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Dealing With Missing Outcome Data in Randomized Trials and Observational Studies

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Although missing outcome data are an important problem in randomized trials and observational studies, methods to address this issue can be difficult to apply. Using simulated data, the authors compared 3 methods to handle missing outcome data: 1) complete case analysis; 2) single imputation; and 3) multiple imputation (all 3 with and without covariate adjustment). Simulated scenarios focused on continuous or dichotomous missing outcome data from randomized trials or observational studies. When outcomes were missing at random, single and multiple imputations yielded unbiased estimates after covariate adjustment. Estimates obtained by complete case analysis with covariate adjustment were unbiased as well, with coverage close to 95%. When outcome data were missing not at random, all methods gave biased estimates, but handling missing outcome data by means of 1 of the 3 methods reduced bias compared with a complete case analysis without covariate adjustment. Complete case analysis with covariate adjustment and multiple imputation yield similar estimates in the event of missing outcome data, as long as the same predictors of missingness are included. Hence, complete case analysis with covariate adjustment can and should be used as the analysis of choice more often. Multiple imputation, in addition, can accommodate the missing-not-at-random scenario more flexibly, making it especially suited for sensitivity analyses.

confounding; loss to follow-up; missing data; multiple imputation; randomized trials

Abbreviations: MAR, missing at random; MCAR, missing completely at random; MNAR, missing not at random; OR, odds ratio.

Missing data are a frequently encountered problem in epidemiologic research (1, 2). Although a lot of effort is put into collecting complete data, even well-designed and -conducted randomized trials suffer from missing data; for example, subjects are lost to follow-up and, thus, data on study endpoints will be missing. Such loss to follow-up may depend on certain patient characteristics. In a trial among geriatric patients, for example, those who suffer from dementia may be less likely to move to another location and are, thus, less likely to be lost to follow-up. Here, we focus on methods that deal with missing *outcome* data in randomized trials and observational studies and, in particular, those situations in which the outcome of interest is the occurrence of an event that is measured only once (i.e., no repeated measures). Examples include the occurrence of fatal or nonfatal cardiovascular events in trials on statin therapy or recurrence of a tumor in an oncology trial.

Several methods have been proposed to handle missing data. One (and still the most widely used) approach is to include only those subjects without missing observations for analysis, which is known as available or complete case analysis (1–4). This approach, however, results in less precision and often biased estimates (5–7). Alternatives to complete case analysis are single and multiple imputation, in which information on observed (baseline) covariates is used to impute the value of the missing outcome using regression techniques (2, 8–10).

Guidelines on the conduct of randomized trials indicate that adjustment for covariates can be considered to reduce bias and increase precision and should be prespecified in the trial protocol (11, 12). In observational studies, covariate adjustment is applied to control for confounding. Interestingly, in both cases, models that are used for covariate adjustment are typically of the same class of (regression) models as the

ones that are used for imputation of missing outcome data. If the same variables are included in both models, the models may, in fact, be identical. This has been put forward in the statistical literature (13–18) but has not received appropriate attention in epidemiologic literature. In this paper, we will show that multiple imputation and complete case analysis with covariate adjustment yield similar results in terms of bias and precision in data with missing outcomes. We illustrate this using simulation studies on randomized trials and observational studies.

MATERIALS AND METHODS

Missing data

When subjects with missing outcomes are a random subset of the individuals in a particular study, the missing data are called missing completely at random (MCAR) (2, 3, 5, 6). In that case, complete case analysis yields unbiased estimates of the treatment effect (2, 3, 5, 6). If, however, missing data are not MCAR, but missingness is related to other observed or documented patient data, this is called missing at random (MAR) (2, 3, 5, 6). For example, if treated women are more likely to have missing outcome data than untreated men, missingness is related to treatment and sex, and complete case analysis may yield biased estimates of the treatment effect (3). Observed patient data can be used as predictors of the values for the missing outcomes. The missing data can then be imputed with predicted values from a multivariable (regression) model that includes these observed patient data. For continuous outcome data, the most likely value based on the multivariable model can be imputed for the missing observation (also known as conditional mean imputation). For missing dichotomous outcomes, the multivariable model yields a probability of a Bernoulli process that is used to generate values for the outcome data (i.e., imputing from a conditional probability distribution) (19). This probability can then be used to impute the missing outcome value by, for example, rounding it to the nearest integer (0 or 1) or by sampling from a Bernoulli distribution. In both situations, however, the single imputed values are not actually observed but, rather, predicted, and imputing the most probable value therefore overestimates the precision and distorts the distribution of the data (8–10, 18, 19). The latter might even induce bias. The imprecision due to imputation rather than observation, however, can be accounted for by means of multiple imputation (2, 3, 6, 8–10). In multiple imputation rather than a single (most likely) value, multiple values (e.g., 10) are sampled from an estimated distribution and imputed (3). Hence, multiple data sets with imputed outcomes are created. Each data set can then be analyzed and, subsequently, results are pooled by using standard techniques taking into account the variation between imputed data sets (8–10).

When missingness of outcome data is not MCAR or MAR, data are said to be missing not at random (MNAR). For example, if missingness is related to unobserved patient data or only to the value of the unobserved outcome, missing data are MNAR, and the aforementioned methods cannot handle data that are MNAR by default. In a clinical setting, however, it seems unrealistic that missing data are completely MNAR, and probably missingness of data partly depends on observed characteristics as well (MAR), in which case applying multiple imputation still results in less biased estimates than not addressing missing data at all (e.g., conventional complete case analysis without covariate adjustment) (20).

Complete case analysis with covariate adjustment

Suppose that a randomized trial is conducted on the effects of a certain lipid-lowering drug on total cholesterol levels and that 1 baseline covariate (e.g., sex) is observed. If all data are observed (i.e., no missingness), 2 (linear) models can be fitted to the data:

$$\mathrm{TC} = \beta_0 + \beta_1 \mathrm{drug} + \varepsilon \quad (1)$$

and

$$\mathrm{TC} = \beta_0 + \beta_1 \mathrm{drug} + \beta_2 \mathrm{sex} + \varepsilon, \quad (2)$$

where TC is total cholesterol. In a randomized trial, confounding is not an issue, so the population value of β_1 is the same in the 2 models. Suppose that the outcome (total cholesterol) is not observed in every subject and that this missingness is related to both treatment and sex, such that, for example, female treated subjects are more likely to have missing outcome data. In that case, missingness is random conditional on treatment and sex (i.e., MAR). Thus, if missingness depends on treatment and sex, missingness is completely at random (MCAR) after conditioning on treatment and sex, that is, within the strata of treatment and sex. Hence, a comparison of treated and untreated within-sex strata including only subjects without missing outcome data then yields unbiased estimates of the treatment effect (3). Stratifying on sex or including sex as a covariate in a regression model is essentially the same. Thus, if missingness indeed depends only on treatment and sex, model 2 will give an unbiased estimate of β_1.

In the case of multiple covariates, the aforementioned models can simply be generalized to the following:

$$\mathrm{TC} = \beta_0 + \beta_1 \mathrm{drug} + \beta_2 X_1 + \beta_3 X_2 + \ldots + \beta_{n+1} X_n + \varepsilon, \quad (3)$$

with $X_1, X_2, \ldots, X_n$ a set of covariates (e.g., sex, age, comorbidity status, and so on). If missingness of the outcome is related to these observed covariates (i.e., variables that are part of the set $(X_1, X_2, \ldots, X_n)$), this again means that data are missing at random (MAR). Hence, conditional on $X_1, X_2, \ldots, X_n$ missingness of the outcome is completely at random, and complete case analysis yields unbiased estimates.

Thus, complete case analysis with covariate adjustment yields unbiased estimates when missing outcome data are MAR, and predictors of missingness of the outcome are included as covariates in the adjustment model. Similarly, multiple imputation will also yield unbiased estimates when outcome data are MAR, when the same or more information is used to impute missing outcome values.

The same argument holds for observational studies, in which confounding by other covariates $(X_1, X_2, \ldots, X_n)$ may bias the estimated effect of the etiologic factor or treatment under study. In that case, model 1 will give biased estimates

of β_1, but model 3 provides valid estimates, as long as all confounders are included in the model and missing outcome data are MAR (i.e., missingness depends at most on the observed characteristics).

Simulation study

Above, we showed that both complete case analysis with covariate adjustment and multiple imputation will yield unbiased estimates when outcome data are MAR. We also conducted a simulation study to show how methods to handle missing outcome data (complete case analysis, single imputation, and multiple imputation; all 3 with and without covariate adjustment) perform under different scenarios. The scenarios focused on continuous or dichotomous missing outcome data and mimicked a randomized trial (i.e., treatment was not related to baseline covariates) or an observational study (i.e., confounding present).

For each scenario, 5,000 data sets were generated of 250 subjects each, of whom 125 were treated and 125 were not treated. These data sets consisted of 3 variables: a dichotomous treatment, an outcome, and a covariate. In the event of continuous outcome data, a continuous covariate was simulated. The outcome and the covariate were standard normally distributed variables and related (Pearson's correlation = 0.7) and sampled from a multivariate normal distribution. In the event of dichotomous outcome data, a dichotomous covariate was simulated, which increased the risk for the outcome (marginal odds ratio (OR) = 4, or OR = 9). To mimic a randomized trial, the treatment and the covariate were not related. When simulating an observational study, the covariate and the treatment were related to induce a confounding effect, such that when the covariate (or confounder) was present, the probability of receiving treatment was increased (OR = 4).

When quantifying treatment effects by means of odds ratios in the absence of confounding, we found that the unadjusted and the adjusted odds ratios may differ because of noncollapsibility of the odds ratio (21, 22). Consequently, the adjusted odds ratio of the treatment-outcome association will tend to be further from the null (i.e., OR = 1) than the unadjusted odds ratio, except if there is no treatment effect (OR = 1). To get around this potential problem, we decided to first evaluate methods to handle missing data in the absence of a treatment effect (OR = 1). Additionally, we simulated a randomized trial with dichotomous outcomes and a nonnull treatment effect (i.e., OR = 0.9, OR = 0.8, or OR = 0.7).

In each data set, missingness on the outcome was created on the basis of either a MAR mechanism or a mechanism that was MNAR. When missing outcome data were created on the basis of a MAR mechanism, the probability of missingness was either 2 or 5 times larger in treated subjects with positive covariate status or with untreated subjects with negative covariate status, compared with untreated subjects with positive covariate status or treated subjects with negative covariate status, respectively. In the event of continuous covariates, missingness was 2 or 5 times larger for treated subjects with covariate values that were smaller than average and for untreated subjects with covariate values that were larger than average. Suppose higher outcome and covariate values indicate better clinical conditions. Then, the aforementioned scenarios of missingness mimic, for example, a trial in which treated subjects with relatively favorable covariate values and untreated subjects with relatively severe comorbidity were more likely to be lost to follow-up, because of either little need to continue or little perceived effect, respectively. Overall, the proportion of missingness was set at 15% or 30%.

We also performed simulations based on an MNAR mechanism, which was assumed to be a mixture of MAR and MNAR. Therefore, in half of the subjects, missingness was related to treatment and the observed covariate (MAR), while in the other half missingness was related to the value of the outcome variable only (MNAR). The probability of (MAR) missingness was set to be 5 times larger for treated subjects with values for covariates that were larger than average and for untreated subjects with covariate values that were smaller than average (compared with untreated subjects with covariate values that were larger than average and treated subjects with covariate values that were smaller than average). The probability of (MNAR) missingness was set to be 5 times larger when the outcome variable was larger than its average (compared with subjects with outcome values lower than average).

Statistical analyses

In each simulated data set, the methods that were applied to handle missing outcome data were 1) complete case analysis, 2) single imputation, and 3) multiple imputation (all 3 with and without covariate adjustment). For complete case analysis, subjects with missing outcome data were excluded from the analysis. In the event of single imputation, first a regression model (a logistic model for dichotomous outcomes and a linear model for continuous outcomes) including treatment and the covariate was fitted, and missing values were imputed by the estimated value (for continuous missing outcome data) or by sampling from a Bernoulli distribution (for dichotomous missing outcome data), for which the probability of success was defined by the probability of the outcome. Multiple imputation was similar to single imputation, in that a regression model was fitted. However, the regression coefficients of the imputation model estimating the missing outcome values were not constant (as was the case in single imputation) but were sampled from the estimated multivariable distribution of the coefficients. Furthermore, in the event of continuous missing outcome data, a random residual was added to each predicted value. For each data set with missing outcome values, 10 imputed data sets were created using a multivariate imputation by chained equations (MICE) algorithm (23).

Treatment effects were estimated by linear (continuous outcomes) or logistic (dichotomous outcomes) regression analysis. Both unadjusted and adjusted treatment effects (adjusted for the covariate) were estimated. For all methods, the mean treatment effects were estimated (mean of the regression coefficients across simulations), including 95% confidence intervals (based on the mean of the lower and upper boundaries of the estimated 95% confidence interval of the regression coefficients across simulations). For dichotomous outcomes, estimated treatment effects and corresponding 95% confidence intervals were exponentiated to calculate odds ratios. Finally, coverage (i.e., the proportion

Table 1. Results of Methods to Handle Missing Continuous Outcome Data (MAR) From Simulations of a Randomized Trial[a]

Method	Average Estimated Regression Coefficient	95% CI	Coverage, %[b]
Reference[c]			
Unadjusted	0.00	−0.25, 0.25	94.8
Adjusted	0.00	−0.18, 0.18	94.6
Complete case analysis			
Unadjusted	−0.32	−0.61, −0.03	41.8
Adjusted	0.00	−0.22, 0.22	95.1
Single (conditional mean) imputation			
Unadjusted	0.00	−0.23, 0.23	89.2
Adjusted	0.00	−0.15, 0.15	81.9
Multiple imputation			
Unadjusted	0.00	−0.28, 0.27	93.6
Adjusted	0.00	−0.22, 0.21	93.1

Abbreviations: CI, confidence interval, based on the mean of the lower and upper boundaries of the estimated 95% confidence intervals; MAR, missing at random.

[a] Numbers are based on 5,000 simulations of data sets of 250 subjects each, in which outcome data were missing in approximately 30% of the observations, and the probability of missingness was 5 times larger when the treatment and covariate were both absent or both present, compared with untreated subjects with positive covariate status or treated subjects with negative covariate status.

[b] "Coverage" indicates the proportion of estimated 95% confidence intervals in which the true value (i.e., 0 in this simulation study) was included.

[c] "Reference" is based on completely observed data sets, without missing observations.

Table 2. Results of Methods to Handle Missing Continuous Outcome Data (MNAR) From Simulations of a Randomized Trial[a]

Method	Average Estimated Regression Coefficient	95% CI	Coverage, %[b]
Reference[c]			
Unadjusted	0.00	−0.25, −0.25	95.1
Adjusted	0.00	−0.04, −0.04	94.9
Complete case analysis			
Unadjusted	−0.85	−1.12, −0.58	0.0
Adjusted	−0.37	−0.62, −0.12	16.2
Single (conditional mean) imputation			
Unadjusted	−0.37	−0.57, −0.17	12.2
Adjusted	−0.37	−0.52, −0.23	3.1
Multiple imputation			
Unadjusted	−0.39	−0.68, −0.09	26.2
Adjusted	−0.39	−0.65, −0.13	15.8

Abbreviations: CI, confidence interval, based on the mean of the lower and upper boundaries of the estimated 95% confidence intervals; MAR, missing at random; MNAR, missing not at random.

[a] Numbers are based on 5,000 simulations of data sets of 250 subjects each, in which outcome data were missing in approximately 30% of the observations based on a mixture of MAR and MNAR mechanisms.

[b] "Coverage" indicates the proportion of estimated 95% confidence intervals in which the true value (i.e., 0 in this simulation study) was included.

[c] "Reference" is based on completely observed data sets, without missing observations.

of estimated 95% confidence intervals in which the true treatment effect was included) was calculated. All simulations and analyses were performed in R for Windows, version 2.10.1 (24). The simulation code is available on request of the corresponding author.

RESULTS

Continuous missing outcome data

In simulations of randomized trial data with missing continuous outcomes, conventional complete case analysis without covariate adjustment yielded biased estimates of the treatment effect (Table 1), that is, mean treatment effect − 0.32 instead of 0, which is in line with the simulated missing outcome scenario. Complete case analysis with covariate adjustment, however, yielded unbiased estimates (mean treatment effect, 0.00). Analyses after single imputation or multiple imputation gave unbiased estimates as well (both for unadjusted and adjusted analyses).

The 95% confidence intervals were smaller (i.e., more precise) when applying complete case analysis with covariate adjustment than when estimating an unadjusted treatment effect after single or multiple imputation. In studies with continuous outcomes, adjustment for covariates that are related to the outcome results in an increased precision (25, 26). This is also clearly shown in the reference data. Still, in the event of missing outcome data, complete case analysis with covariate adjustment resulted in wider confidence intervals than when data were completely observed, as expected (reference). Coverage was close to 95% for both complete case analysis with covariate adjustment (95.1%) and multiple imputation (93.1%). Single imputation resulted in lower coverage (81.9%) due to a bias in the estimated standard errors that are systematically underestimated (i.e., too small) in single imputation, leading to confidence intervals that were too narrow (3, 8–10). For different scenarios on the MAR mechanism and the proportion of missingness, similar patterns for bias and precision were observed (Web Table 1, the first of 3 Web tables posted on the *Journal*'s Web site (http://aje.oupjournals.org/)). When outcome data were MNAR, complete case analysis with covariate adjustment yielded similar estimates as did single or multiple imputation (with or without covariate adjustment), but all methods gave biased estimates (Table 2). When applying covariate adjustment after single imputation or multiple imputation, we found that this did not affect the size of the estimated regression coefficient (i.e., same bias), precision increased, and confidence intervals

Table 3. Results of Methods to Handle Missing Dichotomous Outcome Data (MAR) From Simulations of a Randomized Trial[a]

Method	Odds Ratio[b]	95% CI	Coverage, %[c]
Reference[d]			
Unadjusted	0.99	0.58, 1.71	95.1
Adjusted	0.99	0.54, 1.83	95.0
Complete case analysis			
Unadjusted	0.57	0.29, 1.11	61.8
Adjusted	1.00	0.46, 2.15	94.9
Single (conditional mean) imputation			
Unadjusted	0.99	0.57, 1.71	86.8
Adjusted	1.00	0.54, 1.84	84.6
Multiple imputation			
Unadjusted	0.98	0.50, 1.94	95.4
Adjusted	0.99	0.45, 2.21	95.1

Abbreviations: CI, confidence interval, based on the mean of the lower and upper boundaries of the estimated 95% confidence intervals; MAR, missing at random.

[a] Numbers are based on 5,000 simulations of data sets of 250 subjects each, in which outcome data were missing in approximately 30% of the observations, the probability of missingness was 5 times larger when the treatment and covariate were both absent or both present compared with untreated subjects with positive covariate status or treated subjects with negative covariate status, and the covariate increased the risk of the outcome by odds ratio = 9.

[b] Exponentiated average of the estimated regression coefficients.

[c] "Coverage" indicates the proportion of estimated 95% confidence intervals in which the true value (i.e., odds ratio = 1 in this simulation study) was included.

[d] "Reference" is based on completely observed data sets, without missing observations.

became narrower, and thus coverage decreased (e.g., from 26.2% to 15.8% in the event of multiple imputation).

Dichotomous missing outcome data

For dichotomous missing outcome data (MAR) in a randomized trial, findings were similar to the scenario of continuous missing outcome data. For a 0 treatment effect, unadjusted complete case analysis yielded biased estimates of the treatment effect (OR = 0.57), but complete case analysis with covariate adjustment as well as single imputation and multiple imputation resulted in unbiased estimates (Table 3).

When we simulated a nonnull treatment effect, the results were the same: Complete case analysis with covariate adjustment yielded unbiased estimates (Table 4). Because of the noncollapsibility of the odds ratio, however, the adjusted and unadjusted effect estimates differed. This difference became more apparent with an increase in the treatment effect.

In contrast to continuous outcomes when outcome data are dichotomous, adjustment for covariates that are related to the outcome results in wider confidence intervals. Hence, the confidence interval for the adjusted complete case analysis was wider than the confidence interval for the unadjusted analysis following multiple imputation. Again, coverage was close to 95% for both complete case analysis with covariate adjustment and multiple imputation. As was expected, coverage was substantially lower for single imputation.

In the presence of confounding, again with missing outcome data that were MAR, all unadjusted analyses gave biased estimates of the treatment effect (Table 5). Complete case analysis resulted in the largest bias of the unadjusted analyses (OR = 3.11, instead of OR = 1), and consequently coverage was poor (7.1%). After covariate adjustment, all studied methods provided correct estimates of the treatment effect. Complete case analysis with covariate adjustment and multiple imputation followed by covariate adjustment yielded similar confidence intervals and coverages (95.0% and 96.1%, respectively).

For different scenarios on the MAR mechanism, the proportion of missingness, and the strength of the association between the covariate and the outcome, similar patterns were observed (Web Tables 2 and 3).

DISCUSSION

In the event of missing outcome data that are missing at random (MAR), complete case analyses with covariate adjustment, single imputation, and multiple imputation all yield unbiased estimates. This applies to both continuous and dichotomous outcomes and to randomized trials as well as observational studies. The advantage of complete case analysis with covariate adjustment over the other 2 methods is that it is easier to apply and more transparent. Furthermore, complete case analysis was at least as efficient as multiple imputation, which could be expected since the imputation process adds random variation to the data (18). When missing outcome data were MNAR, the 3 methods gave similar, yet biased, results. Still, applying these methods resulted in less bias than when applying complete case analysis without covariate adjustment.

The results from this study could not have been obtained using empirical data with missing outcomes, since then the mechanism of missingness and the true (unbiased) treatment effect would be unknown. The results from our simulations could, to some extent, have been predicted by the properties of the methods, and we used the simulations to illustrate the performance of the different methods. The main assumption underlying most of our simulations was that missing outcomes were MAR. It has been hypothesized that it is most probable that missing outcomes are related to earlier observed patient data, and therefore missing data are indeed MAR (8–10, 16). Unfortunately, this assumption can never be tested in real data. When missingness of the outcome is fully related to unobserved covariates or missing outcome status itself (MNAR), all methods discussed here yield incorrect estimates. However, it seems unlikely that missingness of outcome data in a randomized trial or observational study is fully explained by an MNAR mechanism. It seems more realistic that, even in a worst-case scenario, the mechanism underlying the missing outcome data is a mixture of MAR and MNAR (a situation still indicated as MNAR). Handling missing outcome data using the methods discussed will then at least give less biased estimates than not addressing the

Table 4. Results of Methods to Handle Missing Dichotomous Outcome Data (MAR) From Simulations of a Randomized Trial Under a Nonnull Treatment Effect[a]

Method	Odds Ratio[b]	95% CI	Coverage, %[c]
	Treatment effect (*odds ratio = 0.9*)		
Reference[d]			
Unadjusted	0.91	0.51, 1.63	95.5
Adjusted	0.90	0.48, 1.67	95.4
Complete case analysis			
Unadjusted	0.70	0.36, 1.45	91.8
Adjusted	0.90	0.42, 1.91	94.8
Single (conditional mean) imputation			
Unadjusted	0.91	0.51, 1.63	87.3
Adjusted	0.90	0.48, 1.68	86.1
Multiple imputation			
Unadjusted	0.90	0.44, 1.84	95.4
Adjusted	0.90	0.41, 1.95	95.1
	Treatment effect (*odds ratio = 0.8*)		
Reference			
Unadjusted	0.82	0.46, 1.46	95.1
Adjusted	0.80	0.43, 1.48	95.4
Complete case analysis			
Unadjusted	0.65	0.32, 1.31	91.9
Adjusted	0.80	0.37, 1.70	95.0
Single (conditional mean) imputation			
Unadjusted	0.82	0.45, 1.46	86.8
Adjusted	0.80	0.43, 1.49	86.2
Multiple imputation			
Unadjusted	0.82	0.40, 1.67	95.2
Adjusted	0.80	0.36, 1.75	95.5
	Treatment effect (*odds ratio = 0.7*)		
Reference			
Unadjusted	0.72	0.40, 1.29	94.8
Adjusted	0.69	0.37, 1.29	94.9
Complete case analysis			
Unadjusted	0.57	0.28, 1.16	92.4
Adjusted	0.69	0.32, 1.47	94.8
Single (conditional mean) imputation			
Unadjusted	0.72	0.40, 1.30	87.0
Adjusted	0.69	0.37, 1.30	86.0
Multiple imputation			
Unadjusted	0.72	0.35, 1.48	95.1
Adjusted	0.69	0.31, 1.51	95.3

Abbreviations: CI, confidence interval, based on the mean of the lower and upper boundaries of the estimated 95% confidence intervals; MAR, missing at random.

[a] Numbers are based on 5,000 simulations of data sets of 250 subjects each, in which outcome data were missing in approximately 30% of the observations, the probability of missingness was 5 times larger when the treatment and covariate were both absent or both present compared with untreated subjects with positive covariate status or treated subjects with negative covariate status, and the covariate increased the risk of the outcome by odds ratio = 4.

[b] Exponentiated average of the estimated regression coefficients.

[c] "Coverage" indicates the proportion of estimated 95% confidence intervals in which the true value (i.e., odds ratio = 1 in this simulation study) was included.

[d] "Reference" is based on completely observed data sets, without missing observations.

Table 5. Results of Methods to Handle Missing Dichotomous Outcome Data (MAR) From Simulations in the Presence of Confounding[a]

Method	Odds Ratio[b]	95% CI	Coverage, %[c]
Reference[d]			
Unadjusted	1.92	1.10, 3.35	37.5
Adjusted	0.99	0.52, 1.90	95.0
Complete case analysis			
Unadjusted	3.11	1.60, 6.06	7.1
Adjusted	0.98	0.42, 2.32	95.0
Single (conditional mean) imputation			
Unadjusted	1.93	1.10, 3.38	40.1
Adjusted	0.98	0.51, 1.89	83.2
Multiple imputation			
Unadjusted	1.94	0.99, 3.80	52.1
Adjusted	0.99	0.40, 2.42	96.1

Abbreviations: CI, confidence interval, based on the mean of the lower and upper boundaries of the estimated 95% confidence intervals; MAR, missing at random.

[a] Numbers are based on simulations of 5,000 data sets of 250 subjects each, in which outcome data were missing in approximately 30% of the observations, the probability of missingness was 5 times larger when the treatment and covariate were both absent or both present compared with untreated subjects with positive covariate status or treated subjects with negative covariate status, and the covariate increased the risk of the outcome by odds ratio = 9.

[b] Exponentiated average of the estimated regression coefficients.

[c] "Coverage" indicates the proportion of estimated 95% confidence intervals in which the true value (i.e., odds ratio = 1 in this simulation study) was included.

[d] "Reference" is based on completely observed data sets, without missing observations.

missing outcome data at all (i.e., complete case analysis without covariate adjustment), because obviously at least the MAR part of the missing outcome data is addressed. We stress that numerous MNAR scenarios are possible and that results from our simulations on 1 MNAR scenario do not necessarily apply to other MNAR scenarios. Assumptions on the MNAR mechanism can be incorporated in multiple imputation and, given the (correctness of these) assumptions, this will give unbiased estimates. Thus, multiple imputation is more flexible than complete case analysis with covariate adjustment and can therefore play an important role in sensitivity analyses.

Some of the simulated scenarios were quite extreme (e.g., 30% missing outcome data in a randomized trial is quite exceptional). Nevertheless, we explicitly chose these scenarios to clearly illustrate the performance of the different methods to handle missing outcome data.

In randomized trials in which covariate distributions are balanced, adjustment for covariates is expected not to affect the estimated treatment effect. Because of the noncollapsibility of the odds ratio, however, the unadjusted (or marginal) and the adjusted (conditional) odds ratios may still differ (21, 22). Thus, in the event of missing outcome data, complete case analysis with covariate adjustment using logistic regression will not (directly) provide an unbiased estimate of the marginal treatment effect but, rather, an unbiased estimate of the conditional treatment effect. When multiple imputation is first applied and subsequently the treatment effect is estimated, it is possible to directly estimate marginal treatment effects. However, conditional models allow for estimating marginal treatment effects as well (27).

In randomized trials with continuous outcomes, adjustment for baseline covariates increases the precision of the estimated treatment effect but does not affect its size (25, 26). Also, misspecification of the adjustment model for continuous covariates will not bias the estimated treatment effect, because treatment and covariate are not related (due to the randomization) (28). Similarly, when missing outcome data are MAR, a complete case analysis with covariate adjustment yields unbiased estimates when conditioning on the predictors of missingness (e.g., baseline covariates), even when the adjustment model is misspecified.

We did not consider missing values for baseline covariates. Obviously, even without missing outcomes, subjects with missing covariate values can't be included in a complete case analysis with covariate adjustment. In observational data, this will typically result in biased estimates. In randomized trials, however, missingness of covariates is typically independent of treatment (the result of randomization), and complete case analysis both with and without covariate adjustment will yield unbiased estimates. When both baseline covariates and outcomes have missing values that are MAR, conditioning on baseline covariates to account for the missing outcomes becomes problematic, and multiple imputations can be a valid alternative.

In this study, we focused on missing data of outcomes that were measured only once. In studies with repeated (i.e., multiple) measurements of the outcome, the last observation can be used to impute the missing observation, called "last observation carried forward" (29, 30). However, this last observation carried forward does not take possible reasons for missingness into account and, in general, the method results in biased estimates (7, 30). Mixed models are a valid alternative, in which possible reasons for missingness (i.e., baseline covariates, as well as postrandomization measurements of the outcome) can be included.

We considered only situations without noncompliance with allocated treatment and, therefore, did not distinguish between intention-to-treat and per-protocol analyses. However, in the event of noncompliance, intention-to-treat and per-protocol analyses can yield different results. The aim of intention-to-treat analysis is to compare 2 randomized groups. Therefore, in intention-to-treat analysis, all subjects that are randomized should be included in the analysis and analyzed as randomized (i.e., according to treatment assignment). When patients are lost to follow-up and their outcome status can't be obtained through external sources, their outcome status is missing, and we can include these subjects in the analysis (and thus conduct an intention-to-treat analysis) only if we assume that those who were lost to follow-up are either nonresponders or have experienced the outcome of interest (7, 29, 31). Such an

assumption is essentially a type of imputation, which typically results in biased estimates of the intention-to-treat treatment effect. In per-protocol analyses, however, patients that do not adhere to the protocol are not included in the analyses at all. In both cases, however, if loss to follow-up is related to observed patient characteristics, missing outcome data are MAR, and we can therefore handle such data using the methods discussed in this paper.

In conclusion, complete case analysis with covariate adjustment and multiple imputation yield similar estimates in the event of missing outcome data that are MAR, as long as predictors of missingness are included. This holds for randomized trials as well as observational studies. Hence, complete case analysis with covariate adjustment can and should be used as the analysis of choice more often. Multiple imputation, in addition, can accommodate MNAR scenarios more flexibly, making it especially suited for sensitivity analyses.

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