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Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis

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Abstract

Background and Objectives: As a result of the development of sophisticated techniques, such as multiple imputation, the interest in handling missing data in longitudinal studies has increased enormously in past years. Within the field of longitudinal data analysis, there is a current debate on whether it is necessary to use multiple imputations before performing a mixed-model analysis to analyze the longitudinal data. In the current study this necessity is evaluated.

Study Design and Setting: The results of mixed-model analyses with and without multiple imputation were compared with each other. Four data sets with missing values were created—one data set with missing completely at random, two data sets with missing at random, and one data set with missing not at random). In all data sets, the relationship between a continuous outcome variable and two different covariates were analyzed: a time-independent dichotomous covariate and a time-dependent continuous covariate.

Results: Although for all types of missing data, the results of the mixed-model analysis with or without multiple imputations were slightly different, they were not in favor of one of the two approaches. In addition, repeating the multiple imputations 100 times showed that the results of the mixed-model analysis with multiple imputation were quite unstable.

Conclusion: It is not necessary to handle missing data using multiple imputations before performing a mixed-model analysis on longitudinal data.

Keywords: Longitudinal studies; Missing data mechanisms; Missing data patterns; Multiple imputation; Mixed models; Statistical methods

1. Introduction

In the field of epidemiology, there is a growing interest in dealing with missing data. The introduction of sophisticated treatment methods to handle missing data, such as multiple imputation [1−3], has contributed substantially to this growing interest. Among the different epidemiological study designs, prospective (longitudinal) studies are probably most hampered by missing data. Also for these type of studies, multiple imputation can be used to replace missing data before analysis. However, it has been argued that longitudinal data-analyzing techniques, such as mixed models, can be used regardless of the presence of missing data [3].

Within a longitudinal framework, different patterns of missing data can be distinguished: intermittent missing data (also known as nonmonotone missing data) and missing data resulting from dropout (also known as monotone missing data) [4,5]. When data for a particular subject in a study is intermittently missing, data are missing at time point t, but are available again at time points after t. When data are missing because of the dropout of a subject at time point t, data are available before time point t but are missing for all time points after t.

In addition to this distinction related to the missing data pattern, there is classic categorization of missing data mechanisms that describes relationships among missing values and their dependency on observed and unobserved variables in the data set [4,6]. More specifically, missing data are known to be completely at random (MCAR) when their absence is not related to both observed and unobserved data. Alternatively, missing data are known to be at random (MAR) when their absence depends on observed data but not on unobserved data. Last, missing data are known to be not at random (MNAR) when their absence depends on unobserved data.

There is a huge amount of literature available on how to deal with missing data in longitudinal studies [7−12]. From this literature, it is suggested that both multiple imputations and mixed-model analysis are valid when missing data are

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What is new?

Key findings

- Multiple imputation of missing values is not necessary in longitudinal data analysis, regardless of the missing data mechanism.
- When the number of imputations is low, the multiple imputation method can be very unstable.

What this adds to what was known?

- The findings of the current study (hopefully) ends the discussion of whether multiple imputation should be used in combination with a longitudinal data-analyzing technique, such as mixed-model analysis.
- Even in relatively simple data sets with missing values, using five imputations led to very unstable results.

What is the implication and what should change now?

- Multiple imputation of missing values should not be used before a longitudinal data-analyzing technique such as mixed-model analysis is performed.

MCAR or MAR. However, there is a current debate regarding whether it is necessary to perform multiple imputations in combination with mixed-model analysis. One of the problems in this debate is that, because most of the literature is highly theoretical, there is a gap between mathematical theory and practical implications. In this article, we attempt to bridge this gap by evaluating the necessity to impute missing data using multiple imputations before performing a longitudinal mixed-model analysis. We do this by comparing a mixed-model analysis with and without the use of multiple imputations. The comparison was performed by analyzing a real-life data set in which missing data are created according to the three types of missing data presented earlier, with a naturalistic missing data pattern including both intermittent missing data and dropouts.

2. Methods

2.1. Data sets

The data sets with missing data are based on a complete real-life data set in which a continuous outcome variable Y was measured six times in 147 subjects. Furthermore, the data set consists of a dichotomous time-independent covariate X_{dich} and a continuous time-dependent covariate X_{cont}. From the complete data set, four missing data sets were created. In all data sets, the first measurement is complete for all subjects. The second measurement was eliminated for 15 subjects (approximately 10%). The third to sixth measurements were eliminated for 25 (17%), 35 (24%), 45 (30%), and 55 (37%) subjects respectively. In the MCAR data set, all missing data were selected randomly from the complete data set. Regarding MAR, two data sets were created—one in which absence was related to the dichotomous time-independent covariate X_{dich} and one in which absence was related to the outcome variable Y measured at $t-1$. In the first MAR data set (MAR_1), absence at different time points was selected randomly from the subpopulation for which the time-independent covariate X_{dich} was coded as one, whereas in the second MAR data set (MAR_2), all observations were eliminated for subjects with the highest values for the outcome variable Y at $t-1$. In the MNAR data set, all observations were eliminated for subjects with the highest values for the outcome variable Y at that particular time point. When the outcome variable is eliminated, the time-dependent covariate X_{cont} is also eliminated. This is comparable with a real-life study, because when a certain subject does not attend a particular visit in a longitudinal study, all data to be collected at that measurement are generally missing. Furthermore, the missing data sets contain both intermittent missing data and dropouts. Table 1 shows descriptive information regarding the outcome variable Y in the different data sets.

2.2. Multiple imputation

From literature about missing data, it is clear that when missing data are imputed, the multiple-imputation method is preferable over single-imputation methods, such as last observation carried forward [1−3,13−15]. Using the multiple-imputation method, various (say, M) imputation values are calculated for every missing value. With the M imputations, M complete data sets are generated, and for each data set created in this way, statistical analyses are performed. The M complete data set summary statistics (in this case, the regression coefficients of the mixed-model analysis) must be combined (i.e., pooled) to obtain one summary statistic. The point estimate of the summary statistic is calculated as the average of the M imputations, whereas the variance of the summary statistic is calculated from two components. One component reflects the within-imputation variance (the average of the variances of the summary statistics of the M imputations) and the other component reflects the between-imputation variance (the difference between the summary statistic of each imputation and the average of the summary statistics of the M imputations).

The major advantage of the multiple-imputation method is that the combined variance is larger than the variance obtained from the single-imputation method. This larger variance reflects adequately the uncertainty that results from estimating missing values.

In the current study, for multiple imputation, data augmentation (DA) was used. DA is an iterative Markov Chain

Table 1. Mean value of the outcome variable Y for the different data sets at the different time points

Time point	N^a	Complete mean (SD)	MCAR mean (SD)	MAR_1 mean (SD)	MAR_2 mean (SD)	MNAR mean (SD)
Y_{t1}	147	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)
Y_{t2}	132	4.3 (0.7)	4.3 (0.7)	4.3 (0.7)	4.2 (0.6)	4.2 (0.5)
Y_{t3}	122	4.3 (0.7)	4.3 (0.7)	4.3 (0.7)	4.1 (0.6)	4.0 (0.5)
Y_{t4}	112	4.2 (0.7)	4.2 (0.7)	4.1 (0.6)	3.9 (0.5)	3.9 (0.5)
Y_{t5}	102	4.7 (0.8)	4.7 (0.8)	4.6 (0.8)	4.3 (0.6)	4.3 (0.5)
Y_{t6}	92	5.1 (0.9)	5.2 (0.9)	5.1 (0.9)	4.7 (0.8)	4.5 (0.5)
N complete		147	43	73	81	75

Abbreviations: SD, standard deviation; MCAR, missing data completely at random; MAR, missing data at random; MNAR, missing data not at random; MAR_1 and MAR_2, first and second MAR data set (see text for explanation).

[a] Number of observations in the data sets with missing data.

Monte Carlo method to generate the imputed values assuming a multivariate normal distribution. DA is recognized as a state-of-the-art method for imputing arbitrary missing data patterns (i.e., for longitudinal data with both intermittent missing data and dropouts) [5,16–18].

Herein, for all multiple imputation models, the observed values of the outcome variable Y at the different time points as well as the covariates used in the mixed-model analyses were used to predict the missing values.

Because there is a discussion in the literature regarding the number of imputations needed to obtain stable results, for all multiple imputations performed in the current study, both five and 50 imputations were evaluated.

2.3. Mixed-model analysis

Mixed-model analysis, which is also known as multilevel analysis or as random effects model analysis, is highly suitable to analyze longitudinal data because an adjustment is made for the correlation between repeated observations within the subject. This is done by modeling the variability among the subjects [19]. The simplest form of a mixed-model analysis in longitudinal studies is a model in which the average value over time is assumed to be different for each subject (i.e., a random intercept). In addition to a random intercept, it is also possible that the relationship between a certain time-dependent covariate and the outcome variable is different for different subjects (i.e., a random slope). With mixed-model analysis, both fixed (i.e., the regression coefficients) and random (i.e., the variance around regression coefficients) effects are estimated simultaneously.

2.4. Analyses

For each data set, two separate analyses were performed, mimicking two different real-life situations that can be encountered when analyzing epidemiological data. The purpose of the first analysis was to analyze the relationship between the outcome variable Y and the time-independent covariate X_{dich}, which occurs, for instance, in the analysis of (randomized) controlled trials in which a particular intervention is compared with a control condition. The purpose of the second analysis was to analyze the relationship between the outcome variable Y and the time-dependent covariate X_{cont}. All multiple imputations and mixed-model analyses were performed in STATA (version 11.1; StataCorp, College Station, TX, USA) with the procedures *mi* and *xtmixed,* respectively.

3. Results

Table 2 shows the results of the analyses regarding the relationship between the outcome variable Y and a time-independent covariate X_{dich}. Table 3 shows the results of the analyses regarding the relationship between the outcome variable Y and the time-dependent covariate X_{cont}.

For the MCAR data sets, mixed-model analyses with and without multiple imputations only gave slightly different results. For both research questions, the regression coefficients obtained from multiply imputed data sets were a bit closer to the regression coefficient obtained from the complete data set compared with the data set without imputations. The standard errors obtained from the analyses with

Table 2. The relationship between the outcome variable Y and the time-independent covariate X_{dich} with and without multiple imputation with different missing data mechanisms

	Regression coefficient	Standard error
Without missing data	0.262	0.104
MCAR		
Without imputing	0.234	0.107
Multiple imputation (M = 5)	0.261	0.104
Multiple imputation (M = 50)	0.256	0.107
MAR_1		
Without imputing	0.242	0.106
Multiple imputation (M = 5)	0.248	0.103
Multiple imputation (M = 50)	0.249	0.108
MAR_2		
Without imputing	0.172	0.091
Multiple imputation (M = 5)	0.150	0.098
Multiple imputation (M = 50)	0.172	0.099
MNAR		
Without imputing	0.194	0.082
Multiple imputation (M = 5)	0.133	0.074
Multiple imputation (M = 50)	0.143	0.074

Abbreviations: MCAR, missing data completely at random; M, number of imputations; MAR, missing data at random; MNAR, missing data not at random.

Table 3. The relationship between the outcome variable Y and the time-dependent covariate X_{cont} with and without multiple imputation with different missing data mechanisms

	Regression coefficient	Standard error
Without missing data	0.186	0.018
MCAR		
Without imputing	0.175	0.020
Multiple imputation (M = 5)	0.177	0.022
Multiple imputation (M = 50)	0.183	0.024
MAR_1		
Without imputing	0.201	0.021
Multiple imputation (M = 5)	0.223	0.034
Multiple imputation (M = 50)	0.213	0.029
MAR_2		
Without imputing	0.158	0.020
Multiple imputation (M = 5)	0.155	0.032
Multiple imputation (M = 50)	0.168	0.027
MNAR		
Without imputing	0.116	0.018
Multiple imputation (M = 5)	0.104	0.025
Multiple imputation (M = 50)	0.113	0.021

Abbreviations: MCAR, missing data completely at random; M, number of imputations; MAR, missing data at random; MNAR, missing data not at random.

and without multiple imputations were, as expected, slightly higher compared with the analyses of the complete data sets.

For the MAR data sets, regarding the regression coefficients, the analyses led to comparable results for the mixed-model analyses with and without imputation. However, they were different from the regression coefficients obtained from the complete data set. Regarding the uncertainty of the estimates, in the analysis with the time-independent covariate X_{dich}, the standard errors were more or less the same for all analyses. However, in the analyses with the time-dependent covariate X_{cont}, the standard errors of the analyses with or without multiple imputation were quite different.

For the MNAR data sets, the regression coefficients were completely different from the analyses of the complete data set without missing data. The comparison of standard errors does not show a straightforward picture. For example, in the analyses with a time-independent covariate $X_{dich.}$, the standard errors of all three analyses were less than the standard errors obtained from the analysis of the complete data set, whereas when analyzing the data with a time-dependent covariate X_{cont}, the standard errors of the multiply imputed data sets were slightly greater.

3.1. Additional analyses

Based on the inconsistent patterns in the magnitude of (especially) the standard errors between some of the analyses with five and 50 imputations, we further investigated the (in)stability of the mixed-model analyses with multiple imputations. As an example, we reanalyzed the relationship between the outcome variable Y and the time-dependent covariate X_{cont}. In these additional analyses, all multiple imputations were repeated 100 times. Fig. 1 summarizes the (in)stability of the different multiple imputations for both the regression coefficients and the standard errors. Fig. 2 shows the distribution of the standard errors of the 100 analyses performed on the second MAR data set. It is clear that using five imputations led to very unstable results in all data sets, but especially for the second MAR data set. For the latter, even the use of 50 imputations is somewhat unstable.

4. Discussion

The purpose of this study was to assess whether it is necessary to perform multiple imputations before performing a mixed-model analysis. This was done by comparing the results of imputed and nonimputed data sets on the point estimates, the standard errors, and the (in)stability of the estimates.

Our data show that the results obtained from the imputed and nonimputed data sets are different. More specifically, the standard errors of the regression coefficients are different and, in general, somewhat greater than when they are

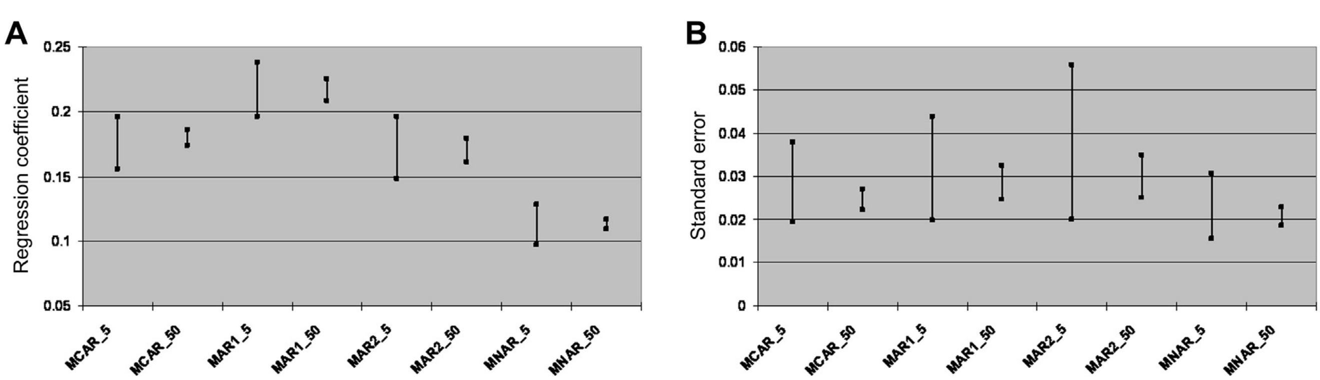

Fig. 1. (A, B) Range in regression coefficients (A) and range in standard errors (B) obtained from 100 mixed-model analyses after multiple imputations for different types of missing data with either five or 50 imputations regarding the relationship between the outcome variable Y and the time-dependent covariate X_{cont}. MCAR, missing data completely at random; MAR, missing data at random; MNAR, missing data not at random.

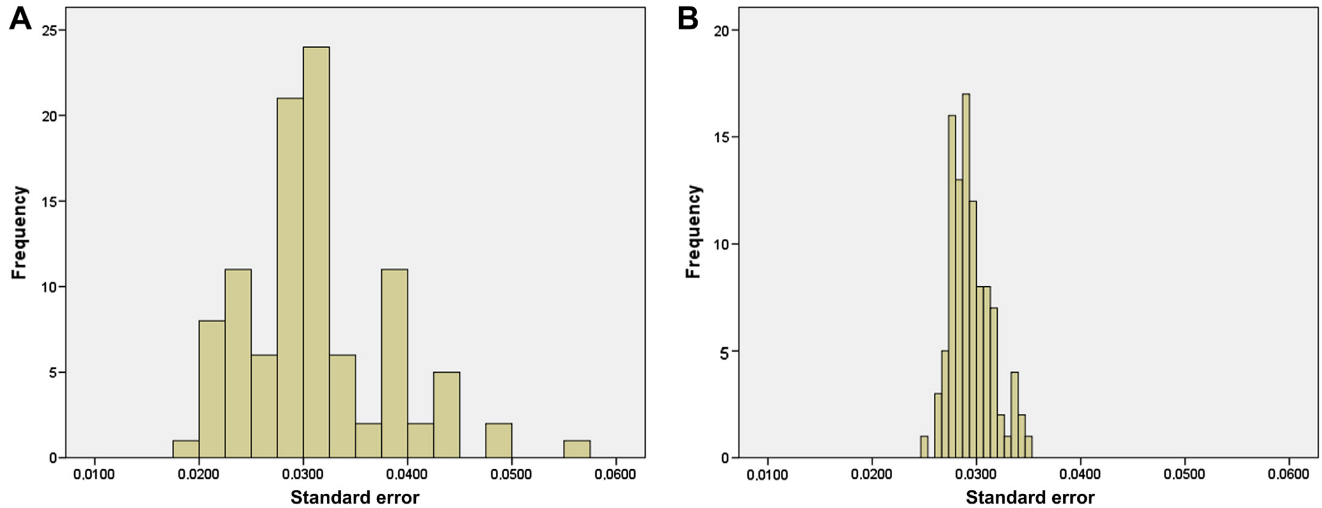

Fig. 2. (A, B) Distribution of the standard errors obtained from 100 mixed-model analyses after multiple imputations regarding the relationship between the outcome variable Y and the time-dependent covariate X_{cont}, performed on the missing data at random data set with either five (A) or 50 (B) imputations.

obtained from mixed-model analyses with multiple imputations than when they are obtained from mixed-model analyses without multiple imputations. This was especially the case in the analysis with a time-dependent covariate X_{cont}. Regarding the regression coefficients, the results are not straightforward in favor of one of the approaches, although for the MCAR data set the multiple-imputation approach seems to be somewhat better. For the MAR and MNAR data sets, however, this was not the case.

For both mixed models and multiple imputation, the assumption is that they are only valid when the incomplete data set is MAR or MCAR. In accordance with the literature [3,20,21], our results show that mixed-model analysis with or without multiple imputation does not lead to valid results when performed on an MNAR data set. Both approaches behave equally unsatisfactorily when the results are compared with the results of the analysis on the complete data set without missing data. This is as expected because both the multiple imputations and the mixed-model analyses use the observed data for the calculations. A big problem, however, is that, in real-life data, it is not possible to evaluate whether incomplete data is MAR or MNAR [3,22,23], which means that it will never be clear whether the results obtained from the mixed-model analysis (either with or without multiple imputations) provides valid results. Furthermore, in real-life data sets, missing data are never completely MCAR, MAR, or MNAR. Some missing observations will be completely random whereas other missing observations will depend on either observed data or unobserved data.

In the analysis regarding the relationship between the outcome variable Y and the time-dependent covariate X_{cont}, the standard errors of the mixed-model analysis with multiple imputations were greater than the standard errors obtained from the mixed-model analysis without multiple imputations. The question we are facing is whether the standard error resulting from the mixed-model analysis without multiple imputation is an underestimation or whether the standard error obtained from the mixed-model analysis with multiple imputation is an overestimation. In the literature, most evidence is given for the fact that the two approaches lead to similar results when the data are either MCAR or MAR, which is, however, not the case in the current study. There are authors who suggest that a mixed-model analysis without multiple imputations led to an underestimation of the standard error [3,24], whereas Enders [22] states, on the other hand, that the imputation phase can use an unnecessarily complex model to deal with the missing data and that this additional complexity can add a small amount of noise to the resulting estimations. Furthermore, Robins and Wang [25] suggest that Rubin's combination rule led to an overestimation of the standard error. In their theoretical article, they suggest an alternative way to obtain the pooled standard error. However, that alternative has, as far as we know, never been used in applied studies.

Because the comparison of regression coefficients and standard errors does not give a straight answer for which of the two approaches is most appropriate, other arguments must probably guide how to decide which solution is the best. A mixed-model analysis without multiple imputations is definitely less complicated because only one data set has to be analyzed, whereas, when performing multiple imputations, multiple data sets have to be analyzed. So it is computationally more efficient to perform a mixed-model analysis without multiple imputations than a mixed-model analysis with multiple imputations. In addition, our data show that the results obtained with multiple imputations can be quite unstable. So, based on these arguments, it can be concluded that it is not necessary to perform multiple imputations before performing a mixed-model analysis. In addition to the fact that this conclusion was expected theoretically [6], it was also found by Peters et al. [26]. They used a slightly different approach to evaluate the necessity of using multiple imputation before a longitudinal mixed-model analysis, but they came to the same conclusion.

The (un)stability of the multiple-imputation method is in contrast with most basic multiple-imputation literature [3,4], which suggests that five imputations should be sufficient to obtain valid inference. However, Graham [27] recognized that some analyses may require many more imputations to obtain valid results. Literature with formal recommendations on how to choose the optimal number of imputations is scarce. Royston et al. [28,29] discuss the impact of the number of imputations on the precision of the estimates and suggest ways of determining the required number of imputations by evaluating the sampling error of the multiple-imputation estimates. In our study, the distribution of the standard errors of the estimate of interest was evaluated over 100 multiple imputations, in which a distinction was made between five imputations and 50 imputations. Especially for the longitudinal analysis with a time-dependent covariate X_{cont}, five imputations do not appear to be sufficient to obtain stable estimates.

Although in the current study performing multiple imputations before doing a mixed-model analysis did not lead to more valid results, there are possible situations in which multiple imputations potentially hold an advantage [22]. When auxiliary variables (i.e., variables that are related to the missing data mechanism but are not used in the model to answer the research question) are measured, they can be included in predicting the missing data without being included in the mixed-model analysis, which probably increases efficiency. Also, in a situation when only covariates are missing, performing multiple imputations before a mixed-model analysis seems to be better. However, the latter hardly exists in longitudinal studies because, in longitudinal studies, mostly all data to be collected at a particular visit are missing for that particular subject.

4.1. Dichotomous outcome variables

In the current study, the analyses were performed on a continuous outcome variable. The reason for this is that the method used for multiple imputations in our work assumes a multivariate normal distribution. For dichotomous outcome variables, sophisticated multiple-imputation methods are only available for monotone missing data patterns (i.e., longitudinal data without intermittent missing data) [5]. Several authors, however, suggest that for dichotomous outcome variables as well, the same procedures can be used as for continuous normally distributed variables [30,31]. Royston [32], on the other hand, suggests using multiple imputation by chained equations to impute categorical data. One major problem with the imputation of dichotomous outcome variables is the rounding of the imputed values, which further complicates the multiple-imputation method [33]. In general, it is not expected that the conclusions based on logistic mixed-model analyses with and without multiple imputation would be different from the ones based on the linear mixed-model analyses presented herein. Therefore, in addition to the earlier mentioned complexity of the multiple-imputation approach, performing multiple imputations before performing a logistic mixed-model analysis is probably also not preferable over performing a logistic mixed-model analysis without imputing the missing data.

4.2. Alternative approaches

Although in the literature most researchers use a mixed-model approach with or without multiple imputations, there are some alternative methods available to deal with missing data in longitudinal studies, such as selection models and pattern-mixture models [34–37]. Both are used frequently in econometrics and are supposed to deal with MNAR data sets. The general idea of a selection model is that the analysis is split into two parts (i.e., a two-part model). The first part is the regression equation of interest and the second part is a regression equation that predicts the response probabilities. The basis of a pattern-mixture model is more or less the same. Using this approach, first, subgroups of subjects with the same missing data pattern are created. During the next step, the model coefficients are estimated within the different subgroups. During the last step, the subgroup-specific coefficients are combined to get one regression coefficient that accounts for data being MNAR. Although both methods have some potential in dealing adequately with missing values, they also have some disadvantages (i.e., computational complexity and their reliance on knowledge about the missing data mechanism) and are therefore not much used in real-life epidemiological studies.

4.3. Limitations

Surprisingly, in the current study, even in the MCAR data sets, the results of the mixed-model analyses were different from the results obtained from the data set without missing data. This probably has to do with the fact that we only created one MCAR data set, which makes it possible that the created MCAR data set was not completely MCAR [38]. However, the most important issue in this article is the discussion regarding the need for multiple imputations in combination with a mixed-model analysis and, therefore, this potential bias is not really a big issue.

The current study shows that multiple imputations are not necessary before performing a longitudinal mixed-model analysis. However, it should be stressed that this does not imply that multiple imputations have no additional benefit over any type of standard analyses. In many situations, multiple imputations can be highly beneficial [1−4,6].

5. Conclusion

Based on the results of our comparisons, and taking into account the computational complexity and the relative instability of the multiple imputations, it can be concluded that there is no obvious gain from handling missing data using multiple imputations before performing a mixed-model analysis on longitudinal data. Beyond the question of whether to use multiple imputations before performing a mixed-model analysis, however, we stress the importance of describing as completely as possible the missing data mechanisms in the study data set, and interpreting the results of the statistical analyses accordingly.

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