHEAD trial, which both the previous meta-analysis of intentional weight loss ⁽²³⁾ and the present study included, participants received three group and one individual session per month for the first six months ⁽²⁵⁾. For the next six months they were offered two group and one individual session per month. For the remaining four years, they had one in-person session and one phone/email contact per month ⁽²⁵⁾. And Look AHEAD achieved good results, with average weight loss of 8.5% in the first year, maintained at 4.7% by the fourth year ⁽²⁶⁾.

An analysis of weight loss trials going back to the 1960's indicated that active follow-up was consistently associated with improved success rates compared to passive follow-up; combining active follow-up with behaviour therapy improved outcomes even further ⁽²⁷⁾. The present study confirms that, to paraphrase Hall and Katan ⁽⁹⁾, long-term benefits require long-term active practitioner contact.

Relevance

The primary strength of the present study is its deliberate consideration of the effect of intensity of intervention, i.e., of contacts between participants and practitioners, on weight loss outcomes. However, while the findings of the study may seem encouraging on one level, the limitations of this approach should be obvious; this is *intensive* and requires substantial resources for any study to pull off.

If intensity of contact between participant and practitioner in a study is required to achieve modest weight loss, this is hardly encouraging for the scalability of the intervention. Perhaps it is little wonder that the average weight loss in intervention trials is 3-6kg ⁽⁸⁾.

There is one important factor to bear in mind in thinking about the present study; relative to baseline weight, all BMI categories lost <5% of bodyweight. This is independent of intensity of intervention. Thus, a valid interpretation of the present study is that *irrespective* of the intensity of contact, the average weight loss was still below the minimum threshold considered for cardio-metabolic benefits.

In the context of the efficacy of bariatric surgery ⁽²⁸⁾ and emerging drugs like semaglutide [a GLP-1 agonist that promotes satiety] ⁽²⁹⁾, lifestyle interventions increasingly seem like majoring in the minors when it comes to weight loss.

However, for some individuals the minors may be all that is required to lower cardiometabolic risk, and no intervention should ever be discarded due to modest effect sizes, particularly where the overall evidence suggests modestly lower mortality risk from achievable weight loss targets.

Application to Practice

Studies like this do carry important implications for practice, particularly for nutrition professionals and coaches who work privately with individuals. The effect of number of contacts, and the primacy of the therapeutic relationship, is evidence not only in lifestyle interventions but from other domains, such as psychotherapy. This is arguably the top-line application of the present study, which represents the most up-to-date synthesis of evidence on this topic.

However, this particular intervention – weight loss – requires that in application, we return to the principles we started this Deepdive with: efficacy, effectiveness, and safety. While efficacy is the point in principle that weight loss occurs with energy deficits, the primary takeaway of this study is that the effectiveness of weight loss may be improved with increasing contacts for individuals [in addition to other behavioural correlates of weight loss success <u>outlined in this long-form article</u>].

However, it is crucial that safety is not overlooked; weight loss is not a benign intervention. It carries risks, and it is incumbent on practitioners to weigh-up risks and benefits appropriately. Evidence-based practice is also safe practice.

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