Author’s response to reviews

Title: Sex differences in dementia: On the potentially mediating effects of educational attainment and experiences of psychological distress

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Author’s response to reviews:

Reviewer 1:

QUESTION/COMMENT: This is an interesting paper attempting to investigate the association of sex differences in dementia by including distress, age and education in the model. The introduction is well written and gives a good overview of the rationale. An interesting read but may need some additional checks.

ANSWER: Thank you for this and for your helpful comments!

QUESTION/COMMENT: On page 6: row 46 I would not talk about the 'effect' of sex but rather the association of sex with dementia. I do think the authors skip a little bit too fast over the age effect. If women reach an older age than men and age is one of the strongest risk factors for dementia and men are no longer part of the statistics because they died of CVD or in fact survived because they did not have CVD risk factors which are also dementia risk factors, then surely age is a major factor as is also shown in the analyses. I would like a little more attention to that age-effect.
ANSWER: The authors couldn’t find the phrase “effect of sex” on p. 6, row 46, but noticed that it occurs in several other places in the manuscript. We definitely agree that it might make more sense to write “the association of sex with dementia”, at least when previous findings/results are discussed more generally. Accordingly – we have changed the wording in a number of places, see e.g., p. 2, row 60.

If we interpret the second part of your comment correctly, it refers to how the “sex > age > dementia link” is discussed in the text. What the reviewer says about (potentially sex-specific) selection effects is certainly correct and now discussed briefly on p. 12, row. 389-392 as well as on p. 11, row 344-347. However, the reason that we do not discuss the age effect in our analysis more in detail is the following: We know that sex is significantly associated with age in the present sample as all men were born in 1930, while the women were born in 1908, 1914, 1918, 1922 or 1930. This is also the main reason why a path between sex and age was specified in the model (i.e., it was primarily added as a control). Given that we know this to be the case, we wanted to be very careful when discussing the role of age-related selection or other age-related risk factors in relation to the sex-dementia association. Simply because our empirical analyses don’t really allow us to draw any conclusions in this respect. We find, however, that this is a theme well worth exploring in the future, not least considering the need for more research on how the relationship between, e.g., cardiometabolic factors and dementia risk varies by sex and age (see, e.g., Nebel et al. 2018).

QUESTION/COMMENT: How valid is the depression question? Why was not a standard questionnaire used?

ANSWER: Previous depression (yes/no), is self-reported and indicates whether or not an individual had suffered from depression prior to the baseline examination, which was considered crucial given the issues related to reverse causality bias. We absolutely agree that data on clinically diagnosed depression earlier in life/before the baseline examination (e.g. from hospital records) would have been preferable but, unfortunately, such data was not available. This is indeed a limitation and we discuss it briefly on p. 12, row 368-372.

QUESTION/COMMENT: My main concern is the lack of crucial other variables such as SES related to education and distress as also outlined in the introduction and related to SES, distress and dementia other in particular CVD risk factors which could have explained the association such as smoking drinking obesity (stress eating) etc and on the other hand engaging in psychosocial activities (exercise, meeting people etc) which could have offset and explained the effects in reverse.

ANSWER: We definitely agree that it would have been very interesting to add more variables to further explore the “causal chain” between education/sex and dementia. As the reviewer notes, it is plausible that CVD factors such as smoking, drinking, obesity etc. could mediate the potential effect of distress on dementia, i.e., education/sex > distress > smoking/drinking/obesity/psychosocial activities > dementia. However, before further such more detailed analyses of mediation are undertaken, we think that the potential link between distress and dementia needs to be more well documented and fully confirmed in the sample used. Unfortunately, as discussed in the paper, the possibility of reverse causality bias prevents such definite conclusions at this stage.
Still, we would encourage future studies, with longer follow-ups, to look further into these issues and, hopefully, our study could constitute a starting point for more fine-grained mediation analyses.

Turning to the question of SES, which is usually operationalized as either education, income, occupation or as a composite of these measures. Because these measures are often highly correlated and ‘reflect overlapping resources in terms of social standing’ (see, e.g., https://academic.oup.com/esr/article/26/4/465/510825), we chose to only include education in order to avoid issues related multicollinearity. Additionally, since SEM requires that paths are drawn between included variables whenever an effect is expected, they can easily become very complex when adding many variables and we wanted to keep this first, explorative model as “simple” as possible. The reason for choosing education over any of the other measures was that it has a more well-established association with dementia. Also, just like in many other countries, substantial gender differences in access to education lasted well into the 20th century in Sweden.

QUESTION/COMMENT: In the results I would have liked to have seen in text the % of women with depression and dementia and difference in education.

ANSWER: Thank you for noticing, the requested numbers have now been added in the text (p. 7, row 194-202).

QUESTION/COMMENT: I am not clear what was done with the FA results and the schema in fig 1. The results could benefit from a good look from a SEM specialist also considering the low numbers of people with dementia. I found them not so easy to follow.

ANSWER: The conceptual model in Figure 1 illustrates the hypothesized relationships between education, sex, general psychological distress and dementia, i.e., it represents the first model that was tested, which was not properly stated in the manuscript. This has now been clarified on p. 8, row 228-230. Aside from that, the authors received a range of detailed and constructive comments concerning methods from Reviewer 3 and have made a number of changes in accordance with these. We hope that these changes facilitated your interpretation and made the section clearer. Also, the limitations associated with the relatively low number of dementia cases are discussed on p. 11 & 12, row 361-368.

QUESTION/COMMENT: I gathered the female sex is related to an older age, lower education and more distress but distress in further analyses and from the table but not fig 2 no longer relates to dementia. So, in the final model, education and distress are no longer related to dementia? For education as the authors surmise that can happen when you include APOEe4. So I am not sure whether we can conclude that the female association with dementia is mainly explained by education and age? Distress itself is associated with the female sex and education but no dementia in controlled analyses? There is also the reverse causality issue of distress being caused by dementia onset which was addressed by the authors.

ANSWER: Thank you for pointing out the need for clarifications! The authors do not propose that the following conclusion is drawn: “the female association with dementia is mainly explained by education and age”. Rather, our main conclusions are the following:
First: Female sex predicts low educational attainment and, in turn, both of these factors predict general psychological distress in older individuals without dementia. Thus, the results underline the importance of attending to education and distress as ‘gendered’ risk factors (or potential risk factors) (see clarifications p. 9, 288-292 & p. 12, row 374-381).

Second: As to education, a direct effect on dementia could not be observed in any of the analyses. However, we suspect that the lack of a significant direct effect could be the result of unmeasured interactions (e.g. with APOE ε4) (p. 10, row 309-316).

Third: It cannot be concluded with certainty that distress mediates the effects of female sex on dementia, although this hypothesis was partly supported by the data (Table 3, M2 + Figure 2). In response to your third question, distress was significantly associated with dementia in the controlled analyses but not when we increased time from baseline to diagnosis (by sequentially excluding dementia cases). By extension, this means that reverse causality cannot be definitely ruled out at this stage (p. 10-11, row 322-342).

Reviewer 2:

QUESTION/COMMENT: This is a timely and sound study. Although there are several limitations which precludes firm conclusions, these are thoroughly accounted for. The present study may encourage further investigations on this topic of interest for a broad audience (researchers, clinicians and the general public).

ANSWER: Thank you!

Reviewer 3:

QUESTION/COMMENT: The authors "seek to shed further light on the complex and multifaceted relationship between dementia and social inequity by exploring the extent to which the effect of female sex on dementia is mediated by differences in levels of educational attainment and experiences of general psychological distress." This is an important question, which has not received as much as attention was one would assume prima facie. As a reviewer of this resubmission, my aim was to improve the impact of the study. All critiques are offered in the spirit of strengthening the authors presentation of their study. Thank you for the opportunity to review your work. I look forward to seeing it published in the future.

ANSWER: Thank you for your helpful and constructive comments!

QUESTION/COMMENT: In the opening paragraphs, it is true that women have greater lifetime risk of dementia, including in Sweden (see Beam et al., 2018). The authors, however, cite that dementia risk is greater in women than men at age 65, but this might not be the case even in Sweden. Beam et al. (2018) found that age 65 rates of dementia risk in a Swedish sample of men
and women were nearly identical. The authors are encouraged to acknowledge these differences in Sweden.

ANSWER: The sentence that you point to (p. 1, row 14-16) does in fact refer to estimates of lifetime risk at age 65. However, this was not entirely clear and a clarification has now been made. Likewise, the reference to Beam et al (2018) has been included in the same section but in relation to the discussion of potential sex differences (and conflicting evidence) in prevalence/incidence.

QUESTION/COMMENT: The authors posit that depression is a plausible risk factor of dementia, a view not widely supported including in the Study of Dementia in Swedish Twins (Brommelhoff et al., 2009). While the authors acknowledge that reverse causality is a plausible rival hypothesis, they are strongly urged to consider depression as a prodromal syndrome of dementia.

ANSWER: The authors definitely agree that the risk factor vs. prodrome debate has been controversial and, as it seems, consensus concerning the direction of causality does not yet seem to prevail (see. e.g., Kivimäki & Singh-Manoux, 2018; Livingston et al., 2018). Indeed – some high-quality studies have indicated that depression should primarily be considered a prodrome of dementia (e.g., Singh-Manoux et al., 2017). Others alike suggest that mid-life depression, or recurrent depressive episodes, does in fact increase dementia risk and thus that it constitutes a potential independent risk factor (e.g., Dotson et al., 2010; Barnes et al., 2013). Moreover, a number of systematic reviews suggest that it might actually be both ways, i.e., while earlier-life depression constitutes a potential risk factor, late-life depression is likely to be primarily a preclinical sign (Byers et. al 2017; Bennet et al, 2014). Finally, in the debate (Kivimäki & Singh-Manoux, 2018; Livingston et al., 2018) following the the Lancet Commission’s report on Dementia Prevention, Intervention, and Care in 2017, the depression-dementia link was one of the themes discussed. In this debate, Livingston et al. state, among other things, that while depression is a probable prodrome of dementia “we do not know it is only that”. All in all, the magnitude of the controversies surrounding the depression-dementia link was poorly referred in the original manuscript and the authors have now, hopefully, made a number of clarifications (p.2, row 32-42). The reference to (Brommelhoff et al., 2009) has also been added.

With that said, “previous depression” is still kept as an indicator of distress in our analyses. The reason for this is twofold and the first part relates to what has been described above, i.e., it appears as if more research is still needed before it can definitely be concluded that depression is only a prodromal sign. Second, our analyses do not focus on depression as such. The latent construct includes only the covariance between the manifest indicators, implying that previous depression should, in the current study, merely be considered an indicator of the more general notion distress.

QUESTION/COMMENT: Karlsson et al., 2009 and Karlsson et al., 2010 (p. 3, line 24-26) are not indexed properly, that is, they are in APA Style. This occurs elsewhere in the manuscript (e.g., p.4). The authors should review the manuscript for style used by BMC Psychiatry.

ANSWER: Thank you for noticing, this has now been corrected.

QUESTION/COMMENT: It is unclear whether excluding the 23 persons with MMSE scores less than 24 reduces the possibility of reverse causality. The listwise deletion of these cases may
introduce unnecessary bias in the study (namely MNAR missing data mechanism), as these persons probably are not a random sample of the population sample. What proportion of these persons were eventually diagnosed with dementia? And does the rate significantly differ from the rest of the sample? If the rate reflects the base rate of diagnosis in Sweden, it seems reasonable to include them in the analytic sample.

ANSWER: The authors agree that excluding these cases (n=31, excuse us, we specified the wrong number in the original manuscript) is unlikely to remedy the issue of reverse causality. However, as MNAR refers to cases where missing data “on a variable Y is related to values of Y itself” (Enders, 2010: 8), we are not sure that the exclusion of these cases would necessarily introduce such bias? 6 (19.4%) of the excluded individuals had developed dementia by 2012 and the corresponding proportion in the full sample was 16.4% (the difference was not significant). In that sense, it might therefore have been reasonable to include them. However, the main reason for excluding these cases was that we wanted to circumvent possible bias in relation to the factor indicators since cognitive impairment is likely to affect the understanding of/responses given to other survey questions. Unfortunately, this rationale was not properly accounted for in the manuscript and has now been clarified on p. 3, row 83-87.

QUESTION/COMMENT: How did the authors handle the APOE E4 e2/e4 allele configuration? Please justify the decision to include/exclude these cases.

ANSWER: The APOE e2/e4 carriers were not excluded from the analysis and the reason for this is twofold. First, while the combined effects of the two differing (ε2/ε4) alleles genotype are yet to be fully understood (see e.g. https://www.sciencedirect.com/science/article/pii/S0149763413002340), a large meta-analysis of clinical and autopsy-based studies showed that the risk of AD was increased also in individuals with the ε2/ε4 genotype (OR 2.6, ref. ε3/ε3) (https://jamanetwork.com/journals/jama/article-abstract/418446). Second, the relative frequency of e2/e4 carriers in the present sample is very small (approx. 1.5%). Thus, given that current evidence concerning the effect of the ε2/ε4 genotype on AD risk, and the vast empirical evidence to support the increased risk implied by ε4, the ε2/ε4 carriers were kept in the analysis. A clarification of this has been made on p. 4, row 111-115.

QUESTION/COMMENT: Given how loneliness was coded, the authors should characterize loneliness as chronic loneliness. For example, persons who report feeling lonely for less than 5 years are, nevertheless, still lonely at time of data collection.

ANSWER: Thank you for pointing this out, changes have now been made in accordance with your suggestion.

QUESTION/COMMENT: What proportion of data were missing? Can the authors supply arguments (i.e., univariate t-tests; Enders, 2010) for whether the missing data mechanism is MAR or MNAR? That is, what are the correlates of missingness in the model. And were these correlates included in the imputation model? What was the imputation procedure used (e.g., data augmentation or multiple imputation with chained equations? Data augmentation assumes that all variables have the same distribution, but this seems an unwise decision given the mixture of nominal and ordered categorical responses included in the data table. How many iterations were
required for the missing data algorithm to converge? Finally, what was the rationale for using only 5 imputed data sets? The general consensus is to use as many imputed data sets as the mean percentage of missing data in the data table. Increasing the number of imputed data sets will improve precision of the standard errors and may encourage confidence that hypothesis tests were unbiased.

ANSWER: The proportion of missing data for included variables is the comments below Table 1. The highest rate was found for longstanding stress (12.4%) and the lowest rate was found for depression (0.4%). As noted by Enders (2010: 17) “MCAR is the only missing data mechanism that yields testable propositions” (e.g. by means of univariate t-tests). This, however, was not considered applicable in our case, given that we had good reason to believe that the missingness in our data had not occurred completely at random (MCAR). Through bivariate logistic regressions it was confirmed that missingness in, e.g., stress was predicted by depression. Accordingly, a range of predictors other than those included in the CFA/SEM were used in the imputation procedure, e.g., SES (occupational class), sleep and current depression. Multiple imputation was carried out using Bayesian estimation where data is generated from an MCMC (Markov chain Monte Carlo) simulation and imputed using an unrestricted H1 model. Three such different models are available in MPlus, all of which allow a combination of categorical and continuous variables. The present study uses the default, i.e., the Variance-Covariance model (for more details, see: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.570.9342&rep=rep1&type=pdf). 18000 iterations were needed for the algorithm to converge. A brief clarification has been made on p. 6, row 173-175.

The use of 5 datasets was motivated by a simulation study by Asparouhov & Muthén (2010), which concludes that increasing the number of imputed data sets from 5 to 50 when using the WLSMV estimator does not improve the results (http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.570.9342&rep=rep1&type=pdf).

QUESTION/COMMENT: TLI and CFA both are incremental fit indexes. Because they are highly correlated, only one should be reported (typically the TLI is more conservative and preferred).

ANSWER: Yes, this is true, CFI is no longer reported in the manuscript.

QUESTION/COMMENT: The modification indices seem to suggest that a one-factor model may be too simplistic, as including residual correlations suggests a multifactor solution. The authors might present an exploratory factor analysis to identify whether a single factor solution is adequate. One possibility is that the latent variable is not really one "psychological distress" variable, but rather two variables that may index social connection and depressive symptomatology.

ANSWER: First, it should be noted that the one-factor solution was theoretically motivated, i.e., we hypothesized that the five indicators could be united by the more general notion distress, which is the focus of the present study. Thus, even though it is plausible that “sub dimensions”/single items such as depressive symptomatology and social connection are separately associated with dementia, we wanted to investigate their commonality and joint association with on the one hand female sex/education and, on the other, disease occurrence. Also, given the small number of items
a one-factor solution with added residual covariances was deemed more appropriate since 3 or more items per latent factor is generally recommended (see, e.g., Brown 2012).

With that said, we conducted an exploratory factor analysis to explore the possibility of a 2-factor structure (results not shown in the paper as it is somewhat beyond of its scope, but is available upon request). The results demonstrated that although the overall fit of the 2-factor model was good and on par with that of the 1-factor solution (incl. residual covariances), there were several cross loadings and the factors were highly correlated (approx. 0.6). For instance, F1 was significantly related to 4/5 items and F2 was significantly related to 3/5 items. Thus, given the theoretical rationale outlined above, we decided to continue with the 1-factor solution and instead include the residual covariances.

QUESTION/COMMENT: Age and cohort appear to be conflated. How was cohort taken into account? It also seems strange to include age as a mediator? Might it be worth testing whether age is a moderator of the effect of education on dementia rather than mediator?

ANSWER: Yes, the authors agree that this should be clarified. The variable included in the analysis is “age at baseline”, not cohort. However, because the sample is drawn from a birth cohort study (1908, 1914, 1918, 1922, 1930) the age variable is, in a sense, “grouped” by cohort. Since adding both measures would introduce unnecessary multicollinearity to the model, and given that the study does not focus on cohort effects, only age was included. In order to avoid confusion, the age-variable, instead of birth year, is now included in the descriptive Table 1. As to the “age as mediator question”; we agree that it seems strange to look upon age as a mediator and do not propose that such a conclusion should be drawn. However, because SEM requires that paths are drawn between included variables whenever an effect is expected, and given that we know sex to be significantly associated with age in the present sample (all med born in 1930, women born in 1908, 1914, 1918, 1922 or 1930), a path between sex and age was specified. A clarification has been made p. 8, row 232-234. We also agree that the potentially moderating effect of age on education would be interested to examine, yet find it to be somewhat outside of this study’s scope.

QUESTION/COMMENT: Please report unstandardized regression parameters from probit analyses. In analyses with binary dependent variables and binary covariates, it is easier to interpret unstandardized results, which do not depend on the variances of the covariates.

ANSWER: Yes, the authors completely agree and have made changes accordingly (in all results tables and in the text). Thank you for noticing.

QUESTION/COMMENT: In the tables, please report point and interval estimates rather than point estimates and p-values. Probability values do not allow for conclusions to be drawn about the precision of the point estimates.

ANSWER: Again, we agree and have included CIs in all result tables.

QUESTION/COMMENT: The authors suggest that lack of power may have caused effects of distress on dementia may have vanished when time to diagnosis of dementia was increased. What was the overall power to detect hypothesized mediating effects given the sample size?
ANSWER: The authors agree that the term power was used somewhat sloppily here and it has now been removed (p. 11, row 342-343). We have not conducted a power analysis of our own because, as shown by Fritz & MacKinnon (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2843527/), a sample size of approx. 660 (ours is 861 in the structural models) is sufficient for power 0.8 when using the Sobel test, even when effects are small. Mplus uses the delta method, which in most cases is equivalent to Sobel, see e.g. here: http://www.statmodel.com/discussion/messages/11/9365.html?1396831771 and here: https://www.statmodel.com/download/Delta%20method%20and%20Sobel.pdf). Moreover, the only test for mediation that might require a sample size larger than what we have is Baron & Kenny’s (1986), which we do not use (Fritz & MacKinnon, 2010).

QUESTION/COMMENT: The discussion section mainly summarizes the findings presented in the results. Could the authors provide implications of their finding that age and psychological distress mediate effects of female gender on dementia risk whereas education does not? Further, what are the implications that education mediates effects of female gender on psychological distress, which then has a direct correlation with dementia risk?

ANSWER: Indeed – practical implications of the study findings were not explicitly discussed in the original manuscript. The reason for not doing that could be summarized as follows:

We find that there are limitations that preclude more definitive conclusions (such as “age and psychological distress mediate effects of female gender on dementia risk whereas education does not”). First and foremost, the limitations concern the possibility of reverse causality bias (see also the discussion on interaction effects on p. 10, row 312-316 and the response given to reviewer 1 above about the age effect). Thus, we find that presenting such firm conclusions and potential implications thereof might be somewhat premature. Therefore, at this stage, the main implication of our findings would be that they underline the importance of attending to both education and distress as ‘gendered’ phenomena when considering the nature of their association with dementia - in future studies as well as in clinical practice. A clarification has been made on p 12, row 378-381. Finally, our hope is to encourage further investigations of the current hypotheses (see p. 12, row 386-389).