Published in final edited form as:

Obes Rev. 2014 January ; 15(1): . doi:10.1111/obr.12111.

Association of Run-in Periods with Weight Loss in Obesity Randomized Controlled Trials

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Abstract

Study-level design characteristics that inform the optimal design of obesity randomized controlled trials (RCTs) have been examined in few studies. A pre-randomization run-in period is one such design element that may influence weight loss. We examined 311 obesity RCTs published between January 1, 2007 and July 1, 2009 that examined weight loss or weight gain prevention as a primary or secondary endpoint. Variables included run-in period, pre-post intervention weight loss, study duration (time), intervention type, percent female, and degree of obesity. Linear regression was used to estimate weight loss as a function of 1) run-in (yes/no), and 2) run-in, time, percent female, body mass index, intervention type. Interaction terms were also examined. Approximately nineteen percent (18.6%) of the studies included a run-in period with pharmaceutical studies having the highest frequency. Although all intervention types were associated with weight loss (Mean = 2.80 kg, SD=3.52), the inclusion of a pre-randomization run-in was associated with less weight loss ($p=0.0017$) compared to studies that did not include a run-in period. However, this association was not consistent across intervention types. Our results imply that in trials primarily targeting weight loss in adults, run-in periods may not be beneficial for improving weight loss outcomes in interventions.

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Financial Disclosures: Dr. Affuso has received consulting fees and grants from organizations interested in obesity interventions. Dr. Allison has received book royalties, consulting payments, grants, and donations from numerous for-profit and not-for-profit entities with interests in obesity RCTs.

Keywords

Randomized clinical trials; run-in periods; obesity

Introduction

Currently available obesity treatments are only of moderate efficacy and not all treatments work for all individuals. Thus, it is critical to identify and evaluate new alternative treatments for both efficacy and safety. Furthermore, as the National Institutes of Digestive and Kidney Diseases wrote, “Well conducted clinical trials are the fastest and safest way to find improved treatments and preventions...”¹. Yet, several important questions remain unanswered about how to best design, interpret, and analyze randomized clinical trials for obesity treatments and in many cases these issues remain completely unaddressed. One important question concerns the value of run-in periods.

There are differences of opinion regarding the value of run-in periods in RCTs and different types of run-in procedures². A run-in procedure is typically some period of time in which patients are enrolled in a trial and must do something (e.g., keep a food diary, try to lose weight on diet alone or on placebo) prior to randomization. Some run-in procedures use a placebo to eliminate placebo responders (e.g., all participants receive a placebo in a blinded fashion)³. In contrast, some eliminate participants that do not lose more than a certain amount of weight or otherwise appear to be non-compliant^{4,5}. The Food and Drug Administration’s (FDA) 1996 Guidance for the Clinical Evaluation of Weight Control Drugs⁶ advocated that RCTs include a 6-week behavioral weight reduction run-in period designed to: 1) identify placebo responders and 2) avoid unnecessary treatment with drugs in those who could lose weight through diet and exercise. It has been noted that run-in periods such as this select a particular subset of patients and, therefore, reduce generalizability of the trial results.^{2,4} While generalizability is an important issue, significant lack of compliance can invalidate a study entirely.

A group of leading European obesity researchers⁷ opined that run-in periods in obesity treatment: (a) are unnecessary given the ‘stability’ of the obesity diagnosis; (b) may decrease the pre-to-post weight loss; and (c) may increase the placebo-corrected weight loss. During the 2004 FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting, most of the panelists were in favor of abolishing the run-in period. Dr. S. Yanovski stated, “...there is really not a lot of scientific justification anymore for the run-in.”⁸. Pre-meeting comments from the industry suggested that most patients entering obesity RCTs had tried diet and exercise programs and had failed. There was also concern from the committee regarding data interpretation at the end of trials that used run-in periods. Dr. D. Orloff, former FDA Director of the Division of Metabolic and Endocrine Products, asserted that removing the 6-week run-in period would render the results more generalizable and simplify the measure of effect as placebo-subtracted weight loss from baseline.⁹ The final suggestion by the committee was to remove the current run-in design and encourage companies to include a stabilization or screening period for ascertaining baseline values of weight and comorbidities and the most recent draft guidance from the FDA makes no mention of run-in periods¹⁰. In contrast, the 2007 draft guidance from European Medicines Agency (EMA), the European equivalent of FDA, wrote “Patients enrolled in these trials should have been subjected to an appropriate weight reducing diet run in period for a specified minimum time and all patients should be given similar instructions, advice and encouragement with regard to diet and behaviour modification and exercise.”¹¹ In the RIO-North American study of rimonabant, patients completed a 4-week placebo, single-blind, run-in period, but were not excluded

from the randomization to the treatment phase of the trial based on WL or response to placebo during the run-in phase¹².

Despite the widespread use and frequent recommendation for the use of run-in periods, a thorough search of the literature revealed no papers offering data evaluating the association of using a run-in period with total WL or the WL difference (i.e., estimated treatment effect) between a treatment and control group in obesity RCTs. Although we found one paper evaluating the association of run-in with attrition.¹³ Therefore, the purpose of this study was to investigate the association of pre-randomization run-in periods on participant weight loss (WL) in obesity randomized controlled trials (RCT).

Methods

Literature Search

Articles, abstracts and doctoral dissertations were retrieved using searches performed on electronic databases: PubMed, Cochrane Library, ISI Web of Science, PsycInfo, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Dissertation Abstracts. We searched PubMed with and without MeSH headings to identify publications for inclusion, using the following limits: date, RCTs and human studies.

Study Search Terms—In each database, studies of type “Randomized Controlled Trials” were searched (where that option was available) using the following keywords : Obesity, adiposity, overweight, overeat, overfeed, binge eating disorder, fat overload syndrome, weight gain, weight cycling, weight reduction, weight loss, weight maintenance, weight decrease, weight control, body weight, body mass index and anti-obesity agents. Document types selected were: Review, Article, Meeting Abstract, Doctoral Dissertation or Proceedings Paper.

Inclusion Criteria—All studies were evaluated according to the following inclusion criteria: 1) the data were from human studies; 2) the study was an RCT; 3) the study had a total sample size of at least 30 participants at enrollment; 4) the study protocol included an intervention period of at least 8 weeks; 5) weight loss and/or weight gain prevention was a primary or secondary outcome variable; 6) the publication was available in the English language; and 7) the study was published between January 1, 2007 and July 1, 2009. Details of study retrieval, selection, and coding are contained in Appendix 1.

Statistical Analysis—Because overall values from each study sample (i.e., study level data) were to be used for treatment arm level missing data imputation, missing values were imputed (using 30 imputations with IBM SPSS Statistics, version 20, Chicago, IL) in stage 1 for these three study level variables (mean age, mean baseline BMI, percent female) using linear regression models. A second imputation was performed for treatment arm level variables (weight loss in kg, BMI loss, SD of weight loss in kg, SD of BMI loss) that had missing data for weight loss using study variables in the model [arm-level treatment type, mean age, percent female, overall mean BMI, run in period (Y/N), weight loss as a primary outcome (Y/N)]. Standard deviation imputations were constrained to the minimum and maximum of the observed data range.

The imputed data were analyzed in SAS (SAS Institute, Cary, NC) using PROC MIANALYZE. General linear models (PROC GENMOD) were performed with weight loss as the dependent variable and the following study level characteristics as independent variables: number of treatment arms, number randomized, run in, weight loss as a primary outcome (WLPO), total study protocol duration, hereafter referred to as ‘time’, and intervention type. Also entered in the models were participant characteristics: age, percent

female, and baseline BMI. In the initial model, interactions were also examined between run in and number of treatment arms, WLPO, and time. Interactions between time and intervention type were also evaluated. The significance level was assessed at $\alpha=0.05$ (2-tailed) for main effects (associations) and at $\alpha=0.20$ (2-tailed) for elimination of interaction effects (associations) in the initial model building process.

Results

Our inclusion criteria yielded 311 studies with suitable data for analysis as depicted in the PRISMA diagram presented in Figure 1. Table 1 summarizes the characteristics of included studies by primary intervention type. The overall prevalence of run-in periods was 18.6% (range by treatment type: 8.4–29.2%) and was highest among pharmaceutical studies. The unadjusted mean (SD) pre-post intervention weight loss across all treatment arms and intervention types was 2.80 kg (3.52) for non-imputed data. This estimate is likely lower when adjusted for each respective control group, which varies in effect but is not, on average, zero. The reader is directed to a more in depth discussion and quantification of this relationship where we found that increases in control group weight loss are associated with corresponding decreases in treatment group weight loss effects (Dawson et al., in review).

In our initial model (all main effects as well as the interactions described above), run-in period as a single predictor was associated with significantly less weight loss than no run-in period ($p=0.0017$). Time, however, was not a significant single predictor of weight loss in the initial model but was nearly significant ($p=0.0760$) as an interaction term with run-in period (but not with intervention type).

The final model included all first order terms and interaction terms whose p -value was < 0.20 . Four interaction terms remained in this model: the interaction of run-in with WLPO ($p=0.2006$), run-in with time ($p=0.0493$), time with behavioral intervention type ($p=0.1323$), and time with mixed intervention type ($p=0.0221$).

We evaluated the interaction of run-in with WLPO and time separately (Table 2). These results indicated that for studies in which weight loss was not the primary outcome, those with a run-in period had a lower mean weight loss (1.75 kg) than did the studies without a run-in period (2.68 kg); however, the confidence intervals for these values overlapped. Studies in which weight loss was the primary outcome did not differ significantly in weight loss regardless of run-in (2.72 kg compared with 2.79 kg in studies without or with a run-in period, respectively; $p > 0.05$). Thus, the association of a run-in period with WL outcomes differed between studies that focused primarily on weight loss and studies in which weight loss was not the primary outcome.

Figure 2 shows the relationship of the statistically significant interaction between run-in and length of study. Studies < 3 months in duration *with* a run-in period had a significantly lower mean weight loss (0.95 kg) than did studies *without* a run-in period (2.22 kg). Studies of medium length (3 – 6 months) without a run-in period had similar weight loss (2.88 kg) compared with studies with a run-in (2.78 kg). Similarly, in studies of longer duration (> 6 months), studies without a run-in had similar weight loss (2.89 kg) compared with studies with a run-in (2.82 kg).

Discussion

Our findings show that run-in periods, as a study design element, were not consistently associated with the effects of interventions on weight loss. Our examination of trials without WLPO, run-in periods appeared to reduce weight loss compared to no run-in period,

although this finding was not statistically significant. We also evaluated weight loss across categories of study duration as typically seen among obesity RCTs (<3 months, 3–6 months, and > 6 months). Only among trials < 3 months in duration was a trend towards less weight loss observed among trials with a run-in period compared to those without a run-in period. Furthermore, approximately one-fifth of included studies employed the pre-randomization run-in. This overall observed percentage of run-in periods was similar to previous research.¹³ However, run-in periods were found more often in our sample of pharmaceutical trials compared to those reported by Fabricatore et al., 2009, 29.2% and 20.8% respectively. We found no interaction between weight loss and run-in periods for the pharmaceutical interventions ($p=.6648$). The mixed results from our review of the effects of run-in periods on weight loss may be related to the inconsistency among guidelines on the use of run-in periods available in the field of obesity research.

The use of run-in periods in obesity trials has been the subject of debate and likely has decreased over time in the US as the design of obesity trials continue to evolve. Also, run-in periods are currently the subject of debate in the European Union and are being reevaluated by the EMA.¹⁴ In recent documentation calling for modification of the weight control guidelines by this organization, it was stated that “the need for a run-in period in long term trials may be questioned and should be discussed in the context of the guideline revision.” Revised guidelines are expected to be released in mid-2013. However, it is unknown how many adult obesity randomized trials in Europe are presently using a run-in period or what impact the revisions will have on the continued use of run-in periods in study designs.

Strengths and limitations

Strong aspects of this study include the large sample of adult obesity intervention studies with a variety of intervention types; rigorous methods to ensure as many available studies as possible without publication bias; consistent coding, cleaning and completeness of data. We analyzed the fit of our statistical models to ensure the most appropriate characterization, increasing the confidence in our conclusions. Limitations include the narrow date range of studies included, however these recently published studies (2007–2009) are more likely to have been conducted and reported according to recent recommended guidelines.¹⁵ Further, we were unable to analyze some studies due to missing data that could not be obtained or calculated, or was insufficiently described to include with confidence. Finally, the nature of the data limited some of our pre-planned analyses due to violations of some of the statistical assumptions.

Implications for Study Design

Given the additional resources required to implement a pre-randomization run-in protocol, our findings suggest that the costs of this design element may outweigh potential benefits to the evaluation of weight loss outcomes. Furthermore, the run-in period may distort the true effect of the intervention as weight change during the pre-randomization phase¹⁶ is rarely reported in obesity RCTs.

Conclusions

Our findings provide evidence that run-in periods are not associated with greater weight loss outcomes in obesity randomized control trials and may even be detrimental to the elucidation of true treatment effects on weight loss or prevention of weight gain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported in part by NIH Grants R01DK078826, P30DK056336, T32HL079888, T32HL007457, & T32DK062710.

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Figure 1.
PRISMA diagram of study selection process

Figure 2.
Mean (95% Confidence Interval) weight loss at time intervals between studies with and without run-in periods.

Table 1

Sample characteristics of included studies by primary intervention type

	Behavioral (N=59)	Diet (N=106)	Exercise (N=26)	Mixed* (N=48)	Pharmaceutical (N=72)	Total(N=311)
Age, mean (SD), y	47.3(8.4)	46.3 (8.3)	51.5 (11.4)	47.7 (9.6)	48.4(8.7)	47.6 (9.0)
Percentage Female, mean (SD), %	75.8 (21.5)	62.6 (28.4)	73.5 (29.1)	69.4 (30.4)	63.8(26.5)	67.3 (27.5)
Baseline BMI, mean (SD), kg/m ²	33.1 (3.5)	32.0 (3.1)	32.2 (4.7)	32.0 (4.3)	33.1(4.1)	32.5 (3.8)
No. of Subjects Randomized, mean(SD)	199 (240)	128 (168)	122(86)	207 (731)	273(416)	187(382)
Study Duration, mean (SD), wk	35.5(22.0)	28.3 (24.2)	28.2 (16.5)	32.3 (24.9)	30.0 (20.4)	30.96 (22.9)
Studies with a run-in period, No. (%)	5 (8.4)	20 (18.9)	2 (7.7)	10 (20.8)	21 (29.2)	58 (18.6)
Studies with weight loss as the primary outcome, No. (%)	42 (71.2)	77 (72.6)	14 (53.8)	37 (77.1)	36 (50)	206 (66.2)

* Mixed intervention type was defined as having more than one of the above interventions types within one study (e.g., diet and exercise; or diet and pharmaceutical)

Table 2

RUN-IN	WLPO	LS Mean Weight Loss (kg)	Standard Error	95% CI
No	No	2.68	0.324	2.04, 3.31
Yes	No	1.75	0.521	0.72, 2.77
No	Yes	2.72	0.200	2.33, 3.11
Yes	Yes	2.79	0.461	1.89, 3.70

WLPO - Weight Loss as the Primary Outcome

CI – Confidence Interval