Pitfalls of adjusting for mean baseline utilities/costs in trial-based cost-effectiveness analysis with missing data

Andrea Gabrio\textsuperscript{1}, Rachael Hunter\textsuperscript{2}, Alexina J. Mason\textsuperscript{3}, and Gianluca Baio\textsuperscript{1}

\textsuperscript{1}Department of Statistical Science, University College London, UK
\textsuperscript{2}Research Department of Primary Care and Population Health, University College London Medical School, UK
\textsuperscript{3}Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, UK

Abstract

Failure to account for baseline utilities/costs imbalance between treatment groups in cost-effectiveness analyses can result in biased estimates and mislead the decision making process. The currently recommended adjustment approach is linear regression, with estimates that are typically evaluated at the mean of the baseline utilities/costs. However, a problem arises whenever there are some missing follow-up values and the evaluation is restricted to the complete cases. Should the mean of the complete cases or the available cases baseline utilities/costs be used in generating the adjusted estimates? To our knowledge there is no current guideline about this choice in the literature, with standard software implementations often implicitly selecting one of the methods. We use two trials as motivating examples to show that the two approaches can lead to substantially different conclusions for healthcare decision making and that standard approaches which automatically resort to complete case analysis are potentially dangerous and biased. Analysts should therefore consider methods that can explicitly incorporate missing data assumptions and assess the robustness of the results to a range of plausible alternatives.

Key words: Trial-based cost-effectiveness analysis, baseline regression adjustment, Bayesian statistics, missing data

\textsuperscript{*}E-mail: andrea.gabrio.15@ucl.ac.uk
1 Introduction

Routine Cost-Effectiveness Analyses (CEAs) conducted alongside Randomised Clinical Trials (RCTs) are often performed under a frequentist approach to statistical inference and using linear regression methods to derive estimates that account for the imbalance in some baseline variables between treatment groups. Baseline utilities and costs are likely to be highly correlated with the outcomes and therefore failure to adjust for these variables can result in biased estimates (Manca et al., 2005; Van Asselt et al., 2009; Hunter et al., 2015). The adjusted Quality Adjusted Life Years (QALYs) and cost estimates for the “average” individual in each group are typically obtained by setting the baseline utilities/costs to their sample mean values, using bootstrap methods to characterise the sampling distribution of the quantities of interest through a large number of simulations (Briggs et al., 1997; Willan and Briggs, 2006; Ng et al., 2013).

It is likely that some individuals fail to follow-up and their outcome values are missing. To deal with this situation, a standard and popular approach in routine analyses is to restrict the evaluation to the complete cases only (Complete Case Analysis, CCA). However, since baseline values are often available for all or most of the individuals, the adjusted outcome estimates can be derived in two different ways: using either the sample baseline means calculated using the complete cases (CC) or all available cases (AC), i.e. including also those that are observed at baseline but that will be missing at some later follow-up. The second approach is more efficient, but uses a different number of cases to fit the regression compared with those used to derive the average mean parameters.

To our knowledge, there is no current guideline about which approach to use and standard software implementations often implicitly select one of the two. This is problematic as analysts may be unaware of how the adjustment is calculated and that alternatives exist. For example, in STATA, adjusting for baseline utilities at means can be performed using the following commands:

```
reg QALY treatment_group baseline_utility
margins treatment_group, atmeans
```

The first line specifies a linear regression with QALY as the response variable and treatment_group and baseline_utility as covariates. The second line uses the margins function to apply the adjustment by treatment group at the mean of the baseline variable in the model. In R, a similar implementation of the regression adjustment can be performed using the commands:

```
reg = lm(QALY ∼ treatment_group + baseline_utility)
predict(reg)
```

The first line computes the linear regression, while the second line uses the function predict to obtain the adjusted QALYs estimates by treatment group, evaluated at the mean of the baseline variable in the model. By default both functions discard all missing values when fitting the regression and make the adjustment by calculating the mean of the baseline variables on the AC. However, analysts may be unaware of the fact that if only the subset of the complete cases is retained for the variables, then the adjustment will be computed using the mean of the CC.

The main objective of this paper is to show that the application of mean regression adjustment is characterised by some ambiguity and can lead to substantially different cost-effectiveness conclusions depending on how mean baseline values are computed. This may be particularly relevant when model complexity is increased to account for framework-specific issues such as imbalance in other baseline variables, multilevel structure in the data and correlation between outcomes. We demonstrate these pitfalls using two RCTs as motivating examples. Inferences are derived using a flexible Bayesian approach that is easy to implement. However, the same results can also be obtained under a frequentist approach using alternative methods.

The article is structured as follows. Section 2 summarises the most popular methodologies used in trial-based economic evaluations to control for bias in mean QALYs/cost estimates. Section 3...
describes the two motivating data sets, while Section 4 presents the different models used in the analyses. Section 5 shows the results obtained under alternative model specifications, focusing on the impact on the cost-effectiveness conclusions of using either the CC or the AC in the baseline utility/cost adjustment. Finally, Section 6 discusses the implications for decision-makers based on the results obtained and provides some recommendations for analysts to implement mean regression adjustment in routine analyses.

2 Methods

This section reviews some of the most popular approaches to controlling for bias in the estimation of mean QALYs/costs. We focus on three issues: imbalance in baseline variables, multilevel structures in the data and correlation between outcome variables.

2.1 Baseline variables

As a simple example, consider a two-arm RCT with \( i = 1, \ldots, n \) individuals for whom utility \( u_{ij} \) and cost \( c_{ij} \) data are collected at baseline \( (j = 0) \) and successive follow-up points \( (j = 1, \ldots, J) \). Individual QALYs \( e_i \) and total costs \( c_i \) are then usually computed as:

\[
\begin{align*}
e_i &= \sum_{j=1}^{J} (u_{ij} + u_{ij-1}) \delta_j / 2 \\
c_i &= \sum_{j=1}^{J} c_{ij}
\end{align*}
\]

For the utilities, Equation 1 is often referred to as the Area Under the Curve (AUC; Drummond et al., 2005), where \( \delta_j \) is used to re-scale the consecutive time measurements for the percentage of a time unit, typically a year, that \( j \) and \( j-1 \) cover.

Now assume that some participants are lost to follow-up with the number of the complete cases being \( n^{(cc)} < n \) and that the economic evaluation is performed only on these individuals. In many applications, assumptions such as normality and independence between the outcomes are made and bootstrap replicates are used to obtain an empirical estimate of the mean sampling distribution. Within this setting, linear regression adjustment for baseline utility \( u_{i0} \) and cost \( c_{i0} \) data is applied to derive mean QALYs/cost estimates:

\[
\begin{align*}
e_i &= \alpha_0 + \alpha_1 t_i + \alpha_2 u_{i0} \left[ \ldots \right] + \epsilon_{ie} \\
c_i &= \beta_0 + \beta_1 t_i + \beta_2 c_{i0} \left[ \ldots \right] + \epsilon_{ic}
\end{align*}
\]

where \( t_i \) is a treatment indicator variable, while \( \epsilon_{ie} \sim \text{Normal}(0, \sigma_e) \) and \( \epsilon_{ic} \sim \text{Normal}(0, \sigma_c) \) are independent error terms associated with the QALYs and costs, respectively. The notation \( \left[ \ldots \right] \) indicates that other terms (e.g. quantifying the effect of relevant baseline covariates) may or may not be included in the model. Common examples are demographic factors (age, gender, ethnicity, etc.) or some other prognostic factors (stage, size or location of the disease, etc.), which may represent valuable information to include in the model to obtain valid inferences (Hoch et al., 2002; Willan et al., 2004; Vazquez Polo et al., 2005; Nixon and Thompson, 2005). For simplicity, here we assume that only the baseline utilities/costs are included in the regression models.

Once the parameter estimates \( \hat{\alpha} = (\hat{\alpha}_0, \hat{\alpha}_1, \hat{\alpha}_2) \) and \( \hat{\beta} = (\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2) \) from Equation 2 are derived, e.g. using maximum likelihood estimates, then the population means are estimated as:
\[
\hat{\mu}_{ct} = \hat{\alpha}_0 + \hat{\alpha}_1 t + \hat{\alpha}_2 u_0 \\
\hat{\mu}_{ct} = \hat{\beta}_0 + \hat{\beta}_1 t + \hat{\beta}_2 c_0
\]  \hspace{1cm} (3)

where \( u_0 \) and \( c_0 \) are the sample means for the baseline utility and cost variables, respectively. When
some follow-up values are missing and a CCA is performed, \( u_0 \) and \( c_0 \) can be computed using either
the CC or the AC for the baseline variables. Systematic differences between the two sets of cases
may therefore lead to substantially different sample mean values in Equation 3 and consequently
affect the estimates for \( \hat{\mu}_{ct} \) and \( \hat{\mu}_{ct} \).

2.2 Multilevel Structure

Multilevel structures arise when observations on individual units cannot be considered independent,
but instead are correlated because they are nested within groups or clusters of various kinds. For
example, assume that QALYs and costs from Equation 2 are collected from \( s = 1, \ldots, S \) different
sites \((e, c)\).

When confronted with a multilevel structure, three possible approaches that make different
assumptions about the degree of similarity in the data can be used (Gelman and Hill, 2007). The
simplest approach is to ignore group information, implicitly assuming that observations are identical
between sites, in the sense that they are treated as coming from the same group (complete pooling).
This is generally undesirable, because it ignores any variation in outcome levels between sites. A
second approach includes group indicators for each site in the model or fits separate models for each
group, therefore assuming that observations are independent between sites (no pooling). This can
lead to problems as the model tends to overestimate variation between sites.

The final approach is multilevel analysis (or partial pooling), which can be expressed by including structured or random effects. Multilevel models can have different structures based on whether the random effects are applied to the intercept (varying-intercept only), the slope (varying-slope only) or both terms (varying-intercept/slope). In our analysis, we consider a varying-slope only model and extend the regressions in Equation 2 to a multilevel structure by allowing for site-specific baseline coefficients and leave the intercept terms constant.

\[
e_{is} = \alpha_0 + \alpha_1 t_i + \alpha_2 u_{i0} [+ \ldots] + \varepsilon_{ie} \\
c_{is} = \beta_0 + \beta_1 t_i + \beta_2 c_{i0} [+ \ldots] + \varepsilon_{ic}
\]  \hspace{1cm} (4)

We choose this structure as inferences from this model were almost identical to those of a varying-intercept/slope model, i.e. given similar results we keep the simpler model. The parameters \( \alpha_{2s} \) and \( \beta_{2s} \) are the baseline utility and cost structured coefficients associated with the \( S \) different sites, typically assumed to be normally distributed with zero means and variances estimated from the data, i.e. \( \alpha_{2s} \sim \text{Normal}(0, \sigma_{\alpha}^2) \) and \( \beta_{2s} \sim \text{Normal}(0, \sigma_{\beta}^2) \).

In this way, the precision of the site-specific estimates \((\alpha_{2s}, \beta_{2s})\) is improved since information is “borrowed” from other sites. The multilevel model in Equation 4 assumes observations to be similar between sites and can be seen as a compromise between the extreme positions of the complete and no pooling approaches. Multilevel analyses are typically performed in clustered CEA studies but their application to costs and effectiveness considered as a joint bivariate outcome has only recently been explored (Grieve et al., 2010; Gomes et al., 2012b; Ng et al., 2016).

2.3 Correlation

Another potential issue concerns assumptions about the correlation between outcome data. Regression methods that assume independence between QALYs and costs may lead to inefficient estimates when the correlation is substantial. In this case, a joint bivariate normal distribution (BN) could
be specified. For example, the models in Equation 4 can be extended to allow for correlation by assuming:

\[
\begin{pmatrix}
\varepsilon_{ei} \\ \\ \\
\varepsilon_{ci}
\end{pmatrix} \sim BN \left[ 
\begin{pmatrix}
0 \\ 0
\end{pmatrix}, 
\begin{pmatrix}
\sigma_e^2 & \rho \sigma_e \sigma_c \\
\rho \sigma_c \sigma_e & \sigma_c^2
\end{pmatrix}
\right]
\] (5)

where \(\rho\) is a parameter capturing the correlation between the variables. Other approaches that recognise the correlation between outcomes in the parameter estimation can be used, e.g. Seemingly Unrelated Regressions or Two-stage bootstrap [Gomes et al., 2012a,b,c]. Sometimes it is more convenient to represent Equation 5 using conditional probabilities and factor the joint distribution \(p(e, c)\) into the product of a marginal and conditional distribution, e.g. \(p(e)p(c|e)\) [Nixon and Thompson 2005; Baio 2012]. In this case, we can re-express the joint model by keeping the regression framework in Equation 4 and include the term \(\beta_3(e_{i8})\) in the cost model, where the coefficient \(\beta_3 = \frac{\sigma_e}{\sigma_c} \rho\) quantifies the association between costs and benefits.

3 Data

Data from two RCTs are used to illustrate the decision-making consequences of using either the CC or AC in mean baseline regression adjustment: the Men’s Safer Sex (MenSS; Bailey et al., 2016) and the Positive Behaviour Support (PBS; Hassiotis et al., 2018) trials.

3.1 The MenSS trial

The MenSS trial is a pilot RCT of a new digital intervention (the MenSS website) to increase condom use and reduce the incidence of Sexually Transmitted Infections (STI) in young men. One of the objectives is the evaluation of the cost-effectiveness of the MenSS website compared to the control.

Individuals \((n = 159)\) enrolled in the study are men aged 16 or over who report female sexual partners and recent unprotected sex or suspected acute STI. Participants were randomised to receive the MenSS website plus usual clinic care (reference intervention, \(n_1 = 84\)), or usual clinic care only (comparator, \(n_2 = 75\)). Sexual health related resource use was collected via participant responses to questionnaires at 3, 6 and 12 months. Utility scores to calculate QALYs were collected at baseline and at the same time intervals as costs using the EQ-5D 3L instrument.

The proportions of the participants completing utility and cost questionnaires at every time point are 23\% \((n_{cc}^{23} = 19)\) and 36\% \((n_{cc}^{36} = 27)\) for the intervention and control group, respectively. Baseline utility data are available for 85\% \((n_{ac}^{85} = 72)\) of the individuals in the intervention group and 96\% \((n_{ac}^{96} = 72)\) of the individuals in the control group. No baseline cost data are collected.

3.2 The PBS trial

The Positive Behaviour Support trial is a multi-centre RCT involving community intellectual disability services and service users with mild to severe intellectual disability and challenging behaviour. The PBS is a multicomponent intervention, which is designed to foster prosocial actions and enhance the person’s quality of life and his/her integration within the local community. Participants \((n = 244)\) were enrolled from a total of \(S = 23\) sites and randomly allocated on a site basis to staff teams trained to deliver PBS in addition to treatment as usual (reference intervention, \(n_1 = 108\)), or to staff teams trained to deliver treatment as usual alone (comparator, \(n_1 = 136\)). Measures for quality of life (EQ-5D-3L) and health related cost (family and paid carer records) were collected at baseline, 6 and 12 months. An objective of the study is to evaluate the cost-effectiveness of staff training in PBS.
The proportions of the participants completing utility and cost questionnaires at every time point are 88% \((n_{cc2} = 96)\) and 79% \((n_{cc1} = 108)\) for the intervention and control group, respectively. Baseline utility data are available for 95% \((n_{ac2} = 103)\) of the individuals in the intervention arm and for 93% \((n_{ac1} = 127)\) of the individuals in the control arm. Baseline cost data are available for all the individuals. Additionally, three fully-observed baseline categorical covariates are available:

**Living conditions.** The different social environment associated with each individual. Categories are defined based on the different individuals the patients live with: 1) living with others, 2) living alone, and 3) living with parents.

**Level of disability.** The severity of the disability associated with each individual. Categories are defined on three levels: 1) mild, 2) moderate, and 3) severe.

**Type of carer.** The different types of carers to whom individuals were assigned. Categories are defined on two levels: 1) family carer, and 2) paid carer.

### 4 Implementation

#### 4.1 Parameter estimation

The sets of parameters indexing the QALYs and cost models in the most comprehensive scenario which accounts for all complexities described in Section 2 are respectively:

\[
\theta_e = (\alpha_0, \alpha_1, \alpha_{2s}, \sigma_\alpha^2, \sigma_e^2)
\]

\[
\theta_c = (\beta_0, \beta_1, \beta_{2s}, \beta_3, \sigma_\beta^2, \sigma_c^2).
\] (6)

To estimate these parameters we choose a Bayesian approach to exploit its flexibility in extending the model structure in a relatively easy way to account for the increasing complexity associated with tackling the multiple challenges affecting the data. In addition, the Bayesian approach naturally allows the implementation of probabilistic sensitivity analysis, which has become the state of the art method for assessing the impact that parameter uncertainty has on the output of the decision-making process in health economic evaluation ([Claxton et al., 2005; Baio and Dawid, 2015]).

Under a Bayesian framework, prior probability distributions for all parameters in Equation 6 (random quantities) are required. In some cases, we may want to reflect not having strong “a priori” beliefs about the values the parameters may assume, and base the inferences on the observed data alone. This has been shown to numerically correspond to inferences obtained under a frequentist setting ([Briggs, 1999]). Using this approach, for all models we choose Normal priors centred at 0 with a standard deviation of 1000 for all the regression coefficients \(\alpha\) and \(\beta\). Uniform distributions between \((-5, 10)\) are assigned to standard deviation parameters on the log scale. Prior sensitivity to alternative specifications for all parameters suggested that these choices were adequate in this setting.

#### 4.2 Models

Table 1 summarises the different types of models implemented for the economic analysis of the MenSS and PBS studies in this work (Bayesian approach), comparing their structures with those from the models used in the original analyses (frequentist approach).

| TABLE 1 |
|------------------|
| In both studies the original economic evaluation was conducted under a CCA setting using standard linear regressions. The analyses (implicitly) ignored the potential correlation between the outcomes |
by independently modelling the two variables. Baseline utility/cost adjustments were used to obtain QALYs/cost estimates, calculating the mean baseline values from the AC. For the PBS trial, the multilevel structure in the data was incorporated assuming a varying-intercept only model.

For the MenSS trial, we compare the model of Bailey et al. (2016) with an analysis based on both the CC and AC for the baseline utility adjustment, assessing the results under independent and joint models. For the PBS study, we compare the model of Hassiotis et al. (2018) with a set of models of increasing complexity. First, the CC and AC version for the regression adjustment are considered. The model is then extended to incorporate three additional baseline covariates in the regression (Section 3.2). Finally, the multilevel structure is accounted for by a varying-slope only model. For each of these models we compare the impact on the inferences of independence/joint assumptions about the QALYs and cost distributions and the use of the CC or AC in the calculation of the mean baseline utilities/costs.

4.3 Software

All models are fitted using JAGS, (Plummer, 2010), a program dedicated for the analysis of Bayesian models using Markov Chain Monte Carlo (MCMC) simulation. Specifically, we interface JAGS with the freely available statistical software R, using the package R2jags (Su and Yajima, 2015). Samples from the posterior distribution of the parameters of interest are then saved to the R workspace and used for producing relevant statistics and plots. We ran two chains with 30,000 iterations per chain, using a burn-in of 15,000, for a total sample of 30,000 iterations for posterior inference.

For each variable in the model, convergence of the MCMC sampler was assessed using diagnostic measures, such as the potential scale reduction factor (Gelman et al., 2004) as well as measures to assess the adequacy of the posterior sample, such as the number of independent draws (Gelman et al., 2004). The code for the model used on the MenSS data can be found in Appendix A. The code for all the other models is available from the corresponding author upon request.

5 Results

5.1 Descriptive Analysis

Figure 1 shows the histograms of the distributions of the QALYs and cost variables in each treatment group for the two studies.

FIGURE 1

For the MenSS trial (panel a), both QALYs and cost empirical distributions show similar ranges and mean values between the treatment groups. For the PBS trial (panel b), QALYs and costs are on average respectively 20% and 50% higher in the intervention compared with the control.

Figure 2 shows the histograms for the distributions in the control and intervention groups associated with either the CC or AC for the baseline utilities in the MenSS (panels a-b) and PBS (panels c-d) trials, and for the baseline costs in the PBS trial (panels e-f).

FIGURE 2

In the MenSS trial, baseline utilities show mean differences of –0.038 in the control and of 0.037 in the intervention group between the AC and the CC. Similarly, the baseline utilities in the control group for the PBS show a mean variation of 0.054 between the AC and the CC, while differences in the intervention group for the utilities and in both groups for the costs are less pronounced. These discrepancies are due to the CC being systematically different from the AC, with lower/higher values that are consistently underrepresented in the CC.
5.2 The MenSS study

Table 2 shows the posterior results for the two treatment groups of the MenSS trial. Since in this particular case small variations in the inferences are observed with respect to using a joint model, only the results under independence are presented. This, however, is not true in general and before assuming independence it is important that analysts also explore the potential impact on the inferences of accounting for the correlation between outcomes.

TABLE 2

According to the different sets of cases used in the utility adjustment, changes in the QALYs estimates are observed. In particular, going from the CC to the AC, the mean QALYs has an average decrease of 0.03 in the control group and an average increase of 0.013 in the intervention group. This has a substantial impact on the QALYs differential which, at the average value, changes its sign from negative to positive. Because the cost differential is on average negative, this implies that the intervention dominates the control, i.e. lower costs and higher QALYs.

Figure 3 shows a graphical representation of the Cost Effectiveness Plane (CEP; Black [1990]) and Cost-Effectiveness Acceptability Curve (CEAC; Van Hout et al. [1994]) based on the posterior samples of the mean parameters from the models shown in Table 2. Results related to the CC and AC are respectively indicated with red and blue dots and lines.

FIGURE 3

The graphs provide a clear picture about the impact of the two versions of the baseline adjustment on the cost-effectiveness conclusions. At a willingness to pay threshold of \( k = £20,000 \), the CEP (panel a) shows a much larger proportion of samples that fall in the sustainability area for the model based on the AC (Utility model AC (ind)) compared with the model based on the CC (Utility model CC (ind)). In the CEAC (panel b), when the CC are used (red line), the curve shows a low probability of cost-effectiveness for almost all \( k \) values, whereas using the AC (blue line) the probability consistently settles at values close to certainty.

5.3 The PBS study

Table 3 shows the posterior results for the two treatment groups of the PBS trial.

TABLE 3

Changing the model structure produces variations in the economic results. More specifically, incorporating the covariates (Covariate model) leads to an average decrease in the mean QALYs of 0.033 in the intervention group with respect to the simpler baseline utility/cost adjustment (Utility/cost model). This discrepancy is similar for both the independent and joint models based on the CC and AC. Given that all the other quantities barely change, this induces a reduction in the QALYs differential and a less favourable cost-effectiveness assessment for the new intervention.

When the multilevel structure is accounted for (Multilevel model), a substantial average increase of £800 is observed in the mean cost estimates of the intervention group for both the CC and AC versions compared with the other models. Correlation assumptions have a limited impact on mean QALYs estimates, which remain almost unchanged across all models. Conversely, mean cost estimates are lower for the Utility/cost model (ind) and Covariate model (ind) compared to the Utility/cost model (joint) and Covariate model (joint). The results associated with the multilevel models are robust to correlation assumptions but are still sensitive to the use of the CC or AC in the baseline adjustment.
Figure 4 shows the CEP and CEAC based on the inferences for all the models described in Table 3. Results distinguish between the use of CC (red) and AC (blue), as well as between independence (dashed lines) and joint (solid lines) assumptions. CEPs are reported only for their joint versions for simplicity.

At a willingness to pay threshold of $k = £20,000$ the ICERs for all the models indicate a more cost-effective intervention compared to the control. However, the magnitude of the assessment substantially changes between the models. When the multilevel structure is ignored (panels a-d), inferences are sensitive to correlation assumptions. Both the Utility/cost model (ind) and Covariate model (ind) are characterised by CEACs that are shifted upwards by 10% compared to the Utility/cost model (joint) and Covariate model (joint). A substantial decrease of the curves is observed for the Multilevel model (panel f) compared to the others for values of $k$ below £20,000. In this case, however, differences between the independent and joint models almost disappear, which suggests that adjusting for the clustering in the data may also substantially capture the correlation at the individual level.

The results associated with the CC and AC show discrepancies that persist almost regardless of the complexity of the model. This is indicated by the stable gap between the CEACs associated with the two types of regression adjustments for all models. More specifically, results based on the CC indicate a more cost-effective intervention compared with those based on the AC for most values of $k$. Similarly, in the CEPs, the largest proportion of samples falling in the sustainability area is associated with the use of the CC for all models.

6 Discussion

Baseline regression adjustment is generally considered as the reference approach to deal with baseline utility/cost imbalance in CEA, where adjusted mean estimates are obtained by setting the value of the baseline variables to their sample means. This paper has shown the potential ambiguity of this method according to whether the mean baseline values are computed using the CC or the AC. While the two approaches could lead to similar results, our two motivating examples show that this is not always the case.

For the MenSS trial, the cost-effectiveness conclusions derived from the two types of adjustments are completely opposite; for the PBS trial, the differences in the results based on the CC and AC are almost unaltered regardless of the complexity of the model considered. It is therefore important to investigate the reason for these differences. Specifically, the discrepancy in the results between the two approaches is due to the different assumptions they make about the missing values.

Both approaches assume that valid inferences can be obtained from the information contained in the observed data, that is the probability of missingness is independent of the unobserved data after conditioning on the observed data, an assumption known as Missing At Random (MAR; Rubin, 1987). However, if the additional observations from the AC are systematically different from the CC, then the MAR assumption based on the complete case dataset is untrue. This implies that the probability of missingness depends on the unobserved data even after conditioning on the observed data, an assumption known as Missing Not At Random (MNAR; Rubin, 1987). Since, under Rubin’s taxonomy, the categorisation of missingness depends on the available dataset, by including more data the MAR assumption may become more reasonable to justify. In the case of mean baseline adjustment, using all the AC, rather than just the subset of the CC, may therefore provide sufficient information to eliminate the bias associated with a CCA and obtain valid inferences.

The majority of statistical software packages have built-in functions which by default perform the adjustment using either the mean of the CC or AC. This is undesirable as analysts may be
unaware of the type of adjustment the software implements, possibly leading to biased inferences and mislead the final cost-effectiveness conclusions.

A possible strategy to check whether the MAR assumption on the complete case dataset is incorrect is to compare the distribution of the CC and AC for the baseline utilities/costs, for example using visual tools such as histograms or box plots. When the two sets of cases show systematic differences, there is a clear indication that the MAR assumption on the complete case dataset is implausible and the results based on CCA are likely to be biased. In this situation it should be then more reasonable to avoid CCA and use a method that retains the full sample by imputing the missing values, taking into account the variability between the imputations. Examples are Multiple Imputation ([Carpenter and Kenward 2012]) or Full Bayesian analyses ([Daniels and Hogan 2008]). Of course, it is possible that neither of the two adjustment approaches lead to valid inferences as MAR can never be verified from the data at hand. Missing at random can be used as a starting point, if plausible, but the robustness of the results to a set of plausible MNAR departures should always be assessed within sensitivity analysis.

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Appendix A JAGS code

The complete JAGS code for the Utility model CC/AC used in Section 5.2 and applied to the MenSS data is presented below.

```
#Number of individuals in the control (N1) and intervention (N2) group
#QALYs and total costs in the control (eff1,cost1) and intervention group (eff2,cost2)
#baseline utilities in the control (u0_1) and intervention group (u0_2)
model{
    for(i in 1 : N1){  #control
        eff1[i] ~ dnorm(mu.e[i, 1], tau.e[1])
        mu.e[i, 1] <- beta0[1] + beta1[1] * u0_1[i]
        cost1[i] ~ dnorm(mu.c[1], tau.c[1])
    }
    for(i in 1 : N2){  #intervention
        eff2[i] ~ dnorm(mu.e[i, 2], tau.e[2])
        mu.e[i,2] <- beta0[2] + beta1[2] * u0_2[i]
        cost2[i] ~ dnorm(mu.c[2], tau.c[2])
    }
```
#compute mean QALYs based on the mean baseline utilities provided as data

\[
\begin{align*}
\mu_{e.cc}[1] & \leftarrow \beta_0[1] + \beta_1[1] \times u_{0.cc}[1] \quad \text{#mean of complete cases (u0_cc)} \\
\mu_{e.cc}[2] & \leftarrow \beta_0[2] + \beta_1[2] \times u_{0.cc}[2] \\
\mu_{e.ac}[1] & \leftarrow \beta_0[1] + \beta_1[1] \times u_{0.ac}[1] \quad \text{#mean of available cases (u0_ac)} \\
\mu_{e.ac}[2] & \leftarrow \beta_0[2] + \beta_1[2] \times u_{0.ac}[2]
\end{align*}
\]

#from precision to variance and standard deviation

for(t in 1 : 2){
  \[
  \begin{align*}
  \tau_{e}[t] & \leftarrow 1 / \sigma_{e}[t] \\
  \sigma_{e}[t] & \leftarrow \sigma_{e}[t] \times \sigma_{e}[t] \\
  \sigma_{e}[t] & \leftarrow \exp(\log_{e}[t]) \\
  \tau_{c}[t] & \leftarrow 1 / \sigma_{c}[t] \\
  \sigma_{c}[t] & \leftarrow \sigma_{c}[t] \times \sigma_{c}[t] \\
  \sigma_{c}[t] & \leftarrow \exp(\log_{c}[t])
  \end{align*}
  \]
}

#priors

\[
\begin{align*}
\beta_0[t] & \sim \text{dnorm}(0, 0.000001) \\
\beta_1[t] & \sim \text{dnorm}(0, 0.000001) \\
\log_{e}[t] & \sim \text{dunif}(-5, 10) \\
\log_{c}[t] & \sim \text{dunif}(-5, 10) \\
\mu_{c}[t] & \sim \text{dnorm}(0, 0.000001)
\end{align*}
\]

#incremental quantities

\[
\begin{align*}
\Delta_{e.cc} & \leftarrow \mu_{e.cc}[2] - \mu_{e.cc}[1] \quad \text{#QALY increment based on u0_cc} \\
\Delta_{e.ac} & \leftarrow \mu_{e.ac}[2] - \mu_{e.ac}[1] \quad \text{#QALY increment based on u0_ac} \\
\Delta_{c} & \leftarrow \mu_{c}[2] - \mu_{c}[1] \quad \text{#cost increment}
\end{align*}
\]
References

Bailey, J., Webster, R., Hunter, R., Griffin, M., N., F., Rait, G., Estcourt, C., Michie, S., Anderson, J., Stephenson, J., Gerressu, M., Sinang Ang, C., and Murray, E. (2016). The men’s safer sex project: intervention development and feasibility randomised controlled trial of an interactive digital intervention to increase condom use in men. Health Technology Assessment, 20.

Baio, G. (2012). Bayesian Methods in Health Economics. Chapman and Hall/CRC, University College London London, UK.

Baio, G. and Dawid, A. (2015). Probabilistic sensitivity analysis in health economics. Statistical Methods in Medical Research, 24:615–634.

Black, W. (1990). A graphic representation of cost-effectiveness. Medical Decision Making, 10:212–214.

Briggs, A. (1999). A bayesian approach to stochastic cost-effectiveness analysis. Health Economics, 8:257–261.

Briggs, A., Wonderling, D., and Mooney, C. (1997). Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Economics, 6:327–340.

Carpenter, G. and Kenward, M. (2012). Multiple Imputation and Its Applications. John Wiley and Sons.

Claxton, K., Sculpher, M., McCabe, C., Briggs, A., Hakehurst, R., Buxton, M., Brazier, J., and O’Hagan, T. (2005). Probabilistic sensitivity analysis for nice technology assessment: not an optional extra. Health Economics, 27:339–347.

Daniels, M. and Hogan, J. (2008). Missing Data in Longitudinal Studies: Strategies for Bayesian Modeling and Sensitivity Analysis. Chapman and Hall, New York.

Drummond, M., Schulpher, M., Claxton, K., Stoddart, G., and Torrance, G. (2005). Methods for the economic evaluation of health care programmes. 3rd ed. Oxford university press, Oxford.

Gelman, A., Carlin, J., Stern, H., and Rubin, D. (2004). Bayesian Data Analysis - 2nd edition. Chapman and Hall, New York, NY.

Gelman, A. and Hill, J. (2007). Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge University Press, New York, NY.

Gomes, R., Grieve, R., Nixon, R., and Edmunds, W. (2012a). Statistical methods for cost-effectiveness analyses that use data from cluster randomized trials. Medical Decision Making, 32:209–220.

Gomes, R., Grieve, R., Nixon, R., NG, E., Carpenter, J., and Thompson, S. (2012b). Methods for covariate adjustment in cost-effectiveness analysis that use cluster randomised trials. Health Economics, 21:1101–1118.

Gomes, R., Ng, E., Grieve, R., Nixon, R., NG, E., Carpenter, J., and Thompson, S. (2012c). Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. Medical Decision Making, 32:350–361.
Grieve, R., Nixon, R., Simon, G., and Thompson, S. (2010). Bayesian hierarchical models for cost-effectiveness analyses that use data from cluster randomized trials. *Medical Decision Making*, 30:163–175.

Hassiotis, A., Poppe, M., Strydom, A., Vickerstaff, V., Hall, I., Crabtree, J., Omar, R., King, M., Hunter, R., Biswas, A., Cooper, V., Howie, W., and Crawford, M. (2018). Clinical outcomes of staff training in positive behaviour support to reduce challenging behaviour in adults with intellectual disability: cluster randomised controlled trial. *The British Journal of Psychiatry*, 212:161–168.

Hoch, J., Briggs, A., and Willan, A. (2002). Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Economics*, 11:415–430.

Hunter, R., Baio, G., Butt, T., Morris, S., Round, J., and Freemantle, N. (2015). An educational review of the statistical issues in analysing utility data for cost-utility analysis. *PharmacoEconomics*, 33:355–366.

Manca, A., Hawkins, N., and Sculpher, M. (2005). Estimating mean qalys in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Economics*, 14:487–496.

Ng, E., Diaz-Ordaz, K., Grieve, R., Nixon, R., Thompson, S., and Carpenter, J. (2016). Multilevel models for cost-effectiveness analyses that use cluster randomised trial data: An approach to model choice. *Statistical Methods in Medical Research*, 25:2036–2052.

Ng, E., Grieve, R., and Carpenter, J. (2013). Two-stage nonparametric bootstrap sampling with shrinkage correction for clustered data. *Stata J*, 13:141–164.

Nixon, R. and Thompson, S. (2005). Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health Economics*, 14:1217–1229.

Plummer, M. (2010). JAGS: Just Another Gibbs Sampler. [http://www-fis.iarc.fr/~martyn/software/jags/](http://www-fis.iarc.fr/~martyn/software/jags/)

Rubin, D. (1987). *Multiple Imputation for Nonresponse in Surveys*. John Wiley and Sons, New York, USA.

Su, Y. and Yajima, M. (2015). Package ‘R2jags’. [https://cran.r-project.org/web/packages/R2jags/](https://cran.r-project.org/web/packages/R2jags/)

Van Asselt, A., van Mastrigt, G., Dirksen, C., Arntz, A., Severens, J., and Kessels, A. (2009). How to deal with cost differences at baseline. *PharmacoEconomics*, 27:519–528.

Van Hout, B., Al, M., Gordon, G., Rutten, F., and Kuntz, K. (1994). Costs, effects and c/e-ratios alongside a clinical trial. *Health Economics*, 3:309–319.

Vazquez Polo, F., Hernandez, M., and Lopez-Valcarcel, B. (2005). Using covariates to reduce uncertainty in the economic evaluation of clinical trial data. *Health Economics*, 14:545–557.

Willan, A. and Briggs, A. (2006). *Statistical Analysis of Cost-Effectiveness Data*. Wiley, Chichester, UK.

Willan, A., Briggs, A., and Hock, J. (2004). Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Economics*, 13:461–475.
Figure 1: QALYs and cost data distributions for the control and intervention groups in the MenSS (panel a) and PBS (panel b) trials. A dashed line is drawn in correspondence of the mean for each variable and the value reported in the plot. Costs are expressed in £.
| Study | model | Baseline utilities/costs (CC) | Baseline utilities/costs (AC) | Baseline covariates | Multilevel structure | Correlation |
|-------|-------|-------------------------------|-------------------------------|---------------------|----------------------|-------------|
| MenSS | Bailey et al. (2016) | ✓ | ✓ | — | — | ✓ |
|       | Utility model CC (ind) | ✓ | — | — | ✓ |
|       | Utility model CC (joint) | ✓ | — | — | ✓ |
|       | Utility model AC (ind) | — | ✓ | — | — |
|       | Utility model AC (joint) | — | ✓ | — | — |
| PBS   | Hassiotis et al. (2018) | ✓ | ✓ | ✓ | — | ✓ |
|       | Utility/cost model CC (ind) | ✓ | — | — | ✓ |
|       | Utility/cost model CC (joint) | ✓ | — | — | ✓ |
|       | Utility/cost model AC (ind) | — | ✓ | — | — |
|       | Utility/cost model AC (joint) | — | ✓ | — | — |
|       | Covariate model CC (ind) | ✓ | — | — | ✓ |
|       | Covariate model CC (joint) | ✓ | — | — | ✓ |
|       | Covariate model AC (ind) | — | ✓ | — | — |
|       | Covariate model AC (joint) | — | ✓ | — | — |
|       | Multilevel model CC (ind) | ✓ | — | — | ✓ |
|       | Multilevel model CC (joint) | ✓ | — | — | ✓ |
|       | Multilevel model AC (ind) | — | ✓ | — | — |
|       | Multilevel model AC (joint) | — | ✓ | — | — |

Table 1: List of the different models compared in the analysis of the MenSS and PBS data. The models used in the original analyses are indicated with the author’s papers, while specific names are assigned to the models implemented in this work according to the different types of complexities that are accounted for. Different symbols are used to indicate whether the corresponding complexity is addressed (✓), ignored (✗) or not relevant (–).

| Parameter | Utility model CC (ind) | Utility model AC (ind) |
|-----------|------------------------|------------------------|
|           | Mean 95% interval      | Mean 95% interval      |
| Control (t = 1) |                          |                        |
| mean QALY ($\mu_{e1}$) | 0.904 (0.872;0.934) | 0.874 (0.841;0.907) |
| mean cost ($\mu_{c1}$) | 207 (104;307) | 207 (104;307) |
| Intervention (t = 2) |                          |                        |
| mean QALY ($\mu_{e2}$) | 0.902 (0.859;0.944) | 0.915 (0.872;0.957) |
| mean cost ($\mu_{c2}$) | 188 (112;266) | 188 (112;266) |

Table 2: Posterior means and 95% credible intervals of the mean QALYs and cost parameters for the control (t = 1) and intervention (t = 2) group in the MenSS trial. Two alternative models are considered: Utility model CC (ind) and Utility model AC (ind). Cost values are expressed in £.
Table 3: Posterior means and 95% credible intervals of the mean QALYs and cost parameters for the control \((t = 1)\) and the intervention \((t = 2)\) group in the PBS trial. Twelve different models are considered: Utility/cost model CC/AC (ind), Covariate model CC/AC (ind), Multilevel model CC/AC (ind) and their corresponding joint versions. Cost values are expressed in £.
Figure 2: Empirical distributions for the baseline utilities and costs in the MenSS (panels a-b) and PBS (panels c-f) trials computed either on the AC or CC, respectively indicated with the blue and red colour (shown as purple in the graphs when the two colours overlap). A dashed line is drawn in correspondence of the mean for each variable and the value reported in the plot. Costs are expressed in £.
Figure 3: CEP (panel a) and CEAC (panel b) associated with the Utility model CC (ind) (red dots and lines) and Utility model AC (ind) (blue dots and lines) in the MenSS study. Mean differentials (Δe, Δc) and ICERs (darker coloured dots) are reported for both models at the corners in the CEP. In the CEAC, a variation of the willingness to pay parameter up to £40,000 is considered.
Figure 4: CEPs (panels a, c, e) and CEACs (panels b, d, f) associated with the models shown in Table 3 for the PBS study. The results based on the CC (red dots and lines) and the AC (blue dots and lines) are indicated with different colours while correlation assumptions are associated with different line types (solid and dashed lines for joint and independence models). In the CEPs only the results from the joint models are shown. Mean differentials ($\Delta_e, \Delta_c$) and ICERs (darker coloured dots) associated with the CC and AC are reported at the top-right corners. In the CEACs, a willingness to pay range up to £40,000 is used.