Author’s response to reviews

Title: Mortality, cause of death and risk factors in patients with alcohol use disorder alone or poly-substance use disorders: a 19-year prospective cohort study

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Response to reviewers

First, we would like to thank both reviewers for informed and detailed reviews pointing at central parts of the manuscript. We have read all comments carefully, considered their meanings and followed most of them. We will respond to all comments by both reviewers. Together with the revised article, we will also upload a version with “track changes” so that reviewers and editor can see how and where comments and responses have been incorporated into the final version article. During this work we have found two inaccuracies that have been corrected (number of participants with AUD alone is 130, not 131 as first reported, and in the multiple Cox regression analysis for risk of death the interaction between age and participants with AUD alone was overall significantly different from this association in patients with poly-SUDs). Suggestions from the reviewers made the article longer, so we had to remove and rewrite some parts of the article to compensate.

Reviewer 1: Abhijit Nadkarni (Reviewer 1): Interesting paper examining mortality in a longitudinal cohort of AUD and SUD patients and comparing it between those two groups. Although the paper makes for a good read, it might benefit from some revisions as suggested below:
Comment 1: Please do a careful language check. The language is generally good but has some minor errors such as in the abstract 'Being man and...' should have been 'Being male and....'

Our response: Language is a challenge because English is not the first author’s native language. This problem has been met by having a professional English editing company edit the entire article. The mentioned example has been corrected.

Comment 2: Study design: Was this a prospective or historical/retrospective cohort i.e. was it set up to examine this particular question and then followed up over 19 years or was it set up to answer some other questions and this question is now being answered retrospectively. This needs to be clarified in the methods

Our response: This have now been elaborated in the methods/design section, see page 6.

Comment 3: Some information about the clinical settings and counties needs to be provided for international readers to make judgement about external validity

Our response: More details have now been implemented, and a comparison of with a national sample (n = 5000) of patients in facilities for specialized treatment for SUD in Norway in the same period have been added.

Comment 4: At baseline, were there no other sociodemographics available beside age and gender?

Our response: Yes there was. Baseline descriptions have now been elaborated more and a new table 1 with descriptive data is included (also based on reviewer 2’s comment number 9).

Comment 5: Patients with AUD alone tended more often to be men (77% vs 67%, p = 0.055), be older(45.8 vs 32.1 years, p < 0.001), have fewer lifetime psychiatric disorders (3.2 vs 3.9, p =0.027), and be less likely to have lifetime affective disorders (57% vs 69%, p = 0.047), lifetime anxiety disorders (76% vs 88%, p = 0.010), and current personality disorders (63% vs 80%, p = 0.003) at baseline than patients with poly-SUDs'. This appears to be univariate. Could a multivariate analysis be done with ORs as many of these variables will probably be highly correlated.

Our response: Yes, these are bivariate comparisons. Comparing baseline characteristics in subgroups is not an explicit aim for this article. This information is just meant as descriptions of baseline characteristics in different groups, and then it is highly unusual to run multiple analyses. Based on comment 9 from reviewer 2 this part has now been changed and a new table 1 of baseline characteristics has been incorporated.
Comment 6: 'Sampling, subjects and methods at baseline have been described more extensively elsewhere [23, 24]. Ideally a brief summary might be useful for those who might not want to go back to the original publications.

Our response: All the text under methods/sample is meant to be a brief summary of sampling and subjects. More details have now been added (based on your comments 2 and 3). We hope the new Table 1 also is helpful regarding this issue. Since several articles (including two in BMC Psychiatry) have been published with descriptions of sampling, subjects, methods and baseline characteristics we have had concerns and tried to avoid “double publishing”.

Comment 7: Were there any repeated measurements in the 19 years follow up? Especially important as AUDs/SUDs follow a relapsing remitting course

Our response: Yes, there was a follow-up in form of a questionnaire by post in 2004 and second follow-up in 2015/16. The HSCL-25 was used at all three measuring points and the AUDIT/DUDIT was used in 2004 and 2015/16. We would need more repeated measurements to reliably monitor the course of substance use during the 19 years. Given our available data adding repeated measurement to the analysis do not fit well with the aims of the article. Also 33 of the participants had already died in 2004, and of course the deceased participants did not respond at the 2015/16 follow-up.

Comment 8: Were any sample size calculations done at baseline? If this was a convenience baseline sample then it would be useful to show post hoc power calculations i.e. what SMR (95% CI) would be detected at 80% and 90% power given the available sample size

Our response: This was an established cohort from 1997/1998 and no sample size calculations were done by the time of the second follow-up study in 2015/2016. It is well acknowledged, that post-hoc power should not be reported, since it would be the same as reporting p-value in a different way. Moreover, standardized mortality rates are presented in Table 3 (old Table 2) with 95% confidence intervals. None of them include 1, which clearly demonstrates enough power in our study.

Comment 9: 'Bivariate comparisons showed that the deceased were more often males (80% vs 67%, p = 0.013), older (44.3 vs 35 years, p < 0.001), less likely to have lifetime affective disorder (52% vs 70%, p = 0.003), less likely to have experienced the first onset of an SUD before 18 years of age (35% vs 51%, p = 0.009), and more likely to have had AUD alone versus poly-SUDs (65% vs 34%, p < 0.001) at baseline than living patients'. Why were multivariate analysis not done?

Our response: These results are primarily for descriptive purposes to show the actual differences between the groups on central variables, the multivariate analysis for risk of death is performed by Cox regression analysis in new Table 4 (old Table 3). As mentioned in comment 5 we think doing a multivariate analysis here would be highly unusual, and also there would be
methodological problems, e.g. multiple significance testing, with doing several partly overlapping multivariate analysis.

Comment 10: I am unclear about Model 2. Why are outputs for categorical variables like gender and substance use presented as regression coefficients and not HR?

Our response: Because these variables are included in interactions with other variables in the multiple Cox regression analysis and cannot be interpreted isolated as main effects. We have now understood that this way of presenting the results can be confusing and have made changes accordingly. See our response to reviewer 2 comment 12.

Reviewer 2: Michael Roerecke:

Comment 1: Abstract: There should be more details in the Results section, including confidence limits. Please use past tense. The conclusions should be closer to the results, the statement in the first sentence was not investigated in the study.

Our response: We agree, and have made changes accordingly.

Comment 2: The Introduction seems well thought out, however, the cited point estimates for mortality should include confidence intervals.

Our response: We agree about the estimates of mortality, and have made changes accordingly.

Comment 3: Most of what is written in the Sample section should be in the Results. The sampling should be described in more detail, I don't think a reference will suffice.

Our response: Serval articles (including two in BMC Psychiatry) have been published with descriptions of sampling, sample and baseline characteristics and we have had concerns and tried to avoid “double publishing”. We have, based on this comment, decided to move descriptions of the cohort to the results section in this article. Also based on reviewer 1’s comment 6, we have added some more detail to sampling. We also hope our response to your comment 9 and implemented changes with the new table 1 in the results helps here.

Comment 4: What was the source of the mortality rates of the general population?

Our response: The sources have been implemented and referenced in the article. “The reference population for calculating SMRs included all residents in Norway aged 25–84 in 2008. Annual number of all-cause deaths in gender-stratified five-year age groups were obtained from the
Norwegian Institute of Public Health (ref), and annual population figures in the age groups 25–84 in 2008 were obtained from Statistics Norway (ref).”

Comment 5: In the measurements section, I am unsure if subjects were excluded or not if they did not answer some or all of the measures. Please clarify.

Our response: We have clarified this by adding more detail to exactly who was excluded from the cox regression analysis in the statistical analysis.

Comment 6: Was age used as a continuous or categorical variable? Please clearly specify all variables and their treatment in the analyses.

Our response: Age was used as a continuous variable, except for when reporting CMRs (where it should be clear in the new table 3 (old table 2) that there are 4 age categories. We also think that it now comes across clear in the new table 1 (based on your comment 9) and in the revised new table 4, with the footnote, that age is used as a continuous variable.

Comment 7: On page 8, lines 5-8: Please provide more detail on which disorders were clustered together.

Our response: We have included this suggestion.

Comment 8: Of 254 patients, 102 died, among those only 20 women. Given this, I am wondering whether the Cox regression models were seriously underpowered. Many interactions were conducted, was this appropriate from a statistical perspective? Please comment or revise.

Our response: Indeed, sample size should ideally be larger for assessing the considered interactions. We might have missed some interactions and possibly main effects. However in the full model containing all considered variables and interactions, only those three kept in the final, AIC-reduced model, showed some tendencies towards significant differences. The final model contains only five main effects and three interactions, and we feel confident that the results are stable even though the sample size is not so large. A rule of thumb of at least 10 events (i.e. deaths) per coefficient estimated in the model holds for our sample. We comment on this issue under the limitations.

Comment 9: I am missing a comprehensive Table 1 with the patient characteristics at baseline by total, AUD alone, Poly-disorder. Please provide.

Our response: This has now been provided. We also included descriptives and bivariate comparisons between living and deceased participants at the 19 year follow-up study, and
deceased with only AUD to deceased with poly-SUDs at baseline in the table to better answer up the first part of aim 1.

Comment 10: Please provide total N for the current Table 1.

Our response: This has been provided

Comment 11: Why are several CMRs and SMRs mentioned in the text, but not shown in Table 2?

Our response: The CMR for those with opioid use disorder have been removed from the text (see our response to your comment 14). The reason for not putting the SMRs for the age groups by time of death in the table was that it looked very confusing with two different ways of categorizing age in the same table (age at baseline for CMR and age at time of death for SMR). Because deaths spread out over the 19 years observation time the numbers of deceased participants in the age-groups based on age at baseline or age by time of death looked strange in the table, and we wanted the table to show baseline variables. Still, we think that SMR in different age-groups by time of death is interesting and compliments the other results, so we wish to include it in the text.

Comment 12: Why are some of the HRs in Table 3 negative? Are sometimes HRs and sometimes coefficients reported? This is very confusing. It is further unclear what the reference group and what the units are (for example, No. of psychiatric symptom disorders). Please specify in the Methods section.

Our response: We realize that our way to present the results may be confusing for the reader. The reason for presenting HR for affective disorder and regression coefficients for other variables in the model is that affective disorder is the only variable not contributing to the interaction terms and HR can be directly calculated. Regarding variables which are a part of interactions, they cannot be interpreted isolated as main effects. This is why regression coefficients and standard errors were presented for these variables. We have now changed the layout of the table and calculated HR for each variable so that all results are presented as HR. After these changes figure 1 becomes somewhat excessive and is removed from the paper.

“Why are some of the HRs in Table 3 negative?” Negative numbers were for regression coefficients, not hazard ratios. The EXP of these numbers would produce the hazard ratio. We reported coefficients for the variables which were part of interaction terms, as the hazard ratio of such variables has no direct interpretation. The negative coefficient values means that the variable is associated with decreased risk of death.

We have added reference group and units into table 4 (the old table 3) and changed the short form “No.” to “Number”.
Comment 13: Results from the secondary analyses introduced in the Discussion should be moved to the Results section.

Our response: The sentence “We investigated this possibility in a secondary analysis by examining only participants who were older than 50 years at death and found that 54% of these participants with poly-SUDs and 67% of those with AUD alone had somatic disease as a principal cause of death, indicating that the difference between the groups is reduced with increasing age of death.” has been deleted from the article. This is not central to the aims of the article and moving this to the Results would clearly seem out of place. Including this simple comparison was just an attempt to discuss and shed light on the speculation in the previous sentence “The differences in principal causes of death between patients with AUD alone and patients with poly-SUDs can be related to baseline differences in age, as somatic causes of death increase with age.”

Comment 14: Page 15, lines 14-22: Please show that people with opioid disorder did or did not differ from other groups at baseline (this is another reason why a thorough new descriptive Table 1 is needed).

Our response: The parts explicitly with opioid use disorder have been removed from the article. Giving more attention to opioid use disorder will distract from the aims of this article, so we think it is better to remove than to expand these parts.

Comment 15: I find the Discussion in general is repeating the results more than it adds to the literature. What clinical implications does the study have? I only find very general statements in the Discussion. Even the Conclusions are mostly a repetition of the results.

Our response: We did try to discuss our findings by comparing them to other relevant international and national research, and to discuss possible reasons for the results based on study design/sample characteristics. Further we conservatively described clinical implications (last paragraph before limitations) and addition to the literature in the last paragraph under limitations. The main reason for this careful approach was that we are presenting a relatively small Norwegian study on an international arena, and do not want to overrate the external validity. We now understand these attempts have not been good enough. We have tried to improve the discussion and conclusions in line with this comment as best we can.

Comment 16: It should be more prominently featured that the analyses were only crudely adjusted for other risk factors for death, which is only mentioned in one sentence in the limitations. Please expand and discuss more.

Our response: This has been expanded some in limitations, and improved in the discussion.

Comment 17: Page 14, line 12: lifetime affective disorder was associated with a decreased…
Our response: Yes, agree and have made the change as suggested.