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ORIGINAL ARTICLE

Clinical Trials and Investigations

Weight and body composition changes affect resting energy expenditure predictive equations during a 12-month weight-loss intervention

Jared H. Dahle[1] | Danielle M. Ostendorf[2] | Zhaoxing Pan[3] | Paul S. MacLean[4] | Daniel H. Bessesen[2,4] | Steven B. Heymsfield[5] | Edward L. Melanson[4] | Victoria A. Catenacci[2,4]

[1]Integrated Physiology Program, Graduate School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[2]Department of Medicine, Anschutz Health and Wellness Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[3]Department of Biostatistics and Informatics, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[4]Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[5]Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA

Correspondence
Jared H. Dahle, Graduate School of Medicine, Integrated Physiology Program, University of Colorado Anschutz Medical Campus, 12801 East 17th Ave., RC1 South Room 7103, MS 8106, Aurora, CO, 80045, USA.
Email: jared.dahle@cuanschutz.edu

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Abstract

Objective: Mathematical equations that predict resting energy expenditure (REE) are widely used to derive calorie prescriptions during weight-loss interventions. Although such equations are known to introduce group- and individual-level error into REE prediction, their validity has largely been assessed in weight-stable populations. Therefore, this study sought to characterize how weight change affects the validity of commonly used REE predictive models throughout a 12-month weight-loss intervention.

Methods: Changes in predictive error of four models (Mifflin-St-Jeor, Harris-Benedict, Owen, and World Health Organization/Food and Agriculture) were assessed at 1-, 6-, and 12-month time points in adults ($n = 66$, 76% female, aged 18-55 years, BMI = 27-45 kg/m^2) enrolled in a randomized clinical weight-loss trial.

Results: All equations experienced significant negative shifts in bias (measured − predicted REE) toward overprediction from baseline to 1 month ($p < 0.05$). Three equations showed reversal of bias in the positive direction (toward underprediction) from baseline to 12 months ($p < 0.05$). Early changes in bias were correlated with decreased fat-free mass ($p \leq 0.01$).

Conclusions: Changes in body composition and mass during a 12-month weight-loss intervention significantly affected REE predictive error in adults with overweight and obesity. Weight history should be considered when using mathematical models to predict REE during periods of weight fluctuation.

INTRODUCTION

Resting energy expenditure (REE) is the largest component of total daily energy expenditure (TDEE) in sedentary individuals (1) and, when multiplied by an appropriate activity factor, is used to estimate energy intake requirements (2). Although REE can be measured objectively via indirect calorimetry, the cost, time commitment, and need for specialized training and equipment can be prohibitive (3). These obstacles have led to widespread reliance on mathematical equations that use anthropometric measures such as height and weight to predict REE in clinical settings. Numerous studies have investigated the validity of these predictive models on populations

with obesity; however, these studies have largely assessed bias using a cross-sectional approach in weight-stable populations (4-6). Far less is known about how weight change across time affects the validity of REE estimation in such equations. Because obesity management is a dynamic process that can require the calculation of energy intake goals during periods of weight loss, weight stabilization, and weight regain, understanding how weight change affects commonly used REE predictive models may have important clinical implications.

Weight change may influence the validity of REE prediction in mathematical models through its effects on tissue metabolic rates. Dr. Ancel Keys first documented the effects of weight loss on tissue metabolism in his famous Minnesota Starvation Experiment, during which ~35% of the decrease in REE was shown to be independent of the loss of tissue mass (7). This phenomenon of a reduction in REE greater than predicted by the loss of body mass, now known as adaptive thermogenesis (AT), has been widely documented and it was reported to range from as little as ~55 kcal/d (8) to as much as ~500 kcal/d (9). Most studies have suggested that AT dissipates as weight loss stabilizes (8,10,11,12) and completely disappears during weight maintenance (13-15), although long-term persistence has been reported in some populations (9,16,17). Although previous studies have measured longitudinal changes in AT during weight-loss interventions (18-20), most have relied on dual-energy x-ray absorptiometry-based two-compartment linear regression models to predict REE. Although this approach is ideal in a research setting, it is more difficult to replicate in clinical practice where body composition is not routinely measured. Less is known about how AT produced by weight loss might affect the performance of weight- and height-based prediction models that are commonly used in clinical settings.

In one of the few longitudinal studies to investigate how weight change affects REE predictive error in clinically relevant models, Ruiz et al. found that a 12-week dietary intervention in Spanish female individuals who achieved a mean weight loss of ~8 kg had variable impact on 10 predictive equations (21). For example, the popular Mifflin-St-Jeor (MSJ) equation had a mean predictive error of 0.2% at baseline, which increased to 14.4% overprediction at 12 weeks ($p < 0.001$). However, the study included only female individuals, measured changes in predictive error at a single time point (12 weeks), and lacked formal statistical comparisons of key measures such as equation accuracy. Studies that include both male individuals and female individuals and formally assess both bias (defined as mean measured − mean predicted REE) and accuracy (defined as the percentage of individual predictions that fall within ±10% of measured REE) at multiple points during a longer-term weight-loss intervention are still needed.

Therefore, the primary aim of the present study was to characterize the extent to which a 12-month behavioral weight-loss intervention in male individuals and female individuals with overweight or obesity would impact the bias and accuracy of commonly used REE predictive models at 1-, 6-, and 12-month time points. Based on Ruiz et al.'s previous study and the evidence for early, but not long-term, AT, we hypothesized that REE prediction would experience a negative shift in bias from baseline to 1 month, resulting in greater overprediction and decreased accuracy. We further hypothesized that these changes would be reversed by 6 and 12 months as the effects of AT dissipated. As a secondary aim, we sought to identify potential underlying contributors to fluctuations in model bias apart from weight change.

Study Importance

What is already known?

- Mathematical equations that predict resting energy expenditure (REE) are widely used to prescribe calorie goals in clinical weight-loss settings.
- Although such equations are known to introduce group- and individual-level error into REE prediction, their validity has largely been assessed in weight-stable populations.

What does this study add?

- Predictive bias and accuracy of mathematical equations can be significantly impacted even by modest changes in body weight and composition.
- The timing and extent of changes in body weight and composition impact the amount and type of bias (positive or negative) introduced into predictive models.

How might these results change the direction of research or the focus of clinical practice?

- Our findings suggest that adaptive thermogenesis can be elicited earlier and following smaller amounts of weight loss than typically reported, lending support to an early-phase weight-loss model of adaptive thermogenesis.
- Our findings highlight weight history as an important factor that should be considered when using REE prediction to prescribe calorie goals in the clinical setting.

METHODS

This secondary data analysis was conducted on the first two cohorts of a randomized clinical weight-loss trial initiated at the University of Colorado Anschutz Medical Campus in 2018 (funding: National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] R01 DK111622; registered at ClinicalTrials.gov NCT03411356). This study was approved by the Colorado Multiple Institutional Review Board. Inclusion criteria consisted of male individuals and female individuals aged 18 to 55 years with BMI of 27 to 46 kg/m^2. Participants were required to be sedentary (<150 min/wk of voluntary exercise at moderate intensity or greater and <60 min/d of total habitual

physical activity [PA]) during the 3 months prior to enrollment and could not be pregnant, lactating, or planning to become pregnant during the trial. The age range used in the study resulted in both pre- and postmenopausal female individuals being included in the trial.

Individuals with a history of metabolic or chronic disease including diabetes, cardiovascular disease, uncontrolled hypertension or hyperlipidemia, untreated hyper- or hypothyroidism, or cancer within the last 5 years (excluding skin cancer) were excluded from the study. Participants who had undergone previous obesity treatment with surgery, had a history of alcohol or substance abuse or current use of nicotine, or who reported weight loss >5 kg in the 3 months prior to enrollment were also excluded.

Eligible participants were stratified by sex and randomized into one of two intervention groups: daily caloric restriction (DCR) or intermittent fasting (IMF). Randomization was accomplished by study staff and a statistician using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) via block randomization with block size 4. The principal investigator and those assessing outcomes for research purposes were blinded to group assignment. Both groups were provided calorie goals designed to produce a 34.3% weekly energy deficit from baseline-estimated weight-maintenance energy requirements (REE × activity factor of 1.5 based on sedentary behavior) (22). The prescribed macronutrient content of the diet consisted of 55% carbohydrate, 15% protein, and 30% fat. Participants in the DCR group were instructed to limit calories daily throughout the week. Participants in the IMF group limited energy intake to 20% of estimated maintenance requirements on three nonconsecutive days per week, which were considered "fasting" days. On fed days, IMF participants ate ad libitum, but they were encouraged to make healthy food and portion choices. Participants in both groups received a free fitness center membership and PA prescriptions designed to gradually increase their moderate intensity PA to 300 min/wk over the first 26 weeks and then maintain this level of activity throughout the remaining 26 weeks of the study.

Body weight, height, and composition

Body weight and composition were measured at baseline and 1-, 6-, and 12-month time points. Weight was measured with a calibrated digital scale (BWB-800, Tanita Corp., Tokyo, Japan) to the nearest 0.1 kg. Participants also received a cellular-enabled scale (BodyTrace, Inc., New York, New York) which was kept at home and used to remotely report daily weights to the study team. Fat mass (FM) and fat-free mass (FFM) were estimated with dual-energy x-ray absorptiometry (Hologic Discovery Apex version 4.5.3, Hologic Inc., Bedford, Massachusetts). Height was measured at screening to the nearest 0.1 cm with a wall-mounted stadiometer.

REE

REE was measured at baseline and 1-, 6-, and 12-month time points using indirect calorimetry (Truemax 2400, Parvo Medics, Salt Lake City, Utah) with the ventilated hood technique. Before each test, the gas analyzers and flow meter were calibrated per manufacturer recommendations. Participants were instructed to fast for 12 hours overnight and avoid heavy exercise 24 hours prior to the test, which was confirmed by study staff. In the IMF group, REE was measured after a fed day. Upon arrival, participants rested supine, awake, and lightly clothed with access to a blanket in a thermoneutral (22°C-26°C), dimly lit, quiet room for 30 minutes. Respiratory gas exchange was measured for 20 to 25 minutes, and the data from the last 10 minutes was used to estimate REE. REE was calculated using the Weir equation (23). Criteria employed to determine whether the REE measurement was acceptable included stability (coefficient of variance of the final 10 minutes <10%) and average metabolic equivalents <1.10.

Selection of predictive equations

REE predictive equations are referenced in Table 1 (2,24-27) and were included in the analysis based on the following criteria: 1) incorporated measures of weight with optional inclusion of height,

TABLE 1 List of REE predictive equations used in analysis

Reference	REE predictive equations
Harris-Benedict (24)	Men: REE = 66.47 + 13.75 × weight (kg) + 5.0 × height (cm) − 6.75 × age
	Women: REE = 665.09 + 9.56 × weight (kg) + 1.84 × height (cm) − 4.67 × age
Mifflin-St-Jeor (25)	Men: REE = 9.99 × weight (kg) + 6.25 × height (cm) − 4.92 × age + 5
	Women: REE = 9.99 × weight (kg) + 6.25 × height (cm) − 4.92 × age − 161
Owen (26,27)	Men: REE = 879 + 10.2 × weight (kg)
	Women: REE = 795 + 7.18 × weight (kg)
WHO/FAO (2)	**Men:**
	Age 18-30 years: REE = 15.4 × weight (kg) − 27 × height (m) + 717
	Age 31-60 years: REE = 11.3 × weight (kg) +16 × height (m) + 901
	Age >60 years: REE = 8.8 × weight (kg) + 1,128 × height (m) − 1,071
	Women:
	Age 18-30 years: REE = 13.3 × weight (kg) + 334 × height (m) + 35
	Age 31-60 years: REE = 8.7 × weight (kg) − 25 × height (m) + 865
	Age >60 years: REE = 9.2 × weight (kg) + 637 × height (m) − 302

Mathematical equations used to assess changes in bias and accuracy of REE prediction throughout a weight-loss intervention. In all equations, age is measured in years and REE is measured as kcal/d.

Abbreviations: REE, resting energy expenditure; WHO/FAO, World Health Organization/Food and Agriculture Organization.

sex, and age as covariates; 2) developed in healthy adults; 3) included age range of at least 18 to 55 years; and 4) were well-established in REE literature as evidenced by validation in at least 10 previous studies (5,6). Equations that incorporated body composition measures were excluded from our analysis because measures of FM and/or FFM are not universally obtained during clinical weight-loss interventions. Based on these criteria, we selected four equations: MSJ; Harris-Benedict (28); Owen equations for men and women; and World Health Organization/Food and Agriculture Organization/United Nations University (WHO/FAO) equation using both weight and height.

Study outcomes

Two sets of outcomes were assessed for this study. First, raw bias (defined as mean measured − mean predicted REE) and accuracy (defined as the percentage of individual predictions that fall within ±10% of measured REE) were measured at each time point to characterize and compare overall equation performance during weight change. Second, change in bias and accuracy (i.e., baseline bias and accuracy subtracted from 1-, 6-, and 12-month bias and accuracy) was assessed to quantify the hypothesized effects of weight change and AT on REE prediction. Subtracting out baseline bias from measures of bias at 1-, 6-, and 12-month time points allowed us to more confidently isolate possible effects of weight change and AT on REE prediction. In order to better visualize the effects of early weight change and hypothesized AT on shifts in bias, we conducted a post hoc analysis in which participants were divided into two subgroups: 1) a low-weight-loss group (LWLG) that consisted of participants who were at or below the median weight loss at 1 month; and 2) a high-weight-loss group (HWLG) that consisted of individuals above the median weight loss at 1 month. Groups were tracked longitudinally, and changes in bias were assessed for each group at each time point.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute) and Stata version 16.1 (StataCorp LLC, College Station, Texas). The type I error rate was set at 0.05. It is important to note that because the clinical weight-loss trial in the parent study is ongoing and study outcomes remain blinded, all analyses were performed on aggregated data that included both intervention groups. Characteristics of completers and noncompleters were

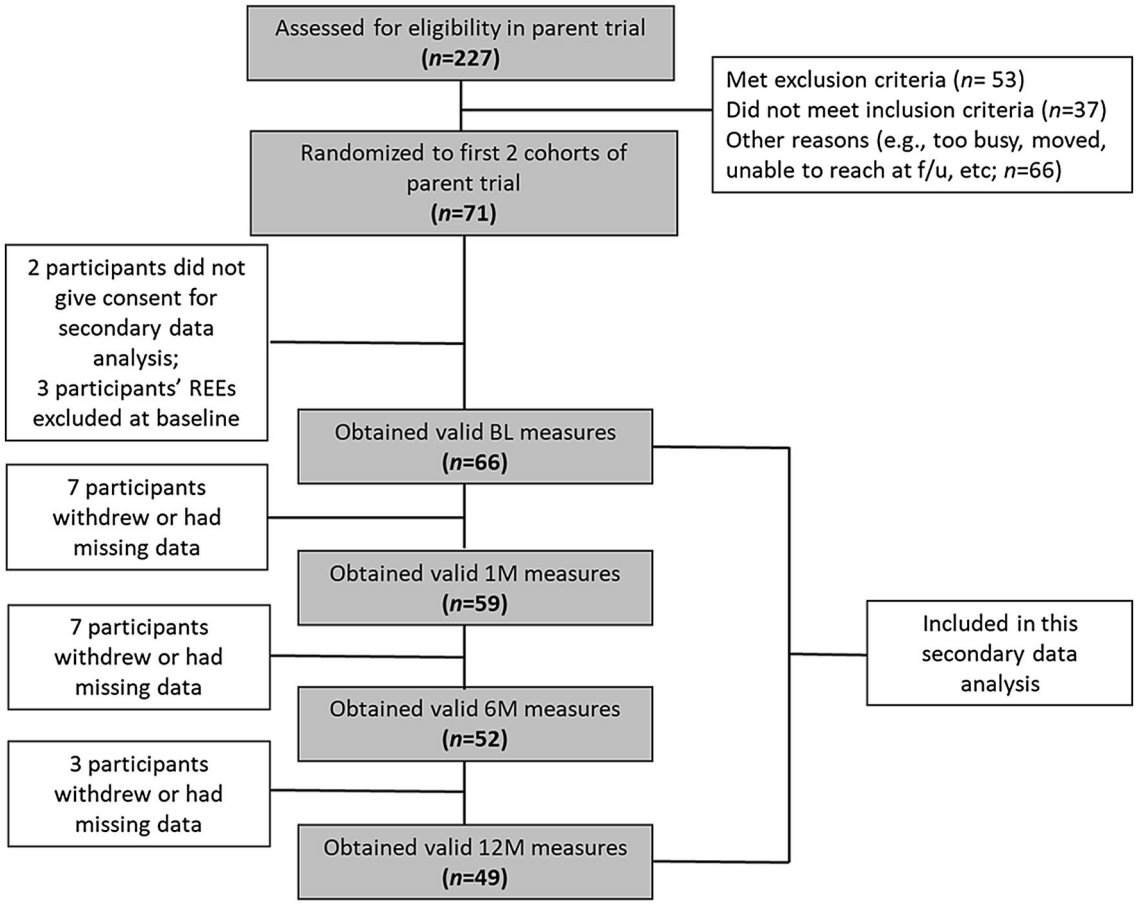

FIGURE 1 Study CONSORT diagram. BL, baseline; REE, resting energy expenditure

TABLE 2 Participant characteristics measured across time

Mean ± SD unless otherwise noted	Baseline ($n = 66$)	1 month ($n = 59$)	6 months ($n = 52$)	12 months ($n = 49$)
Age (y)	40.0 ± 9.8	40.0 ± 10.0	40.6 ± 10.0	40.7 ± 10.0
Sex (male), *n* (%)	16 (24.2)	14 (23.7)	14 (26.9)	13 (26.5)
Ethnicity, *n* (%)				
Hispanic/Latino	13 (19.7)	9 (15.3)	8 (15.4)	7 (14.3)
Not Hispanic/Latino	53 (80.3)	50 (84.7)	44 (84.6)	42 (85.7)
Race, *n* (%)				
White	58 (87.9)	51 (86.4)	46 (88.5)	45 (91.8)
Black/African American	5 (7.6)	5 (8.5)	3 (5.8)	2 (4.1)
Asian	2 (3.0)	2 (3.4)	2 (3.8)	1 (2.0)
Other	1 (1.5)	1 (1.7)	1 (1.9)	1 (2.0)
Anthropometric measures				
Weight (kg)	93.8 ± 16.0	91.4 ± 15.7	87.2 ± 16.4	87.3 ± 17.3
BMI (kg/m^2)	32.9 ± 4.0	32.1 ± 4.1	30.3 ± 4.2	30.4 ± 4.5
% FM	36.8 ± 6.6	35.7 ± 6.8	33.6 ± 7.6	32.9 ± 8.5
% FFM	60.4 ± 6.4	61.4 ± 6.6	63.3 ± 7.3	64.1 ± 8.1
% Weight change from baseline	--	−2.8 ± 2.2	−7.5 ± 5.3	−7.3 ± 7.0
% FM change from baseline	--	−6.4 ± 6.4	−14.8 ± 11.0	−17.7 ± 15.5
% FFM change from baseline	--	−1.3 ± 3.8	−3.9 ± 4.5	−2.5 ± 4.9
Resting metabolic rate (kcal/d)				
Indirect calorimetry (Parvo)	1,649 ± 272	1,591 ± 253	1,575 ± 293	1,632 ± 280
Mifflin-St-Jeor	1,671 ± 261	1,645 ± 257	1,610 ± 269	1,609 ± 281
Harris-Benedict	1,764 ± 301	1,735 ± 291	1,699 ± 300	1,700 ± 314
Owen	1,570 ± 270	1,548 ± 260	1,526 ± 264	1,526 ± 272
WHO/FAO	1,773 ± 298	1,745 ± 287	1,710 ± 292	1,712 ± 304

Aggregated data from participants randomized to both the daily caloric restriction and intermittent fasting groups of the parent trial.
Abbreviations: FM, fat mass; FFM, fat-free mass; WHO/FAO, World Health Organization/Food and Agriculture Organization.

compared using a two-sample *t* test for continuous variables and χ^2 and Fisher exact tests for categorical variables. Data normality was confirmed using the Shapiro–Wilk test. Change in bias from baseline was analyzed using a two-way repeated measures ANOVA with a liner mixed-effects model. Compound symmetry was confirmed as the appropriate covariance structure and the saturated model included fixed effects of time, equation, and their interaction. In order to analyze the accuracy of each equation across time, individual predictions were classified as binary variables (either accurate or inaccurate), and a matched case-control analysis was performed using McNemar χ^2 test. A paired-samples *t* test was conducted to compare changes in bias across time for the two subgroups of the post hoc analysis. Pearson correlation coefficient analysis was used to identify potential underlying contributors to changes in bias over time. An a priori power analysis using Stata software version 16.1 (StataCorp) was conducted on this secondary data analysis. Based on conservative estimates of AT reported in previous studies (8,12,29), it was determined that a sample of 28 participants was sufficient to acquire 80% power to detect a ±55 kcal/d change in bias between time points.

RESULTS

The study Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Figure 1. Of the 71 participants enrolled in the first two cohorts of the parent trial, 2 did not give consent for this secondary data analysis, and 3 had baseline REE that fell outside quality control parameters. Of the remaining 66 participants, 7 participants withdrew or had missing data at the 1-month time point, 7 withdrew or had missing data at 6 months, and 3 withdrew or had missing data at 12 months, resulting in a final retention rate of 74% ($n = 49$) at 12 months. Participant characteristics were not different between participants who withdrew from the study and those who completed the 12-month intervention (data not shown).

Participant characteristics are presented in Table 2 as aggregated data for both intervention groups (DCR + IMF). Weight change from baseline at the 1-, 6-, and 12-month time points was −2.8% (2.2%), −7.5% (5.3%), and −7.3% (7.0%), respectively. Mean BMI decreased from 32.9 (SD 4.0) at baseline to 30.4 (SD 4.5) at 12 months.

Comparisons of bias (least squares mean [SEM]) and accuracy (percentage of accurate predictions) across time are presented in Table 3. MSJ demonstrated the lowest bias at baseline (−22 [16]

TABLE 3 Comparisons of REE predictive equation bias[1] and accuracy[2] across time

	BL ($n = 66$)	1 month ($n = 59$)	6 months ($n = 52$)	12 months ($n = 49$)	BL:1 month	BL:6 months	BL:12 months
Equations	**Bias (kcal/d) (LSM ± SEM)**				**Two-way RM ANOVA (p value)**		
MSJ	−22 ± 16	−55 ± 16	−34 ± 17	20 ± 17	**0.03**	0.47	**0.01**
HB	−115 ± 16	−146 ± 16	−123 ± 17	−71 ± 17	**0.05**	0.63	**<0.01**
Owen	79 ± 16	42 ± 16	51 ± 17	102 ± 17	**0.02**	0.07	0.16
WHO/FAO	−124 ± 16	−155 ± 16	−134 ± 17	−83 ± 17	**0.04**	0.52	**0.01**
	Accuracy (%)				**McNemar χ^2 (p value)**		
MSJ	88	75	79	73	0.09	0.06	**0.01**
HB	68	59	63	69	0.11	0.37	0.78
Owen	67	78	75	63	0.11	0.41	0.37
WHO/FAO	68	58	46	63	0.05	**<0.01**	0.25

Comparisons of bias across time were performed using a two-way repeated measures ANOVA with a linear mixed-effects model. Compound symmetry was confirmed as the appropriate covariance structure, and the saturated model included fixed effects of time, equation, and their interaction. Aggregated data from participants in both the daily caloric restriction and intermittent fasting groups of the parent trial were analyzed, to include both completers and noncompleters. Changes in accuracy were assessed using with a matched case control design with McNemar χ^2 test. Significant p values ($\alpha < 0.05$) indicated in bold.

Abbreviations: BL, baseline; HB, Harris-Benedict; LSM, least squares mean; MSJ, Mifflin-St-Jeor; REE; resting energy expenditure; RM, repeated measures; WHO/FAO, World Health Organization/Food and Agriculture Organization.

[1]Bias defined as [measured - predicted REE] based on least squares means at each time point.

[2]Accuracy defined as percent of individual predictions that fell within ±10% of measured REE.

kcal/d), 6 months (−34 [17] kcal/d), and 12 months (20 [17] kcal/d). The Owen equation had the least bias at 1 month (42 [16] kcal/d) but the greatest bias at 12 months (102 [17] kcal/d). WHO/FAO had the greatest bias at baseline (−124 [16] kcal/d), 1 month (−155 [16] kcal/d), and 6 months (−134 [17] kcal/d). Bias at baseline was significantly different from bias at 1 month ($p < 0.05$), with an average shift of −34 (111) kcal/d across all four equations toward overprediction. Bias at baseline was significantly different from bias at 12 months ($p \leq 0.01$) for all but the Owen equation ($p = 0.16$) and it shifted in a positive direction by an average of 34 (120) kcal/d. MSJ demonstrated the highest accuracy at baseline (88%), 6 months (79%), and 12 months (73%), whereas Owen had the highest accuracy at 1 month (78%). Differences in accuracy varied widely between equations and time points, but only the baseline-to-12-month change in accuracy for MSJ (−15%, $p = 0.01$) and baseline-to-6-month change for WHO/FAO (−22%, $p < 0.01$) were significant.

Changes in weight and bias for the post hoc analysis are presented in Figure 2. In the HWLG, weight change (median [interquartile range]) from baseline to 1 month (−4.1%, −3.5% to −5.5%), 6 months (−9.8%, −6.7% to −12.7%), and 12 months (−9.5%, −6.8% to −11.9%) was significantly different ($p < 0.01$) from the LWLG weight change from baseline to 1 month (−1.2%, −0.6% to −2.3%), 6-months (−4.4%, −0.8% to −7.1%), and 12-months (−4.8%, −1.4% to −8.4%). In the HWLG, baseline bias (mean [SD]) was significantly different from 1 month bias ($p < 0.001$), with an average shift of −69 (108) kcal/d across all four equations toward overprediction. In the LWLG, baseline bias was significantly different from 12-month bias ($p < 0.05$), with an average shift of 44 (103) kcal/d across all four equations toward underprediction.

As an exploratory aim, we assessed the correlation between changes in bias across time and various demographic and anthropometric characteristics to identify potential underlying sources of error that emerged during the intervention. There were no significant associations between change in bias and age, sex, baseline BMI, or change in FM for any equation at any time point. Significant results from the correlation analysis (Pearson r and 95% CI) are shown in Figure 3. From baseline to 12 months, change in bias was negatively and significantly associated with baseline weight in the MSJ ($r = -0.31$ [95% CI: −0.54 to −0.03], $p = 0.03$) and Owen ($r = -0.29$ [95% CI: −0.53 to −0.01], $p = 0.05$) equations (i.e., greater baseline weight associated with shifts toward negative bias). From baseline to 1 month, change in bias was positively and significantly ($r = 0.27$ [95% CI: 0.02 to 0.50], $p = 0.04$) associated with weight change for the Owen equation (i.e., greater weight loss associated with a greater decrease in bias). In all four equations, changes in FFM were correlated with changes in bias from baseline to 1 month ($p \leq 0.01$), with greater decreases in FFM positively associated with a shift toward negative bias; however, the correlation was no longer significant between baseline and 6 months or 12 months.

DISCUSSION

The primary finding of the present study is that bias and accuracy of equations commonly used to estimate REE in clinical settings were significantly affected by changes in weight and body composition at different time points. Bias increased in a negative direction (toward overprediction) from baseline to 1 month in all four equations. Although post hoc analysis suggested that the 1-month shift toward

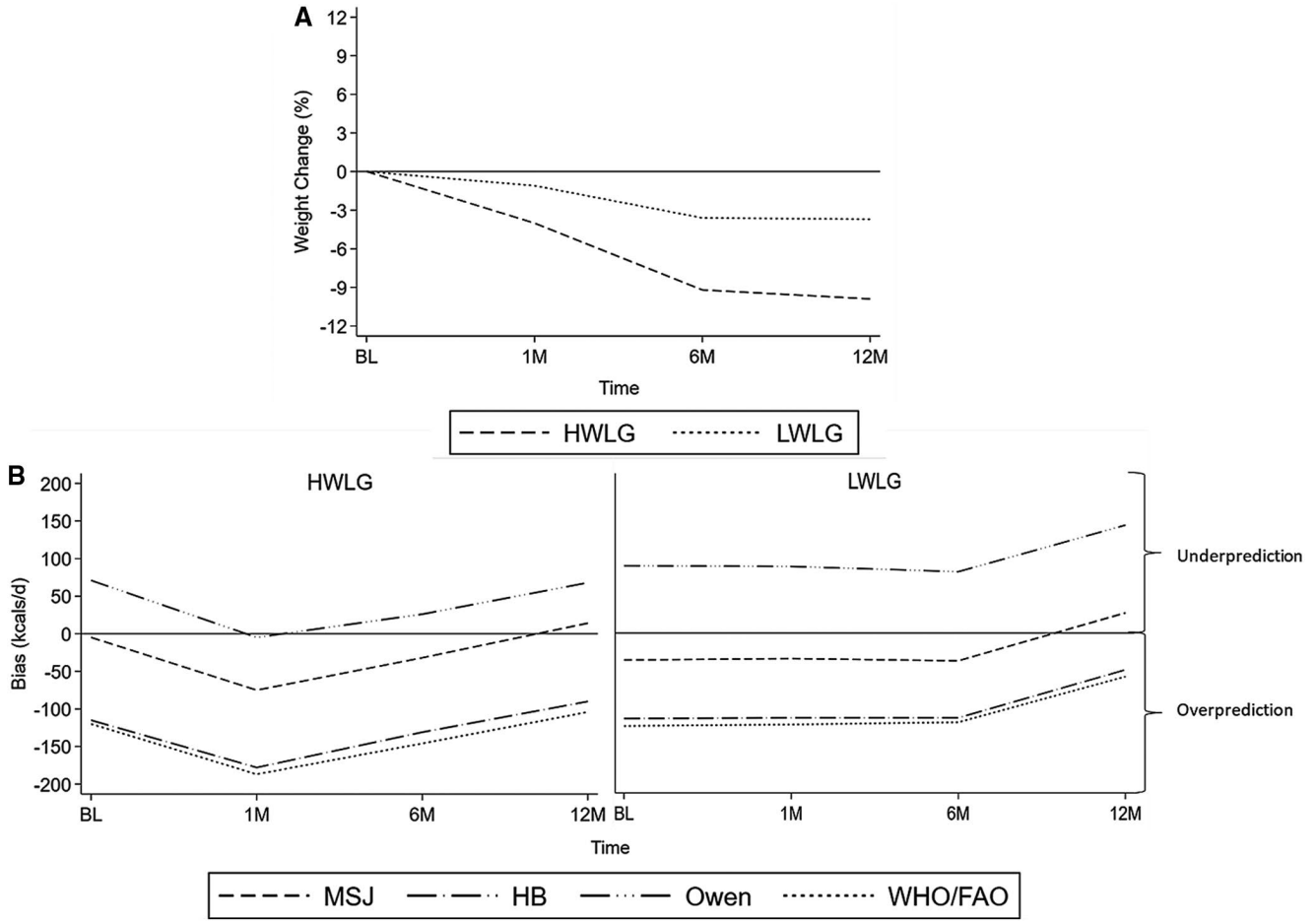

FIGURE 2 Changes in (**A**) weight and (**B**) bias across time for the post hoc analysis. Participants whose weight loss was at or below the median at 1 month were included in the LWLG. Participants whose weight loss was above the median were included in the HWLG. Bias defined as mean measured − mean predicted REE at each time point. HWLG sample sizes: BL: $n = 29$, 1M: $n = 29$, 6M: $n = 27$, 12M: $n = 26$. LWLG sample sizes: BL: $n = 30$, 1M: $n = 30$, 6M: $n = 25$, 12M: $n = 23$. 1M, 1 month; 6M, 6 months; 12M, 12 months; BL, baseline; HB, Harris-Benedict; HWLG, high-weight-loss group; LWLG, low-weight-loss group; MSJ, Mifflin-St-Jeor; REE, resting energy expenditure; WHO/FAO, World Health Organization/Food and Agriculture Organization.

overprediction was driven by greater weight loss, correlation analysis revealed that weight loss, per se, was a less potent predictor of changing bias than changes in FFM. As hypothesized, this early shift in negative bias had largely dissipated by 6 months. However, contrary to our hypothesis, all equations had again shifted beyond their baseline levels of bias, but in a positive direction (toward underprediction), from baseline to 12 months, with significant differences occurring in all but the Owen equation. Because obesity management is a dynamic process that can require estimation of energy intake needs following periods of weight loss, weight stabilization, and weight regain, our study has important clinical implications. Not only did we find evidence that changes in body weight and composition can negatively affect equation validity, but any error in REE prediction induced by such changes would be amplified in clinical settings where predicted REE is used to prescribe calorie goals. The amplification of new error would occur because the standard practice of multiplying predicted REE by PA factors (typically ranging from 1.5-2.0 × REE) to estimate TDEE would lead to a multiplication of bias equal to the amount of the selected activity factor. Therefore, our findings suggest that additional caution should be exercised when using mathematical models to predict REE during periods of weight change.

Overall, MSJ showed the least bias and highest level of accuracy at most time points, which may be attributed to the larger, more heterogenous population from which it was derived compared with the other three equations. However, it also experienced the sharpest decline in accuracy between baseline and 1 month, with a −2.8% mean weight change and −1.3% mean change in FFM, leading to a 13% decrease in accuracy (Table 3). These findings suggest that even modest changes in body weight and composition can exacerbate both the group- and individual-level error already present in mathematical predictive models despite how well matched they are to a specific population.

Our primary hypothesis was that changes in bias would arise from the effects of AT. The appearance of negative bias from baseline to 1 month in all four equations, despite each using different linear regression models derived from different populations, is strong evidence for early AT. Seminal work by Leibel and Rosenbaum found

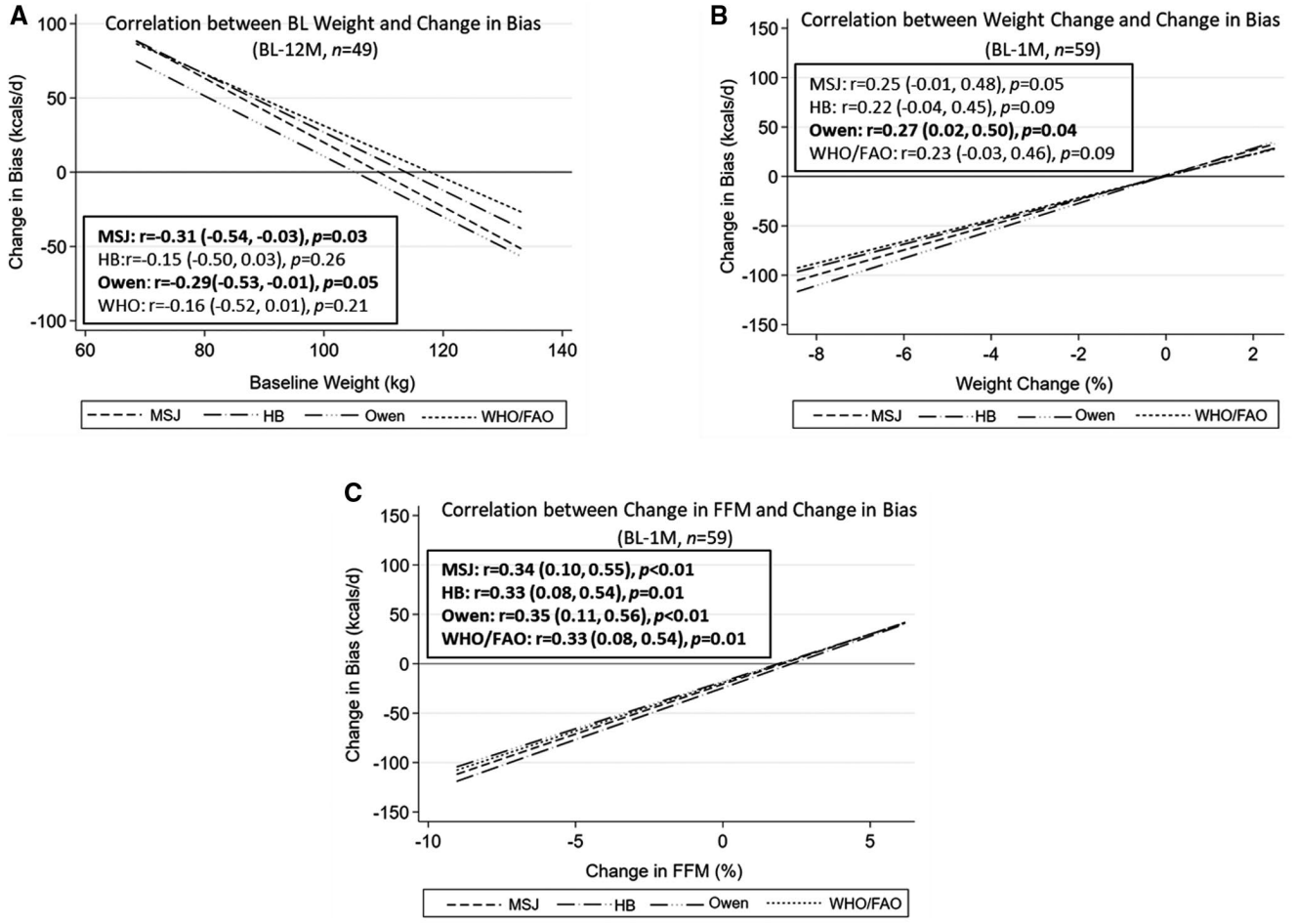

FIGURE 3 Simple linear regression used to assess significant correlations between changes in bias and (**A**) baseline weight, (**B**) percentage of weight change, and (**C**) percentage change in FFM at different time points for each equation. Pearson *r* and 95% CI are reported with significant *p* values ($\alpha < 0.05$) indicated in bold. Bias defined as mean measured − mean predicted REE. BL, baseline; HB, Harris-Benedict; FFM, fat-free mass; MSJ, Mifflin-St-Jeor; REE; resting energy expenditure; WHO/FAO, World Health Organization/Food and Agriculture Organization

that weight loss of ~10% over 6 to 14 weeks was sufficient to elicit AT that ranged from −54 to −137 kcal/d (8), and subsequent studies have reported similar results (11,12,14,19,29). However, the regulatory mechanisms that govern AT are largely unknown. Because FM is the primary tissue lost during a 10% reduction in weight, leptin, with its downstream effects on the sympathetic nervous system, has been posited as a potential regulatory hormone (10,19,30,31). Subsequent studies have found evidence of leptin's role in adaptive thermogenic effects on the nonresting component of TDEE (31-33) but largely have failed to find an association with adaptive thermogenic shifts in REE (29,31,34). Work by Müller et al. cast doubt on the adipose and leptin-centric model of AT regulation and suggested it may instead be an early-phase weight-loss phenomenon tied to changes in FFM (29). Our findings align more closely with Müller's early-phase, FFM-centric model of AT for two reasons. First, the early shift toward overprediction occurred after only 4 weeks of very modest weight loss (−2.8%). This finding is unique and it suggests that AT may be triggered earlier and with much lower levels of weight loss than typically reported. Second, although the loss of FM (−6.4%) during the first month exceeded the loss of FFM (−1.3%), change in bias was correlated with changes in FFM.

The reversal of negative bias at the 6-month time point despite greater overall changes in weight and body composition is also consistent with AT. Weekly weight data obtained from cellular-enabled scales revealed that 52% of participants had begun to regain weight by 6 months, with an average weight gain of 0.35 kg in the month leading up to the official weigh-in (data not shown). Therefore, the group-level reversal in early REE overprediction by 6 months appears driven by a transition toward positive energy balance and the presumed cessation of AT. By 12 months, 76% of participants were regaining weight, with an average change of 0.82 kg/wk. This weight regain coincided with the appearance of significant positive bias that was unexpected, because weight regain has been reported to have a smaller adaptive thermogenic effect on REE than weight loss (8,30,35). Taken together, our findings that commonly used predictive equations experienced significant negative shifts in bias during early weight loss that were reversed at 6 months but then surpassed baseline levels and moved in a positive

direction by 12 months are consistent with AT and underscore the importance of obtaining a thorough weight history in both clinical and research settings where mathematical REE predictive modeling is used.

Our study has several limitations. First, because the parent study is ongoing and primary outcomes are blinded, we were unable to assess the impact of each diet intervention on changes in bias or accuracy over time. Although such data may offer insight into possible mechanisms that underlie changes in REE predictive validity, they would not be expected to affect the primary findings of this study. Second, although timing of menses was recorded, it was not controlled for when measuring REE and may have affected REE measurement in some participants. Finally, our study was somewhat small and homogenous, which may limit its generalizability to the larger population of individuals with overweight or obesity undergoing a weight-loss intervention.

CONCLUSION

We found that changes in weight and body composition during a 12-month behavioral weight-loss intervention significantly affected both the bias and accuracy of clinically relevant mathematical models used to predict REE in adult male individuals and female individuals with overweight and obesity. Our results suggest that the timing, type, and extent of changes in body weight and composition drive the amount and direction (positive or negative) of new bias introduced into predictive models. The development and resolution of new bias coincided with group-level transitions between weight loss, weight stabilization, and weight regain and they were consistent with AT. Importantly, the baseline-to-1-month shift toward overprediction occurred after very modest decreases in weight and body composition and it was correlated with changes in FFM but not FM. These findings lend support to an early-phase weight-loss model of AT and suggest that AT can be elicited more quickly and following smaller amounts of weight loss than typically reported. Our findings have important clinical implications and underscore the need to exercise caution when using mathematical models to predict REE during periods of weight fluctuation. They also highlight weight history as an important factor that should be considered when using REE prediction to prescribe calorie goals.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

VC conceived of and designed the parent study with assistance from EM, PM, and DB. JD conceived of and designed the secondary data analysis. VC, JD, and DO carried out participant visits and performed data collection. JD and SH interpreted the data. JD and ZP performed statistical analysis. JD had primary responsibility for developing the manuscript. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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ORCID

Jared H. Dahle https://orcid.org/0000-0002-8686-0153
Steven B. Heymsfield https://orcid.org/0000-0003-1127-9425
Edward L. Melanson https://orcid.org/0000-0001-9151-9745
Victoria A. Catenacci https://orcid.org/0000-0001-9723-3748

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