Reviewer: 1  
  
Comments to the Author  
This manuscript describes secondary analyses of five randomized controlled trials of nicotine replacement therapy (vs. placebo) with minimal behavior support for smoking reduction among adults who smoke heavily and reported they did not want to quit smoking. Data were pooled across studies and sites to identify latent trajectories of smoking reduction over 6 months using mixture modeling, identify baseline predictors of latent trajectory class, and assess the degree to which latent trajectories over 6 months predict abstinence at 12 months post-enrollment, above and beyond baseline predictors. A 3-class solution was selected and predictors of latent class membership were examined in multiple ways (all possible class comparisons and in only those treated with placebo NRT). Latent class membership predicted later abstinence.  
  
The manuscript presents a sophisticated approach to the study of reduction pathways in multiple clinical trials of NRT for smoking reduction. There are several strengths to the analytical approach, including the use of training vs. test samples, attending to the probabilistic nature of latent class membership, conducting sensitivity analyses at an historical and current cutoff value for CO testing, and assessing increments in distal abstinence prediction using an ROC AUC approach. Despite these strengths, there are significant limitations that reduce the potential impact of this sophisticated analysis.  
  
First, the rationale for the analytical approach is underdeveloped. Although it is reasonable and indeed intuitive to hypothesize that the degree to which people reduce their smoking during reduction treatment will predict later abstinence, the rationale for the specific analytic approaches adopted is not particularly clear or compelling.  The first question posed in the introduction regarding possible trajectories in cigarettes per day over time has been addressed through simpler descriptive analyses in the past. What this new, more sophisticated and complex latent mixture modeling approach adds to extant knowledge is not clearly articulated in the manuscript.

While we agree that smoking trajectories in CPD over time can be quantified using descriptive analysis, doing so requires assigning groups a priori (e.g., active vs. placebo) and measuring the average extent to which those users reduce their smoking. Through structural equation modeling, we can identify those use patterns and identify the patterns best associated with each user probabilistically. This data-driven approach allows us the opportunity to uncover unrealized trends in smoking behavior after an intervention.

Second, the methods are not described with sufficient clarity or detail. The nature and rationale for selection and coding of the predictors included could be more clearly described, for example. The rationale for the cutoffs use for eliminating variables, cases, and imputing values is unclear, and the missing data approach described in the results section appears to deviate from that outlined in the method section in minor ways. The missing data approach was also not described in the pre-registered protocol, which increases the need to provide a compelling justification for the approach adopted.

We will clarify the methods, particularly the coding of categorical predictors and literature-supported cutoffs. Out pre-registered protocol stated that we would use multiple imputation to handle missing data. Given the high degree of missingness in some predictors, we opted instead to drop variables with missing values for a substantial number of participants, and whole cases who were missing a substantial number of variables. Then, to minimize any possible confounding introduced by the multiple imputation procedures, we opted for a simpler method of using mean and median imputation where appropriate.

We acknowledge that our method for feature selection deviates from our pre-registered protocol. We determined that the relatively large number of predictors available in this unique dataset lent best to regularized regression, where feature selection is inherent, as opposed to the stepwise selection method described in the pre-registered protocol.   
  
Third, some of the results are unclear as described or presented. For example, the statement on page 10 that “Within each trajectory, differences in CPD were observed for each week (p’s <.001)” is unclear because no comparator (baseline CPD?) is described, and Figure 2 does not seem to support this. In addition, Figure 3 is unreadable without considerable magnification, and the basis for concluding that being male, older, and less anxious reduced the most based on a comparison of those who reduced on placebo versus did not reduce on active NRT (p. 12) is unclear from the results presented.

We will clarify Figures 2 and 3. In Figure 2, all values are relative to baseline (i.e., percent reduction from baseline), which eliminates the explicit need for a comparator. Any linear slope statistically distinguishable from 0 is meaningful.

Last, the finding that a pattern of near complete reduction in smoking in the first 6 months predicts abstinence 12 months after treatment initiation is not particularly informative, even if assessed and presented in an innovative and sophisticated manner. The distribution of CPD reductions at each follow-up suggest that there was increasing polarization over time, with the modes at 100% and 0% reduction growing with each passing 8 weeks, while the mode at 50% reduction declined over time. Although the complex trajectory model gets at this in a different way, a simpler conceptualization and approach might be to assert simply that achieving abstinence during reduction treatment predicts later abstinence. The authors acknowledge in the manuscript that this is intuitive and expected. What the present analyses add to this intuitive understanding is not sufficiently clear from this fairly technical manuscript.

It is expected that differences from baseline become increasingly polar (by proportion) in a longitudinal study on smoking cessation. Indeed, a substantial minority (44.53%) of participants regressed to or near to their baseline smoking rates, which explains the growing proportion at 0% reduction. We disagree that the mode at 50% declined over time. While variation in CPD among this group (Class 2, n=803, 45.04%) increased throughout the study’s duration, many of these users reduced their smoking further rather than reverting to their baseline smoking rates.

It would, of course, be simpler to assert that achieving abstinence during cessation treatment predicts later abstinence, but this assertion would be incomplete, as not all Class 1 users achieved abstinence during treatment. Further, many Class 2 (the group who reduced by approximately half) users also achieved abstinence after the study period without having achieved cessation earlier. We will clarify this in the discussion.  
  
  
Reviewer: 2  
  
Comments to the Author  
This was a secondary analysis of 5 randomized, placebo-controlled trials for smoking reduction. The goal of the study was to determine if people who use reduction treatment tend to fall into different reduction patterns (i.e., latent class membership), whether these patterns are predicted by baseline characteristics, and whether different latent classes predict biochemically verified smoking abstinence.  Although reduced smoking may not decrease harms of smoking appreciably, offering reduction treatment certainly increases treatment reach and appears to modestly increase the likelihood of achieving abstinence.  While many people who smoke perceive gradual reduction as a viable option for quitting, little is known about which patterns of reduction lead to quitting, or which demographic or smoking characteristics influence such latent classes.  Improving our understanding of the characteristics that lead to successful reduction, or types of reduction patterns lead to cessation, could improve the effectiveness of reduction treatments offered as an alternative to abrupt cessation.  
  
The paper notes that: “In both arms, participants received the same minimal level of behavioral support for smoking reduction and were simply encouraged to reduce their smoking as much as possible, with cessation as the end goal.” Was the cessation end goal stated to participants, or was cessation the primary research outcome? If stated to participants, it would suggest they are interested in making a delayed quit attempt, in other words reducing prior to the ultimate goal of cessation. In addition, aim 1 indicates that participants were asked to reduce prior to quitting.  This implies that participants were more motivated than those not ready to quit but willing to reduce.    
  
It would be helpful to indicate how study was specifically advertised and described to study candidates across sites to help characterize the sample.  For instance, were participant recruited to reduce their smoking to help them quit later during the study? If, as stated in Aim 1, participants were asked to delay prior to quitting, when were they encouraged to quit? How many weeks of reduction was encouraged?  
  
Characteristics of participants in the study should be more clearly described in the text, including differences between study sites. Overall, participants smoked heavily and appeared to report high levels of dependence. Such information will help with comparison across other trials of participants reducing to quit.    
  
At least 1 large trial of NRT for smokers not ready to quit but willing to reduce found that patch vs gum produced differential effects on abstinence.  Specifically, those who used patch were less likely to quit, whereas nicotine gum, at least in combination with other intervention components, increased likelihood of quitting. Is there any evidence in the current study that different forms of NRT produced different effects on reduction or abstinence?  
  
Additional protocol information is needed to contextualize findings within other smoking reduction research.  For instance, it is noted that the behavioral intervention was brief. How many sessions were provided? Did sessions occur in person or over the phone?  
  
Also, how many participants used patch, vs gum vs inhaler? What dosing was used for active NRT?

Unfortunately, we lack some details that would allow us to answer these questions comprehensively. We agree that participants recruited for these trials may have been more motivated to reduce their smoking than other people who smoke. Further, we acknowledge that the recruitment and intervention methods employed in these trials were not perfectly harmonious. We will attempt to clarify meaningful differences between samples, and conduct sensitivity analyses where appropriate.

It is noted that when a participant reported abstinence, CPD was set to 0. Were participants who reported abstinence (or zero cigarettes) included in the average CPD that was then used to predict later abstinence?  If this is the case, then it might suggest that early abstinence predicts later abstinence, which would limit conclusions about relations between smoking reduction and abstinence. The approach taken needs to be described and justified. Including abstainers in latent classes describing reducers is also questionable (its unclear whether abstainers were included or not included).

This is a fair criticism. We will conduct the analysis without the abstainers and quantify differences between those models.