Author’s response to reviews

**Title:** Suicide Attempts in U.S. Adults with Lifetime DSM-5 Eating Disorders

**Authors:**
Tomoko Udo (tschaller@albany.edu)
Sarah Bitlley (sbitley@albany.edu)
Carlos Grilo (carlos.grilo@yale.edu)

**Version:** 1  **Date:** 26 Apr 2019

**Author’s response to reviews:**

To the editor

Thank you for the opportunity to revise and resubmit our manuscript, “Suicide Attempts in U.S. Adults with Lifetime DSM-5 Eating Disorders.” We also want to thank all the reviewers for their very helpful comments, which contributed to a substantially strengthened paper. We carefully responded to each comment by the reviewers. Page and line numbers indicated in our response correspond with a revised manuscript with track changes.

Before outlining responses specific to each reviewer’s comment, we would like to highlight major changes in our manuscript based on questions/comments raised by multiple reviewers.

**Issues of transitional/comorbid diagnosis**

First, all reviewers asked about transitional/comorbid diagnosis and potential impact on our study’s results. The NESARC-III, like most psychiatric epidemiologic studies, is limited in ability to fully capture cross-over/transitional diagnosis because of the focus on establishing first and most recent episodes. Our study on the prevalence of EDs (Udo & Grilo, 2018) found that the lifetime prevalence estimate for any comorbidity between the three EDs (i.e., having lifetime diagnoses of two or more specific EDs) was 0.22% (0.03%). Of those, 0.01% (0.01%) reported lifetime “comorbidity” between AN and BN, 0.02% (0.01%) between AN and BED, 0.13% (0.02%) between BN and BED, and 0.05% (0.02%) amongst all three EDs. If we focus only on those with a lifetime history of any ED, 12% of the respondents met criteria for more than one ED. Our findings echo those with a recent Swedish study with a large cohort of treatment-seeking adults (N = 9622; Schaumberg et al., 2018) which also found that transitions between AN, BN, and BED were rare.

With that important context, we do however consider the Reviewers’ question a very good one and important to address, and thus completed two additional sets of analyses and summarized the
results in two new Supplemental Tables added to the revised manuscript. In the first set of analyses, we applied the hierarchical rule of AN>BN>BED and repeated the analyses we completed to create Table 1 by comparing their risk for SA and SA history with respondents without a lifetime history of specific ED (Supplemental Table 1). The pattern of results did not change, except for the number of SA attempts in BN (total sample) became non-significant, and AORs of SA in BN and BED became smaller. In the second set of analyses, after identifying respondents who met more than one ED diagnosis during their lifetime (n = 73), we compared their risk for SA attempts and SA history with respondents without a lifetime history of specific ED (Supplemental Table 2). We found that prevalence and AORs of SA were much higher in respondents with multiple ED diagnosis (prevalence = 41.5% and AOR = 10.59 [5.92-19.10], respectively). These findings appear to suggest that respondents who may transition from one ED diagnosis to another are at very high risk for SAs and thus represent an important subgroup. We discuss these additional important findings in the discussion (p. 14, lines 7-22).

OSFED and AN subtypes

Reviewer 1 asked about OSFED, which we were not able to investigate due to the NESARC-III study’s patterns of skip-out questions. Reviewer 2 suggested that we include AN subtypes in our analyses. This was a great suggestion, and after looking further into the NESARC-III data, we were able to categorize all respondents with lifetime AN into either restricting type or binge-eating/purging type. We included these subtypes into all analyses, in addition to AN, BN, and BED. These additional analyses and findings strengthened the paper further.

Other changes

As we note below in response to all of the reviewers’ comments, in the revised manuscript, we expanded the discussion substantially to provide greater context and to more fully address the implications of our findings.

In the suggested expanded additional analysis with AN-R and AN-B/P types, we observed that some logistic regression model estimates became invalid/less stable, and we needed to re-code race and education group categories into dichotomous variables (non-Hispanic White vs. other & some college or higher vs. high school/GED or less, respectively). In addition, while revising the analyses and manuscript, we identified an error in either coding or reporting of the results in the original submission. Specifically, the correct sample size of the BED group is actually 318 (which is consistent with our prevalence paper; Udo & Grilo, 2018). We also noticed that AORs for agoraphobia and social anxiety disorder in BN should not have been reported due to invalid model estimates. We emphasize that these corrections resulted in only a few changes (only observed in AORs for comorbid psychiatric disorders) and the results were updated accordingly; the findings were largely unchanged.
Response to reviewers

Reviewer #1:

I appreciate the opportunity to review this timely and important paper. I very much appreciate the aim of the authors’ paper, which is to better understand suicide risk among individuals with DSM-5 eating disorders. I also think the examination of temporal associations between SA and ED onset is a real strength of the paper. Some suggestions and thoughts for further consideration are offered below:

We thank the reviewer for these positive comments and for the very helpful suggestions that significantly improved our manuscript, including directing us to appropriate and relevant studies.

Intro

• The authors state that "Research on the relationship between suicidal behaviors and BED has thus been limited" - can a discussion of what does exist be included?

Thank you. We have added and integrated additional relevant existing literature for context (p. 5, line 18-p. 6, line 1).

• It is suggested authors review some recent meta-analyses on the state of suicide prediction in the field more broadly:


Thank you for directing us to these studies. We have reviewed and incorporated these studies in the introduction (p. 4, lines 5-10).
Method

• Why was Other Specified Eating Disorder not assessed? This seems especially important given that it is the most prevalent ED and has also been found to be associated with SA.

This is an important question. Unfortunately, due to the NESARC-III study’s patterns of skip-out questions (and associated missing data), we were not able to perform analyses examining OSFED. For example, the AUDADIS-5 interview did not specifically ask for frequency and duration of BN/BED symptoms. Rather, the interview simply asked whether binge eating and/or compensatory behaviors occurred at least once a week for at least 3 months (Yes/No). If a respondent answered “No” to this question, the interviewer stopped and the remaining questions related to BN and BED were not asked. This precluded us from investigating whether any (or which) respondents meet the rest of the BN/BED criteria in those instances where respondents did not meet the frequency and/or duration criteria. Due to this skip-out pattern, we were also unable to look at “purging disorder.” Furthermore, in the AN section, different weight control methods are asked in a separate question (e.g., use enemas, laxatives, diuretics or other medicines vs. exercise a lot or fasting) whereas these compensatory behaviors were lumped together asked in one question in the BN/BED section. This also means that it is possible that “no history of ED” might include some respondents who potentially met lifetime OSFED. These issues are limitations and were have added and expanded discussion accordingly (p. 19, lines 22-23).

• Regarding comorbidity, eating disorders often shift over time. For instance, someone may transition from AN to BN (see Eddy et al., 2008). Was this considered? If so, how?

Transitional diagnosis certainly happens. In our paper that reported the prevalence of AN, BN, and BED (Udo & Grilo, 2018), we reported that the lifetime prevalence estimate for any comorbidity between three EDs among U.S. adults (i.e., having lifetime diagnoses of two or more specific EDs) was 0.22% (0.03%). Of those, 0.01% (0.01%) reported lifetime “comorbidity” between AN and BN, 0.02% (0.01%) between AN and BED, 0.13% (0.02%) between BN and BED, and 0.05% (0.02%) amongst all three EDs. Thus, the prevalence of meeting more than one ED diagnosis is low. We do note that most psychiatric epidemiology studies tend to be very limited in terms of their ability to drill down on detailed history of each disorder; for example, the AUDADIS-5 asks questions about age at the first ED onset, the
number of ED episodes, age at the last ED episode, and duration of the last ED episodes, but no information about the timing was not collected for other episodes. This issue is not specific to the AUDADIS-5 and is an important limitation to consider when interpreting our data (p. xx, lines xx-xx). However, our findings are very consistent with a recent Swedish study with a large cohort of treatment-seeking adults (N = 9622; Schaumberg et al., 2018) that also suggested that transitions between AN, BN, and BED were rare.

As one way to address this important question of transitional diagnosis, we completed two additional analyses, which are now presented as Supplemental Tables. In one analysis, we applied the hierarchical rule of AN>BN>BED and repeated the analyses we completed to create Table 1 by comparing their risk for SA and SA history with respondents without a lifetime history of specific ED (Supplemental Table 2). The pattern of the results did not change, except for the number of SA attempts in BN (total sample) became non-significant, and AORs of SA in BN and BED became smaller. In another analysis, after identifying respondents who met more than one ED diagnosis in their lifetime (n = 73, 12% of those who met lifetime diagnosis of any ED), we compared their risk for SA attempts and SA history with respondents without a lifetime history of specific ED (Supplemental Table 3). We found that prevalence and AORs of SA were much higher in respondents with multiple ED diagnosis (41.5% and 10.59, respectively). These findings appear to suggest that respondents who may transition from one ED diagnosis to another are at higher risk for SA and are an important population at elevated risk for SA. We briefly added and addressed these findings in the discussion (p. 14, lines 7-22).

- The overall prevalence for the EDs in this sample appears much lower than other epidemiological studies; what do authors make of this?

We previous discussed and explored some of possible reasons for discrepancies with other studies in our prior publications. In the Udo & Grilo (2018) paper, we included a number of sensitivity analyses.


Thus, we did not devote much discussion of this particular issue in the current paper. However, we highlighted the need to replicate and extend our current findings and for further epidemiological study of ED in general (p. 20, lines 1-2).

**Results**

- Overall, might there be an issue with the results stemming from the use of a mixed age sample and use of lifetime prevalences (see Kraemer et al., 2006; Kraemer, 2009). Did authors consider survival curves or separate analyses within age-matched subgroups?

A possibility of cohort effects is an interesting question. Thus, we conducted Cox proportional hazardous models to test for age-cohort effects on odds of reporting SA (i.e., 18-29, 30-44, 45-59, and 60+ years old [reference]), adjusting for other sociodemographic variables. However, we found in all EDs, age cohort-by-lifetime ED diagnosis was not significant, and that even the confidence intervals of hazardous ratio are quite large (e.g., AHR = 7.219, 95% CI = 0.89-58.35 for AN). This instability is likely due to a small sample size when further breaking down into different age groups. Thus, we decided not to include these exploratory analyses and results in the revised manuscript; we did, however, add this important point to the revised discussion with relevant references (p. 20, lines 10-12).

- Can estimates that address possible issues with multicollinearity be provided (eg. VIF)?

Survey procedures in SAS unfortunately do not calculate indices of multicollinearity. Instead, we tested correlations among all independent variables, and found that they were not correlated (mostly r < .10 with largest r = 0.34 between education and income). Although this is not a test of multicollinearity, we ruled out the issue of multicollinearity in our analyses because it is very
unlikely that more than three variables are highly correlated with any given two variables are not highly correlated.

Discussion

- Results regarding SA onset in BED are in contrast to Forrest et al., 2018 where most adults experienced suicidality onset prior to BED onset; what do authors make of this discrepancy? Also, given the later age of onset for BED, one could argue SAs would be more likely to occur before BED onset, and yet the opposite was found. Can authors comment on this?


Thank you for directing us to the study by Forest and colleagues (2017) which we have added and integrated in the discussion (p.17, lines 6-11). We note here that due to missing data in that study, the sample sizes for this analysis were very small particularly for SA (n = 1 for adults 18-29, n = 3 for 30-44, and n = 3 for 45-59, and n = 1 for 60+ years old). Our study had much larger Ns for the relevant analyses. Nonetheless, we noted that these methodological differences and mixed findings speak to the need for further research.

- Could the authors briefly discuss why there was a greater number of reported SAs in BED?

We did not statistically compare the number of SA attempts between AN, BN, and BED in the analyses presented in Table 1. We did, however, compare the number of SA attempts when applying the hierarchical rule and found that there were no statistically significant differences between three ED groups.

- The methodological differences mentioned in the first paragraph on page 12 should be more thoroughly discussed. How do these methodological differences prevent the authors from reasoning out the different findings on the prevalence of SAs in their sample and previous samples?
We expanded our discussion of the methodological differences between our study and Crow et al. (p. 14, line 23-p.15, line 9).

• Among those with SA history, why might the duration of illness be different for AN and BN?

Thank you for noting this. This is an interesting question and finding but the reasons are uncertain and difficult to address with further analyses. We briefly and cautiously added discussion of this particular finding (p. 15, line 19-p. 16, line 1).

• Can authors discuss a bit further about why SA might be as likely to precede ED onset as follow?

Thank you. This is an interesting question but one that is difficult to address either with the NESARC-III data or with the existing empirical literature. We noted this finding and cautiously added brief potential clinical speculations as to why SA may precede BED onset (p. 17, line 12-p. 18, line 2) and the need for further research.

• More should be stated about the fact that these reports are retrospective and the longer the time period between an event and retrospective report, the greater the risk of recall error. Overall, the interpretations of the findings should make clear that you are assessing the association between retrospective reports of ED and SA.

Thank you for this suggestion. Yes, we agree. We specifically emphasized this point as part of limitation sections in the discussion. We emphasized that this is a cross-sectional study that retrospectively assessed lifetime history of ED symptoms, and is therefore susceptible to recall biases. We, however, also note that use of a structured diagnostic interview may offset part of this particular issue by virtue of focusing respondents on onsets (p. 19, lines 19-22).
Reviewer #2:

The current study used a nationally representative sample of U.S. adults to examine the prevalence and correlates of suicide attempts in individuals with a lifetime diagnosis of anorexia nervosa, bulimia nervosa, or binge eating disorder. Strengths of the study include the large epidemiological dataset (N > 36,000) and structured interviews to determine prevalence of psychiatric disorders. Specific comments regarding ways to improve the manuscript are listed below:

Introduction:

• It may be useful for the authors to note some of the changes in the ED diagnostic criteria from DSM-IV to DSM-5 that could further highlight the importance of conducting the current analyses.

Thank you for this great suggestion. We highlighted some significant changes in ED diagnostic criteria between DSM-IV and DSM-5 (p. 6, lines 14-23).

Methods:

• Were eating disorder diagnoses made based on a hierarchy such that someone with lifetime AN would not be diagnosed with lifetime BN? Or do the ED groups listed in Table 1 represent non-independent samples? I think this should be clarified. Relatedly, do the authors have data on AN subtype? There is some support that prevalence of attempts may differ based on subtype (AN binge-eating/purging vs. AN restricting), so adding such analyses would strengthen the paper.

We did not apply hierarchical rules and therefore the ED groups in Table 1 do represent non-independent samples. We clarified this in each table by including this sentence, “All ED groups are not mutually exclusive as respondents may have had multiple lifetime ED diagnosis”, so that it is clear to the readers when they read them.

In response to this excellent comment, and to similar comments by the other two reviewers on transitional diagnoses, we performed two additional sets of analyses. The first new analysis included applying the hierarchical rule and repeating the analyses presented in Table 1
(Supplemental Table 2). The pattern of the results did not change, except for the number of SA attempts in BN (total sample) became non-significant, and AORs of SA in BN and BED became smaller. In the second new analysis, after identifying respondents who met more than one ED diagnosis in their lifetime (n = 73, 12% of those who met lifetime diagnosis of any ED), we compared their risk for SA attempts and SA history with respondents without a lifetime history of specific ED (Supplemental Table 3). We found that prevalence and AORs of SA were much higher in respondents with multiple ED diagnosis (41.5% and 10.59, respectively). These findings appear to suggest that respondents who may transition from one ED diagnosis to another are at very high risk for SA and thus represent an important subgroup. We discuss these additional important findings in discussion (p. 14, lines 7-22).

Thank you very much for the excellent suggestion that we also examine AN subtypes. We included the Piesetsky et al. (2013) study and integrated it throughout the manuscript as a reference for this point. Importantly we performed additional analyses. We were able to categorize respondents with AN into restricting (ANR) and binge-eating/purging (AN-BP) subtypes, and completed all the analyses including these two subtypes, including overall AN. Overall, we found that ANBP subtype was at higher risk for SA compared with ANR, which is similar to the Piesetsky et al (2013) paper. We also found some noticeable differences in the patterns of the associations between SA and comorbid psychiatric disorders between ANR and ANBP. We discussed these findings in the discussion section (p. 18, line 3-p. 19, line 14). We believe that inclusion of the AN subtypes greatly strengthened the study and paper. We also modified the abstract to reflect these changes, and added how these two subtypes are operationalized based on the AUDADIS-5 in Supplemental Table 1.

Results/discussion:

• On page 10 of the results, the authors note that suicide attempts were associated with shorter duration of illness in BN but longer duration of illness in AN. Do the authors have any thoughts on why this may be? I wonder if suicide attempts in AN are more related with chronicity whereas severity (e.g., potentially representing greater dysregulation) is more related to attempts in BN. Also, given that length of illness was associated with attempts in AN, did the authors consider controlling for this variable in examining clinical characteristics of EDs by SA history? It would be interesting to see whether impairment in AN based on attempt history remained after accounting for duration of illness.
Thank you for noting this. Other reviewers also commented on this particular finding. We ran logistic regression analyses to see if odds of reporting psychosocial impairments were greater in those with SA history with adjusting for years of ED episodes. After examining the results, AORs and 95% CIs indicated that the study is possibly underpowered to examine this important question about the role of lengths of EDs in the relationship between risk for SA and ED (e.g., AOR = 2.15 [0.87-5.34] for AN symptoms interfered with normal daily activities). We expanded our revised discussion to address this and cautiously integrated the reviewer’s interesting suggestion that SA in AN may be related with chronicity whereas severity is more related with SA in BN, as well as suggesting investigation of the role of lengths of illness in SA risks in ED (p. 15, line 19-p. 16, line 1). Those suggestions make good clinical sense and should guide future research.

• Finally, the discussion seemed mainly to be a restatement of the findings in the results. I think it would be helpful if the authors commented on how these findings may fit within the broader literature on eating disorders and suicide attempts. I also think including a greater discussion of the role of comorbidity in associations between EDs and suicide attempts is important. For example, according to Table 3, 86% to 96% of individuals with EDs who endorsed a history of suicide attempts also had a history of a mood disorder. Thus, it is possible that associations between EDs and suicide attempts are actually being driven by the mood disorder diagnosis. If so, this would have implications for suicide prevention (i.e., the importance of targeting the mood disorder vs. focusing on ED symptoms).

Thank you for these suggestions for refining the discussion. Following this and similar suggestions by Reviewers 1 and 3, we modified our discussion section and, in particular, attempted to provide greater for the findings. Additionally, as suggested, we noted a possible role of mood disorders (p. 17, line 12-p. 18, line 2).

Minor comment:

• There are some typos throughout the manuscript, so the authors should proofread carefully prior to publication.

Thank you. We carefully went through the manuscript for grammatical errors and typos.
Reviewer #3:

The aim of this study is to examine prevalence and correlates of suicide attempts and DSM-5 eating disorders in a nationally representative sample of US adults. This is the first study to examine suicide attempts in DSM-5 eating disorders using a nationally representative sample of adults in the US and adds significantly to the literature. The use of the NESARC dataset, a rigorously collected epidemiological study, is a major strength of the paper. The paper is well written with a clear rationale. The tables are clearly laid out, analyses are appropriate to the questions, and clearly described. However, a few minor limitations weaken the paper in its current form:

1. The authors did not address any diagnostic cross-over of lifetime eating disorder status. Many individuals will meet criteria for more than one diagnosis over the course of their life. Where there any individuals in this dataset who met lifetime criteria for more than one ED diagnosis, and if so, how were these individuals categorized?

This is an interesting and important issue brought up by all reviewers. Transitions across ED diagnoses happen. In our paper that reported the prevalence of AN, BN, and BED (Udo & Grilo, 2018), we reported that the lifetime prevalence estimate for any comorbidity between three EDs among U.S. adults (i.e., having lifetime diagnoses of two or more specific EDs) was 0.22% (0.03%). Of those, 0.01% (0.01%) reported lifetime “comorbidity” between AN and BN, 0.02% (0.01%) between AN and BED, 0.13% (0.02%) between BN and BED, and 0.05% (0.02%) amongst all three EDs. Thus, the prevalence of meeting more than one ED diagnosis is low. We do note that psychiatric epidemiology studies tend to be very limited in terms of their ability to drill down on detailed history of each disorder; for example, the AUDADIS-5 asks questions about age at the first ED onset, the number of ED episodes, age at the last ED episode, and duration of the last ED episodes, but no information about the timing was not collected for other episodes. This issue is not specific to the AUDADIS-5 and is an important limitation to consider when interpreting our data. However, our findings are very consistent with a recent Swedish study with a large cohort of treatment-seeking adults (N = 9622; Schaumberg et al., 2018) that also suggested that transitions between AN, BN, and BED were rare.

As one way to address this important question of transitional diagnosis, we completed two additional analyses, which are now presented as Supplemental Tables. In one analysis, we applied the hierarchical rule of AN>BN>BED and repeated the analyses we completed to create
Table 1 by comparing their risk for SA and SA history with respondents without a lifetime history of specific ED (Supplemental Table 2). The pattern of the results did not change, except for the number of SA attempts in BN (total sample) became non-significant, and AORs of SA in BN and BED became smaller. In another analysis, after identifying respondents who met more than one ED diagnosis in their lifetime (n = 73, 12% of those who met lifetime diagnosis of any ED), we compared their risk for SA attempts and SA history with respondents without a lifetime history of specific ED (Supplemental Table 3). We found that prevalence and AORs of SA were much higher in respondents with multiple ED diagnosis (41.5% and 10.59, respectively). These findings appear to suggest that respondents who may transition from one ED diagnosis to another are at higher risk for SA, and are an important population at elevated risk for SA. We briefly addressed and discussed these findings in discussion (p. 14, lines 7-22).

2. Please check that the references are correct and match up. The authors refer to one of their previous papers (page 7, bottom paragraph) using citation 37. Citation 37 does not appear to match (not a previous paper on DSM-5 diagnoses in NESARC) and subsequent citations do not seem to match up correctly.

Thank you. We have reviewed and made the corrections. We also added more references because of revisions to the manuscript but made sure that the in-text citations and reference list match.

3. The authors cite the recent meta-analysis from Smith and colleagues that find eating disorder status is a significant risk factors for suicide attempts in the introduction. This meta-analysis found that ED status was a significant but only a weak longitudinal risk factor for suicide attempts and not a predictor of death by suicides. Given that the authors only found BED onset to typically precede suicide attempt and AN and BN were closer to 50/50, it would be helpful to contextualize these findings in the discussion in the context of the Smith meta-analysis. It is unclear from the meta-analysis and these data if close monitoring of eating disorder symptoms would yield positive predictive value in national suicide prevention efforts.

Thank you for this point which parallels other reviewers’ comments as well. As we detailed above in response to the other reviewers, we have substantially revised the discussion section to provide greater context for our findings and this included integration of additional relevant literature including the important meta-analysis by Smith and colleagues (p. 17, line 12-p. 18, line 2).
We also cautiously added brief discussion of the 50/50 onset for AN/BN versus the finding for BED as we noted in response to Reviewer 2. Here we integrated and contrasted findings reported by Forest and colleagues (2017) (p.17, lines 6-11). It is indeed unclear whether close monitoring of ED symptoms would have positive impact in national prevention efforts.

Minor typos:

1. Page 6, second full paragraph: Should be "a multi-stage probability sampling was employed"

2. Page 11, second paragraph appears to be missing a word ("which was statistically significant from 50%")

Thank you. We carefully went through the manuscript for these and any other grammatical and typo errors.