**Reviewer: 1**  
  
1. Title:  This is a bit vague and should include at least a sub-title stating “A tutorial” or “A review of analytic and pictorial approaches” or etc.  In short, a clear and descriptive title is needed.

Author response: We have added ‘A Tutorial’ to the title to indicate that it is a tutorial.

2. Abstract: I suggest a structured abstract so that the structure of the work can be made clear and then followed in the MS.  For example a “results” section can summarize the number and name of the methods described.

Author response: Thank you for your suggestion. We have re-structured the abstract. The revised text reads as follows:

“ ….”

While systematic reviews of substance abuse interventions hold great promise for informing what works for whom and under what conditions, such reviews must contend with missing data. Missing data can limit the accuracy of statistical analyses or the relevance of the evidence base. Current methods for analyzing missing data require assumptions about the reasons that the missing data occur. In this tutorial, we examine methods for exploring missingness in a dataset in ways that can help identify the sources and extent of missingness, as well as clarify gaps in evidence. Using a subset of data from Tanner et al. (2016), we demonstrate the use of exploratory missingness analysis (EMA) including techniques for numerical summaries and visual displays of missing data. These techniques examine the patterns of missing covariates in meta-analysis data and the relationships among variables with missing data and observed variables including the effect size. The case study shows complex relationships among missingness and other potential covariates in meta-regression, highlighting gaps in the evidence base.

2. Overall: This MS reads long, at times uses too casual prose, and can make much better use of headings to guide the reader.  Thus, please copy edit to make more succinct, clear, and structured.  As for headings, I suggest the use of first level headings and third level.  At present there is a long succession of, sometimes unclear, second level headings.

Author response: We have tried to remove the text that reads as more conversational. We have also structured headings so that they follow your suggestion.

3. Overall:  Please also make clear up front, how this review adds to other review of missing data methods (for meta-analysis) to date.  EG, the paper mentions Pigot et al., 2019.

Author response: As suggested by the reviewer, we have noted that the contribution of this article is to advocate for EMA and to demonstrate one. The revised text reads as follows:

“Various researchers have suggested analysts can better understand missingness in their data through exploratory analyses, including visual and numerical summaries (Cheng, Cook, & Hofmann, 2015; Buja, Cook, & Swayne, 1996) akin to classical exploratory data analyses (Tukey, 1962). These explorations, which occur before running confirmatory statistical analyses, can shed greater light on key issues relevant to missingness. Tools for doing so are only now emerging in statistics, but these tools have yet to gain broader traction in quantitative disciplines (Tierney, 2017; Tierney & Cook, 2018). **Nor has this approach garnered much discussion among meta-analysts, where missing data is a common problem**. **Rather, the focus in meta-analysis has instead been on methods to estimate models with incomplete data.”**

4. The Introduction reviews different types of missing data in meta-analysis and this is great (Section: Missing Data in Meta-Analysis).  This would be better as a table where each type is given a descriptive name and definition, then this section can briefly touch upon methods for handling each ‘scenario’ and then locate the present work in scenario two.

Author response: We appreciate this comment and agree that it would be clearer to lay out the different types of missingness in a table. However, given that we focus only on the one type of missingness we felt that adding a table might belabor the idea of this taxonomy of missingness.

5. Next is what might be the Method section?  With a Notation introduction and introduction to the study dataset.  Regarding the latter, please describe more clearly the key findings of the Tanner-Smith meta, as this should thread throughout the MS to arrive at implications of the analyses for what was found in this particular meta-analysis.  As it stands, the Tanner-Smith data is used for example, but a substantive story revealed by these suggested analyses can be clearer.

Author response:  
  
*Minor points*

6. Treatment as Usual is the common term or Usual Care.  I would use either of these consistently and define at first use.  Once the MS gets into the ‘results’ the terms Group 1 and Group 2 are used, and these do not help the reader.

Author response: We have defined *usual care* in the revision. The revised text reads as follows:

“Some reported effects contrasted a given intervention with a placebo or with a "usual care" condition where individuals received services but no explicit drug treatment (e.g., youth in residential care who receive standard residential services but not drug treatment).”

7. When referring to Tanner-Smith variables be as exact as possible rather than summarizing.

“net of intervention type” what does this mean?

Author response: We have clarified this. The revised text reads as follows:

“However, they did not find strong relationships between the characteristics of adolescents in the studies and the effectiveness of interventions after controlling for intervention type.”

8. At some point in this MS, the process of reaching out to study authors to obtain missing data should be discussed.  Perhaps in the introduction as a way to underscore the importance of this study (i.e., provide data on poor response rates).

Author response: This is an excellent point. We have added the following in the introduction:

“Third, and the focus of this article, missingness may refer to information that could not be extracted from a completed study by a meta-analyst (Pigott, 2001). This may occur if a study fails to report enough detail for analysts to back out effect estimates, standard errors, or study- and effect-level characteristics. **When this occurs, it is often reasonable to reach out to the authors of primary studies with requests for missing information, however a recent study found that responses rates to such inquiries are low (around 12%) and responses that include the missing information are even less frequent (about 0.5%) (Polanin, 2020)**.”

We also note at the beginning of the Discussion section:

“Missing data is and will continue to be an issue with most meta-analyses that can affect what we can learn about substance abuse interventions from research syntheses.

**Attempts to recover missing information by contacting primary study authors should be encouraged, however empirical research suggests that such inquiries are unlikely to resolve missingness entirely (Polanin et al., 2019, 2020)**.”

9. “Principles of Missing Data” does not seem an accurately descriptive sub-heading?

Author response: We appreciate this and have removed this heading in our re-structuring of this article.

10. “Much of the literature on MAR tests compares specific models for dropout in longitudinal studies, which is almost never an issue for the metaanalyst (Molenberghs et al., 2008; Rhoads, 2012).” This sentence is unclear to me.  Why would this not be an issue for a meta-analysts?

Author response: Our point is that the MAR tests are for specific model specifications for dropout in longitudinal studies, and these models are seldom used in statistical analyses typical of a meta-analysis. If meta-analysts have the opportunity to re-analyze the raw data of primary longitudinal studies, this would be of concern for meta-analysis in that it would involve re-computing an effect size from a primary study or could be used in an individual participant data meta-analysis. We have removed this sentence to avoid confusion.

11. The MCAR and MAR review can certainly be reduced as it is well addressed in the literature and only need to be briefly defined here.

Author response: This is a great point. We have reduced it to a single paragraph so that it motivates specific aspects of EMAs.

12. Watch out for 2 sentence paragraphs, which make the work come across as underdeveloped.  
  
Author response: Thank you for pointing this out. We have tried to remove all of them or add to them so that they are more informative.

**Reviewer: 2**  
  
*Major comments*

1. To me the main point of the manuscript is the exploratory analyses to diagnose missing data. However, authors spent too much space discussing other aspects, including missing data analysis method, quantifying missingness, missing mechanisms and patterns, etc., which have been discussed a lot in the area. In addition, the focus of exploratory analyses is diluted and unclear. I think a more intuitive and clear way of presentation would be to start with exploratory analyses, then briefly introduce other relevant aspects. For example, introduce MCAR, MAR and MNAR at “Relating Missingness to Observed Values”. The “Data” section is also unnecessarily long with too many details. I feel the manuscript can be cut into half of the current length, then the point will be much clearer.

Author response: Thank you for your suggestion. We have restructured the manuscript so that we introduce concepts that might motivate a given exploratory analysis, and then immediately demonstrate the relevant tools. We feel this gives more focus to the exploratory analysis tutorial, and it more directly connects concepts with tools.  
  
*Minor comments*

1. Authors didn’t explain what meta-regression is and its relationship to meta-analysis, and used the two words interchangeably. It would be helpful to discuss and distinguish the two terms in the introduction.

Author response: As suggested by the reviewer, we have added this in the introduction. The new text reads as follows:

“Alternatively, meta-regression is a statistical model analogous to standard linear regression, wherein effect estimates are regressed on covariates pertaining to those effects, including study- and effect-level information (Hedges, 1982a,b; Cooper, Hedges, & Valentine, 2019). For example, a meta-analyst may examine how the effectiveness of interventions is related to the type of treatment (e.g., type of therapy provided), how or on whom it was implemented, or the context in which it was studied (see Cooper, Hedges, & Valentine, 2019).”

2. In page 13, line 45-46, please name the list of software that “conduct a standard EDA actually delete observations with missing values”.

Author response: This is pretty much any software that does EDA. Defaults in everything from R to Stata are to use observed variables and omit missing values according to different rules (e.g., complete cases, pairwise complete cases, etc.). We have not added a list since it would comprise nearly all standard software.

3. Please increase the resolution of the figures. Some labels are hard to see clearly.

Author response: We think that might be an issue with RStudio. We have replaced images with higher resolution files.

4. There is no equation label for the fraction formulas in “Quantifying the Amount of Missingness” (although I think the whole section may be removed).

Author response: This may also be an RStudio issue. These have now been fixed.

5. The whole illustration of the exploratory analyses is based on the data from Tanner-Smith et al. (2016), so I feel it may be good to acknowledge original investigators in the manuscript.

Author response: Thank you for pointing this out. We have added to end of the first paragraph of the Data section:

“We are grateful to Tanner-Smith et al., who furnished their raw data, which will be used to illustrate useful tools to exploring missingness in this tutorial.”

We have added an acknowledgement section in the paper.

**Reviewer: 3**

1. Emphasis is placed on meta-regression models and I would suggest that you adjust the title of the paper accordingly. I suggest you make it explicit that you refer to missing covariate values and you refer to aggregate data meta-regression models. My first impression was that the paper was either about missing outcome data or missing statistics (e.g. missing standard errors). The idea is useful but not so straightforward as with simple regression models. The regression analysis on the study level characteristics complicates things.

Author response:   
  
2. The paper is very long and it takes a lot of pages to reach the main target of the journal. The plots for the exploratory analyses appear on page 14!  I suggest you reduce it to facilitate the reader.

Author response: As suggested by the reviewer, we have re-structured the paper so that it gets into the exploratory analysis more quickly (after introducing the topic and data). In this revision, concepts are introduced alongside analysis tools. We feel this makes the article a little more direct.

3. The case of missing statistics, which is very common, is missing as an example. I suggest you make it explicit you refer to missing covariate values and you do not talk at all about other types (e.g. publication bias)

Author response: Thank you for pointing this out. We now make this clear in the introduction.

4. The implications of different missing rates across groups should be discussed more. For example, in RCTs such a difference is an indication of MNAR, in observational data this perhaps has implications on adjusting effect estimates.

Author response: This is a good point, and one we address when examining the relationship between missingness in a variable and observed values of other variables. There is clearly a difference in missingness rates for inpatient versus outpatient studies, for instance. We stop short of concluding MNAR based on this. Mainly, attrition from an RCT is a different process than those that induce the type of missingness in a meta-analysis addressed in this article (e.g., imprecise reporting or reporting not aligned to coding protocols). It could be indicative of MNAR, but it would also be consistent with MAR.

5. Since the paper focuses on meta-regression I would expect to see some general discussion on when we can actually do something about missing data. What if we have only 10 studies? What is the relationship between number of studies and predictors? What are the minimum/maximum levels of missingness that we can actually work with? What if a covariate is missing in 70% of the studies? It does not make much sense to me to employ an imputation method. What if we have covariates that do not differentiate across studies or dichotomous predictors with few events.

Author response: We have added a quick summary on page XX of the statistical guidance. Typically, the rule of thumb is that you probably need to do some sort of adjustment if you have more than 10% missingness, and that most adjustments work best with less than 40% missingness. There are conditions (MAR data and highly informative auxiliary variables used in the imputation models) where MI can return valid estimates even under higher rates of missingness.

6. Meta-regression is associated with a lot of pitfalls (Thompson and Higgins). Any thoughts on these regarding missing data (ecological bias, variables not differentiating across studies, confounding)?

Author response: Any method that seeks to adjust for missingness is only valid if the original model is valid. In that sense, we are assuming that the meta-regression is correctly specified. That said, some of the issues you raise, such as variables not differing between studies, can affect explorations of relationships between missingness and observed data. We kind of see that in Figure XX, where nearly all of the treatments are outpatient.

7. Along with Figure 4, why not have a figure/Table with boxed for each pair of predictors colored to represent the number of missing values on both predictors. That would clearly allow us to see if subsets of predictors tend to miss together

Author response: Thank you for your suggestion. We have added this plot (Figure 3) before the upset plot. It reveals similar patterns, but the patterns are a little more evident.

8. It seems to me that Figures 5-7 are used as a tool for exploring whether missing data are correlated to the observed effect size. Is this used as a method of testing for MAR? Confounding is another reason why there are such big differences in density plots in these Figures.

Author response:  
  
*Minor comments*  
  
9. Page 22 of 36, first line: “and that” is probably a mistake. Rephrase what you want to say.

Author response: We have edited that line and deleted “and”.

10. Page 22 of 36, line 12. You say that it is not always the case that the missingness mechanism is known to the researcher. I would say that it is never known, and we can only hypothesize on it. I think this is an important aspect of missing data that should be made clear.

Author response: This is a really good point. Our motivation for suggesting EMA is that mechanisms are seldom known and are instead assumed (or as you correctly put it, “hypothesized”), and that EMAs can help inform these assumptions. We have edited that paragraph to reflect this issue.   
  
Thompson SG, Higgins JP. How should meta-regression analyses be undertaken  
and interpreted? Stat Med 2002;21:1559–73.