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Analyzing weight loss intervention studies with missing data: which method should be used?

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Abstract
Objective: Missing data due to study dropout is common in weight loss trials and several statistical methods exist to account for it. The aim of this study was to identify methods in the literature and to compare the effects of methods of analysis using simulated data sets. Methods: Literature was obtained for a 1-y period to identify analytical methods used in reporting weight loss trials. A comparison of methods with large or small between-group weight loss, and missing data that was, or was not, missing randomly was conducted in simulated data sets based on previous research. Results: Twenty-seven studies, some with multiple analyses, were retrieved. Complete case analysis (n ¼ 17), last observation carried forward (n ¼ 6), baseline carried forward (n ¼ 4), maximum likelihood (n ¼ 6), and multiple imputation (n ¼ 2) were the common methods of accounting for missing data. When comparing methods on simulated data, all demonstrated a significant effect when the between-group weight loss was large ($P < 0.001$, interaction term) regardless of whether the data was missing completely at random. When the weight loss interaction was small, the method used for analysis gave considerably different results with mixed models (P ¼ 0.180) and multiple imputations (P ¼ 0.125) closest to the full data model (P ¼ 0.033). Conclusion: The simulation analysis showed that when data were not missing at random, treatment effects were small, and the amount of missing data was substantial, the analysis method had an effect on the significance of the outcome. Careful attention must be paid when analyzing or appraising studies with missing data and small effects to ensure appropriate conclusions are drawn.

Keywords
method, should, be, used, loss, intervention, studies, missing, analysing, data, weight, which

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Analyzing weight loss intervention studies with missing data: Which methods should be used?

Marijka J. Batterham, Linda C. Tapsell & Karen E. Charlton

Keywords: Missing data, weight loss, multiple imputation

Abstract

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Methods: *Literature was obtained for a 1-y period to identify analytical methods used in reporting weight loss trials. A comparison of methods with large or small between-group weight loss, and missing data that was, or was not, missing randomly was conducted in simulated data sets based on previous research.*
Results: *Twenty-seven studies, some with multiple analyses, were retrieved. Complete case analysis (n ¼ 17), last observation carried forward (n ¼ 6), baseline carried forward (n ¼ 4), maximum likelihood (n ¼ 6), and multiple imputation (n ¼ 2) were the common methods of accounting for missing data. When comparing methods on simulated data, all demonstrated a significant effect when the between-group weight loss was large (P < 0.001, interaction term) regardless of whether the data was missing completely at random. When the weight loss interaction was small, the method used for analysis gave considerably different results with mixed models (P ¼ 0.180) and multiple imputations (P ¼ 0.125) closest to the full data model (P ¼ 0.033).*
Conclusion: *The simulation analysis showed that when data were not missing at random, treatment effects were small, and the amount of missing data was substantial, the analysis method had an effect on the significance of the outcome. Careful attention must be paid when analyzing or appraising studies with missing data and small effects to ensure appropriate conclusions are drawn.*

INTRODUCTION

Missing data in weight loss intervention trials is common, generally resulting when participants drop out of the study. This is referred to as a monotonic pattern of missing data [1], where the participant remains in the study until a certain point after which all data are missing. Data also may be missing arbitrarily when participants miss an assessment, or when there is a mechanical or operator failure with equipment or procedures.

Available statistical methods for dealing with missing data include the following:

- *Complete case analysis*: Data from only the subset of participants with a measurement at every time point are analyzed.
- *Single imputation methods*: Last observation carried forward (LOCF) and baseline carried forward (BCF) were a single value for each participant (the last observation observed or the baseline measurement) is used to replace the missing values for that participant.
- *Maximum likelihood* (ML): Identifies population parameters most likely to produce the sample data [2,3]. In this analysis, a form of maximum likelihood is used in the linear mixed model [4] which uses the available data at each time point allowing for the use of partial datasets.
- *Multiple imputation* (MI): This method involves three steps:
    1) several data sets are generated where the missing values are imputed by random draws from a plausible distribution,
    2) the individual data sets are analyzed using standard methods to determine the parameters of interest, and
    3) the parameter estimates from the individual analyses are combined accounting for both the individual sample variance and the extra variance introduced by the missing data [5].

Statistical models used include general linear or linear mixed model for repeated measures.

Missing data falls into one of three patterns [1]. Missing completely at random (MCAR) refers to missing data that is unrelated to the study outcome or intervention. In data that is missing at random (MAR), the missing data pattern depends on some observed characteristic (e.g., those who have not lost weight at the first follow-up may be more likely to drop out than those who have lost weight). Missing not at random (MNAR) occurs when the missing data (missingness) depends on an unobserved characteristic. For example, if those who have not lost weight drop out of the study before any follow-up weight was recorded, then the data is dependent on the amount of weight loss even though this is not measured. It is most tenable that the mechanism of attrition in weight loss trials is MAR or MNAR. A recent systematic review, for example, showed that several characteristics predicted drop out in weight loss studies [6] with five of six studies that investigated initial treatment effectiveness reporting an increased dropout rate in those who had lower initial weight loss. In this contribution, we review the types of methods used in the weight loss literature and compare the effects of MCAR and "not MCAR" (a combination of an MAR and MNAR pattern) using simulated data sets from weight loss trials.

METHODS

To obtain a sample of studies from which to extract representative sample sizes and dropout rates in weight loss trials, a PubMed search was conducted (November 2010). The primary search term was weight loss diet and limits were imposed to select only studies in the previous year, which were randomized controlled trials in adult humans published in English.

Trials were included if the weight data analysis was reported and presented and the intervention was dietary related (not pharmaceutical).

From the retrieved studies and data from existing trials [7–9] an analysis of two simulated data sets was conducted. The simulations were developed to represent a weight loss trial conducted over a 1-y period with a rapid weight loss in the first 3 mo, followed by a slower weight loss over the rest of the trial. Starting weights, SDs, and the correlation structures were obtained from data from our research group [7–9]. Weight loss at each time point (baseline, 3 mo, and 12 mo) was estimated using data from the completer analysis in a previously published paper [10]. This group of researchers showed an effect of a high-protein diet over 12 mo and demonstrated a significant difference in weight loss at 3 and 12 mo between the treatment and control groups using t tests adjusted for multiple comparisons (Bonferroni adjustment, $P < 0.017$). A second data set was simulated that demonstrated a smaller between-group interaction, but still showed a significant between-group difference in weight change between base-line and 12 mo-1.89 kg (95% confidence interval [CI], -3.62 to -0.16; $P = 0.033$).

Data were simulated from a multivariate normal distribution with a fixed correlation structure. Weights and SDs for the full case analyses are presented in Tables 1 to 4, the correlation matrix based on our previous research [9] was (1, 0.987, 0.954, 0.987, 1, 0.967, 0.954, 0.967, 1) for the treatment group ($n = 53$) and (1, 0.966, 0.933, 0.966, 1, 0.962, 0.933, 0.962, 1) for the controls ($n = 53$). To generate the missing data, participants were randomly removed in approximately equal numbers at each post-baseline time point to generate a reduced data set (MCAR) with a monotone pattern of missingness. For comparison, a data set in which the participants dropping out were randomly removed only from the half of the population that lost the least amount of weight at 3 mo, meaning those who were "failing," were overrepresented in the dropouts, this data set contained both MAR and MNAR cases (not MCAR).

The full, complete case, LOCF, and BCF data sets were analyzed using a repeated measures analysis of variance in the general linear model (SPSS V19.0, IBM Corporation, Armonk NY). ML estimation was conducted using the linear mixed model on all available data (using SPSS version 19.0 or SAS V9.2, Cary NC). MI (PROC MI using SAS v9.2) was followed by analysis using the linear mixed model, the default of five imputations was used for all models [1] with an additional comparison with 20 imputations for the lower weight loss models. The F statistics were combined using the combchi macro [3] for combining P-values from imputations [11]. An ad hoc sensitivity analysis [1] was performed on the not MCAR data set imputations with the small difference. The purpose of the sensitivity analysis is to demonstrate what procedures are available when it was suspected that the MAR assumptions are violated. Constant values were obtained to add to the multiply imputed values by using a small (0.2, treatment) and medium (0.5, control) effect size as defined by Cohen [12] and suggested in Enders [2].

RESULTS

Twenty-seven studies were used to determine a representative sample size and dropout rate [9,10,13–37]. Table 5 provides summary statistics for the baseline sample sizes and completers, the dropout rates, and the methods used to account for missing data and analysis. The simulations were based on the identified sample sizes with rounding to whole participant numbers. One hundred and six participants were simulated separately in equal sample sizes of 53

in the treatment and control groups. The two dropout rates were 24% (approximate average) and approximately double this (47%) for the high dropout.

Tables 1 to 4 show the results of the different methods of analysis on the simulated data sets. In all analyses, the interaction effect was significant when the time X group interaction (treatment) effect was large and there was an average amount of missing data (Tables 2 and 4).

Tables 1 and 3 show the results of the analyses of the data sets with large amounts of missing data. When the data are MCAR, there is a significant interaction term for the full data analysis.

Table 1: Weights at study time points for all analysis methods, 47% missing data, small-effect MCAR

	Full			Completers			Maximum likelihood			LOCF			Imputed			BCF		
	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n
Treatment																		
Baseline	88.00	1.68	53	89.52	2.43	28	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53
3 mo	80.68	1.69	53	82.03	2.35	28	81.89	1.94	40	82.66	1.66	53	81.10	1.66	53	84.05	1.66	53
12 mo	77.69	1.74	53	78.67	2.45	28	78.67	2.45	28	80.89	1.72	53	77.02	1.86	53	82.27	1.75	53
Change	10.31			10.85			9.33			7.11			10.98			5.73		
Control																		
Baseline	87.20	1.75	53	88.78	2.53	28	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53
3 mo	81.46	1.73	53	82.72	2.35	28	82.45	1.98	39	83.19	1.67	53	81.93	1.79	53	84.00	1.67	53
12 mo	78.78	1.93	53	79.73	2.66	28	79.73	2.66	28	81.61	1.82	53	78.23	2.01	53	82.42	1.83	53
Change	8.42			9.05			7.47			5.59			8.97			4.78		
Type 3 fixed effects																		
Time	0.000			0.000			0.000			0.000			0.000 *	0.000 †		0.000		
Group	0.884			0.923			0.879			0.950			0.867	0.994		0.922		
Interaction	0.013			0.096			0.059			0.170			0.180	0.083		0.617		

BCF, baseline carried forward; LOCF, last observation carried forward; MCAR, missing completely at random

* m = 5 imputed data sets.

† m = 20 imputed data sets

Table 2: Weights at study time points for all analysis methods, 24% missing data, large-effect MCAR

	Full			Completers			Maximum likelihood			LOCF			Imputed			BCF		
	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n
Treatment																		
Baseline	88.00	1.68	53	87.43	1.95	40	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53
3 mo	79.18	1.69	53	77.67	1.97	40	76.94	1.77	46	79.46	1.87	53	78.14	1.69	53	81.26	1.76	53
12 mo	76.19	1.74	53	75.49	1.96	40	75.49	1.96	40	77.81	1.90	53	76.22	1.71	53	78.94	1.89	53
Change	11.81			11.94			12.51			10.19			11.78			9.06		
Control																		
Baseline	87.20	1.75	53	86.61	2.03	40	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53
3 mo	82.96	1.73	53	84.29	2.03	40	83.50	1.81	46	85.09	1.78	53	82.96	1.73	53	84.15	1.76	53
12 mo	80.28	1.93	53	80.33	2.19	40	80.33	2.19	40	82.10	1.92	53	80.28	1.93	53	81.75	1.89	53
Change	6.92			6.28			6.87			5.10			6.92			5.45		
Type 3 fixed effects																		
Time	0.000			0.000			0.000			0.000			0.010			0.000		
Group	0.149			0.213			0.147			0.232			0.157			0.512		
Interaction	0.000			0.000			0.000			0.000			0.000			0.000		

BCF, baseline carried forward; LOCF, last observation carried forward; MCAR, missing completely at random

Table 3: Weights at study time points for all analysis methods, 47% missing data, small-effect not MCAR

	Full			Completers			Maximum likelihood			LOCF			Imputed			BCF		
	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n
Treatment																		
Baseline	88.00	1.68	53	89.12	2.09	28	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53
3 mo	80.68	1.69	53	80.44	2.08	28	80.22	1.86	40	82.03	1.73	53	80.08	0.96	53	83.42	1.72	53
12 mo	77.69	1.74	53	77.55	2.21	28	77.55	2.21	28	80.51	1.81	53	76.99	1.01	53	81.89	1.82	53
Change	10.31			11.57			10.45			7.49			11.01			6.11		
Control																		
Baseline	87.20	1.75	53	89.38	2.22	28	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53
3 mo	81.46	1.73	53	81.29	2.21	28	83.19	1.81	39	82.37	1.68	53	80.66	1.02	53	82.93	1.73	53
12 mo	78.78	1.93	53	78.36	2.56	28	78.37	2.56	28	80.82	1.85	53	77.41	1.16	53	81.38	1.90	53
Change	8.42			11.02			8.83			6.38			9.79			5.82		
Type 3 fixed effects																		
Time	0.000			0.000			0.000			0.000			0.000[*]	0.000[†]		0.000		
Group	0.884			0.837			0.993			0.983			0.932	0.934		0.807		
Interaction	0.013			0.596			0.180			0.000			0.125	0.012		0.919		

BCF, baseline carried forward; LOCF, last observation carried forward; MCAR, missing completely at random

[*] m = 20 imputed data sets.

[†] Ad hoc sensitivity on 20 imputed data sets

Table 4: Weights at study time points for all analysis methods, 24% missing data, large-effect not MCAR

	Full			Completers			Maximum likelihood			LOCF			Imputed			BCF		
	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n	Mean (kg)	SE (kg)	n
Treatment																		
Baseline	88.00	1.68	53	87.75	1.88	40	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53	88.00	1.68	53
3 mo	79.18	1.69	53	78.45	1.84	40	79.03	1.80	46	80.17	1.72	53	78.95	1.66	53	80.98	1.77	53
12 mo	76.19	1.74	53	75.79	1.89	40	75.79	1.89	40	78.17	1.80	53	76.66	1.75	53	78.98	1.86	53
Change	11.81			11.96			12.21			9.83			11.34			9.02		
Control																		
Baseline	87.20	1.75	53	87.96	1.97	40	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53	87.20	1.75	53
3 mo	82.96	1.73	53	82.91	1.93	40	83.05	1.79	46	83.78	1.71	53	82.56	1.75	53	83.39	1.72	53
12 mo	80.28	1.93	53	80.11	2.20	40	80.11	2.20	40	81.06	1.90	53	79.62	1.98	53	81.27	1.91	53
Change	6.92			7.85			7.09			6.14			7.58			5.93		
Type 3 fixed effects																		
Time	0.000			0.000			0.000			0.000			0.000			0.000		
Group	0.149			0.276			0.397			0.489			0.434			0.599		
Interaction	0.000			0.000			0.000			0.000			0.000			0.000		

BCF, baseline carried forward; LOCF, last observation carried forward; MCAR, missing completely at random

None of the other methods produce a significant interaction at a level of <0.05; however, the mixed model, MI (with 20 imputations), and complete case analysis give similar P-values to the full data set analysis and approach significance. When the dropout rate depends on the initial weight loss and the percentage dropout is large, none of the commonly used methods produce a result similar to that given by the full data set (Table 3). An ad hoc sensitivity analysis was conducted by calculating effect sizes based on the SD of the change in weight between week 12 and baseline in the completers (SD = 3.73), a constant value of 0.746 kg (small effect) was added to the imputed values in the 20 multiply imputed treatment groups a value of 1.865 kg (medium

effect) in the control groups. This sensitivity analysis produced a significant interaction term (P = 0.012, Table 3, Fig. 1).

Table 5: Characteristics of published weight loss trials: sample size, dropout rates, methods for accounting for missing data and analysis

Study sample sizes	**Number (range)**	
Sample size (median and range)		
Commencing	105	(18–446)
Completing	67	(12–407)
Dropout (mean percent, 95% CI)	23	(18–28)
Methods of accounting for missing data used[*]	**Number** (%)	
CC	17	(46)
BCF	4	(11)
LOCF	6	(16)
MI	2	(5.5)
ML[y]	6	(16)
Other imputation	2	(5.5)
Statistical analysis method	**Number** (%)	
Repeated measures ANOVA/GLM	12	(41)
Mixed model[z]	7	(24)
Two group test (t test, Mann-Whitney test)	6	(21)
ANOVA, MANOVA, ANCOVA	4	(14)

ANOVA, analysis of variance; BCF, baseline carried forward; CC, complete case; CI, confidence interval; LOCF, last observation carried forward; ANCOVA, analysis of covariance; MANOVA, multivariate analysis of variance; GLM, general linear model; MI, multiple imputation; ML, maximum likelihood

[*] More than one method could be employed in each of the 27 studies.

[y] Refers only to studies where ML was used on partial data set.

[z] Mixed model may have been used on CC or single imputation data sets referred to in this way to distinguish from those studies using ML as the method of accounting for the missing data.

DISCUSSION

Complete case analysis, LOCF, and BCF continue to be used to analyze missing data in weight loss trials despite substantial literature identifying the limitations and biases of these methods. Complete case analysis is only valid if the data are MCAR [38] and even in this case the analysis is inefficient as the sample size is reduced. Although LOCF and BCF are computationally straight forward, they are not developed using any statistical procedures, and as such there is no guarantee they are valid even when assuming MCAR [39,40]. Both have been shown in some circumstances to demonstrate elevated type I error rates dispelling the belief that this procedure is always conservative [41,42]. In weight loss trials, some recidivism is common in longer studies. Carrying forward a value at an early time point where the weight loss is greatest may introduce bias [41]. ML and MI are the currently preferred methods for dealing with missing data in the general context [3,40,43,44] when the data are MCAR or MAR.

When commonly used methods were compared on simulated data sets to demonstrate the differences obtained with different amounts and types of missing data, all methods gave statistically significant results when the interaction effect was large, regardless of whether the amount of missing data was average or high. The methods gave vastly different results when the missingness pattern depended on the initial weight loss and when the amount of missing data was large (47%). Despite the significant results with all methods when there was a large effect,

examination of the weight estimates and changes at the different time points (Tables 2 and 4) clearly demonstrates differences between the methods with the recommended methods (ML and MI) giving results much closer to the actual values.

Computationally, the mixed model and MI should produce equivalent results when the same variables are used in both models [45] however the mixed model performs poorly when there are large amounts of missing data and the data are not MCAR. Multiple imputations with the default setting of 5 imputations also performed poorly results better matched the true values when 20 imputations were used. This supports the literature when a higher number of imputations is recommended with large amounts of missing data [45]. When the amount of missing data is large and effect sizes small it is important to consider a range of different methods and compare the results (sensitivity analysis).

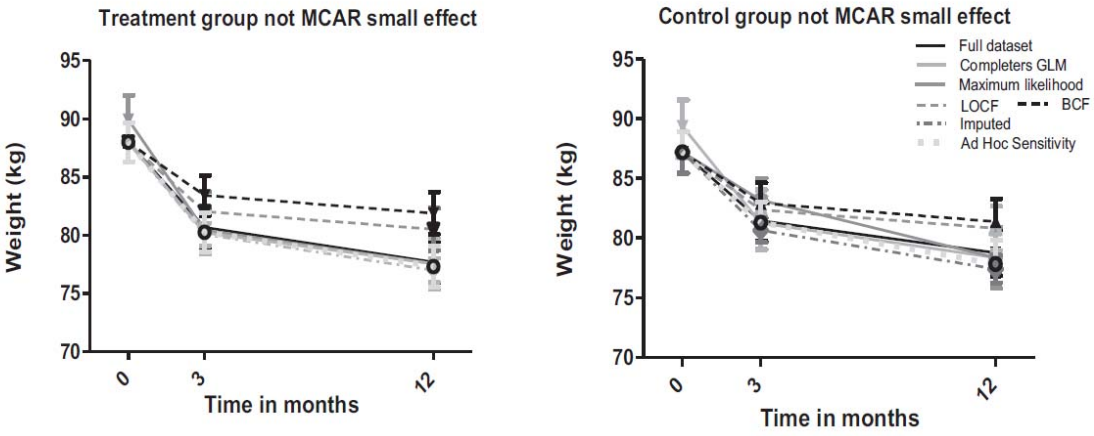

Fig. 1. Change in weight over time for all methods of handling missing data, not missing completely at random (MCAR) dataset with 47% missing data

A previous analysis [46] examined the performance of different methods for handling missing data in weight loss trials, however, this research based the analysis on 12 studies using a variety of supplements, meal replacements, and pharmaceutical treatments as opposed to dietary interventions. These researchers [46] reviewed the literature from an earlier period (2000–2006) and reported the different methods employed in weight loss studies, which included a pharmaceutical arm. They reported that 59% of studies used LOCF, 11% ML, 2% MI, and 16% a completers-only analysis. Our later analysis of the literature suggests that inappropriate methods are still frequently used; however, the complete case analysis was the most common method in the studies we reviewed. This previous research [46] concluded that the mixed model and imputation were the best approaches, with MI performing better when missing data rates were greater (30%–38%) because mixed models were more susceptible to inflated type 1 error rates. Our results are consistent with this conclusion; however, we caution that the result is dependent on the effect size, as well as the amount of missing data. Despite finding a mean dropout rate of 26.3%, the analysis in this previous work [46], the comparison of analysis methods involved 12 data sets with an average of only 15% of missing data. The present study investigated small data sets with a higher dropout rate, as this is our experience of nutritionally based clinical weight loss trials [9]. Additionally 2 of the 27 retrieved studies reported dropout

rates >47% and a recent systematic review reports dropouts ranging from 10% to 80% in weight loss studies [6].

Almost a decade ago, Gadbury et al [47] discussed the use of both ML and MI as preferred methods to analyze data in obesity research. However, these authors only examined a single weight loss scenario in which there was a 7 kg between-group treatment difference with missing data ranging from 20% to 50%. In the current analysis, smaller differences are considered and the choice of method has a substantial effect on the conclusions drawn in this case.

ML and MI are recommended for use when the data are MAR [46,47]. More recently, missing data analysis has focused on models for MNAR data [2,39]. Two classes of MNAR models, selection models and pattern mixture models, are most commonly described in recent literature [2,39,40]. Because these models are computationally complex, a simpler approach (ad hoc sensitivity method) is used in this study. This method is easier to describe and still demonstrates the concept of testing the sensitivity of the models to their implicit assumptions [1]. The ad hoc analysis showed the effect of assuming that those who dropped out lost less weight than those who remained by adding weight to each imputed value. This brought the interac-tion effect closer to the real value for the full data set. This is not surprising, as in this case the missing data were constructed to be not MCAR by preferentially removing participants who had lost the least amount of weight, thus making this adjustment return the estimates closer to the real value. In a real weight loss trial situation, this information is not usually available.

Given that there is generally always missing data in weight loss studies, it is not possible to "prove" the validity of the assumptions, therefore simulations such as the ones presented in this study are necessary. Missing data that was generated to be MCAR or not MCAR was employed to highlight the effects that these assumptions may have on outcomes of analyses. These assumptions are not possible to test in real clinical studies, although it is likely that data in weight loss trials are MAR or MNAR. When data are not MCAR, it is important to consider various approaches and include reasonable variations from the assumptions to draw sensible conclusions.

Although more complicated to employ than the conventional complete case or single imputation methods, the inclusion of mixed model and imputation procedures in the more commonly used statistical packages such as SPSS (with MI from version 17.0, IBM Corporation, Armonk NY) and STATA (with MI from version 11, College Station, TX), in addition to their longer-standing inclusion in SAS (Cary, NC), makes these procedures more available to the nutrition practitioner. Linear mixed models allow more flexibility than standard repeated measures analysis, including the inclusion of time-varying covariates, fixed and random effects, and different covariance structures that are useful for studies with more than two time points and have been used in a number of nutrition intervention studies for these reasons [48–50].

CONCLUSION

In the case of a moderate amount of missing data and a substantial effect size, all methods of analysis will give significant results. The mixed model or MI are the preferred methods because they give the most accurate estimates. When the amount of missing data is considerable, sample sizes are modest or results are of borderline significance. Several techniques should be employed and the results compared as a sensitivity analysis to ensure that

results are valid and plausible. In agreement with previous research, our results do not support the use of last observation or baseline carried forward for analysis of weight loss trials with missing data.

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