Nutrition 29 (2013) 1024–1029

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

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

Marijka J. Batterham Ph.D. [a,*], Linda C. Tapsell Ph.D. [b], Karen E. Charlton Ph.D. [b]

[a] National Institute of Applied Statistics Research Australia, University of Wollongong, New South Wales, Australia
[b] School of Health Sciences, University of Wollongong, New South Wales, Australia

ARTICLE INFO

Article history:
Received 16 November 2012
Accepted 30 January 2013

Keywords:
Missing data
Weight loss
Multiple imputation

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 = 17), last observation carried forward (n = 6), baseline carried forward (n = 4), maximum likelihood (n = 6), and multiple imputation (n = 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 ($P = 0.180$) and multiple imputations ($P = 0.125$) closest to the full data model ($P = 0.033$).
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

MB was responsible for the study design, data collection and simulation, data analysis, and drafting the manuscript. LT and KC were responsible for study design and reviewing the manuscript.

* Corresponding author. Tel.: +61 2 4221 8190.
E-mail address: marijka@uow.edu.au (M. J. Batterham).

0899-9007/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2013.01.017

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.

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 baseline 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

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