Author's response to reviews

Title: The impact of imprecisely measured covariates on estimating gene-environment interactions

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Author's response to reviews: see over
Robert Lyles

We want to thank the reviewer for his detailed comments and in particular for going to the lengths of replicating our simulations. We address each point in turn.

General

We have highlighted the importance of our main finding that confounder measurement error does not influence the estimate of the interaction, though we have been careful to phrase this more precisely and in context, in keeping with comments by Ian White. (page 14)

Major compulsory revisions.

Scenario 1

1. The reviewer is correct that we do assume genotype to be independent of both the exposure and the confounder. We believe that this is generally reasonable in most epidemiological settings, because it is unlikely that genotype will influence an environmental exposure such as dietary intake, or an environmental confounder that is associated with the exposure and the outcome. Similarly other potential confounders such as age or sex are unlikely to be related to most genotypes under study. This appears to be acknowledged by comments by Ian White, but in line with both reviewers’ comments, we have stated the assumption more explicitly, and with further justification in the discussion. (page 14 i)

2. We are pleased that our simulations were presented clearly enough for the reviewer to replicate them. We think the difference between our findings are because we made a typo when we said the residual error was ~N(0,2). We meant ~N(0,4) so that the residual standard deviation is 2, not the variance. We get the same findings as the reviewer when we use the incorrect value stated in the manuscript. We have now corrected this in the text (page 5). We formatted our results to 2 decimal places, and at this level the slight variation in the standard errors is not apparent. However, to more decimal places, we agree that they are smallest when the measurement error variance for the confounder is zero (as you might expect). We now include the standard errors in the table, including more decimal places. (table 1)

Scenario 2.

Our typo for the residual error persists in scenario 2, and we think this explains the discrepancies with the reviewer’s simulations.

Now regarding the empirical standard deviations of the estimates of beta2 and beta3. We were aware of this and were hoping to include the solution in with other work. However, given that this has been noted here, and that the regression calibration results have been queried by another reviewer (see Ian White’s comments), it would appear more appropriate to deal with it here. Actually, beta2 is fine (allowing for sampling error); it’s beta3 that’s the problem. This problem is caused by the preponderance of zeros in the interaction component, introduced by multiplying the
dummy variable for genotype by the continuous exposure. As the reviewer says, this violates some of the assumptions behind the regression calibration algorithm. The result is that the regression calibration gives the poor estimates that Ian White queries in the illustrative example. Our simple solution is to treat the interaction component, not as a separate variable measured with error forming a second variable to calibrate in the regression calibration, but to base it on the fitted values derived for the exposure variable. This approach provides a function that meets the requirements for regression calibration. Comparing standard regression calibration with my adaptation on the data simulated in scenarios 1 & 2 backs this up. (Note that Stata’s rcal command has a bug in it when more than two error-prone variables are included, so you need to write your own code to perform the regression calibration). Of course, this only works if genotype is assumed to be measured without error. This assumption is likely to be much closer to the truth than assuming the exposure is measured without error, and is not without parallel. It is my understanding that Nick Day and colleagues perform a similar trick with their regression calibration for the EPIC data when they have a large proportion of non-consumers (e.g. meat intake). We have altered the text accordingly (page 8).

Minor essential revisions.

a) Indeed the estimates of beta4 are heavily biased. We have now commented on this in the text (page 9).

b) We have now added several references on the effect that measurement error in a confounder has upon the estimated regression parameters for the exposure, and on power (page 9).

c) The models assumed by the reviewer for generating data and the models fit to the data are correct, and we have made this more explicit in the text for each scenario (pages 6 and 7).

d) We have added more detail to the tables, as suggested (tables 1-3).

Discretionary revisions.

i) We have extended the simulations to binary data and have added a comment on these in the discussion (page 15 iv).

ii) We agree that the ratio estimator is rarely used in practice. However, we felt obliged to comment on it because the paper most closely related to ours makes use of this way of presenting the interaction effect [Wong et al 2004, ref 34]. At first glance our paper appears to contradict some of the findings in Wong et al. and we wanted to make clear that this was because their conclusions are based on the ratio estimator, rather than the standard interaction term coefficient.
We wish to thank the reviewer for her thoughts and relating our findings to practice. We address each point in turn.

General

We agree with the reviewer that our results are applicable more widely than just gene-environment interactions, but could also apply to any interaction between 2 variables – one continuous with measurement errors, and the other binary without measurement errors, where the binary variable is independent of the confounder. We believe genotype will often be independent. However, if the binary variable is not independent of the confounder, then we might expect different findings. Similarly, if the binary variable is not genotype, then not only is there more chance it will be correlated with the confounder, but we might also expect this to be more prone to measurement error itself. So we are happier restricting our comments to gene-environment interactions where we can be reasonably confident the binary variable is not subject to much measurement error, and is independent of the confounder. For example, I think that many apparent concentration biomarkers of dietary intake could be subject to some genetic influence.

Major compulsory revisions.

a) We have extended our simulations to the situation where the binary variable (genotype) is measured with error. It behaves just like any other error-prone exposure, contributing an additional component of error to the estimates. Whilst plausible, and certainly more likely than some laboratory researchers would have us believe, it is however not unreasonable to assume it is measured without error. We have commented on this situation in the text (page 15 v).

b) We have already looked at this situation, but the resulting tables became very large for very little additional value. The results are much as you would expect given the results for exposure measurement error alone and confounder measurement error alone. We would be happy to include a comment to this effect in the text if the reviewer thought it beneficial.

c) We have extended our simulations to investigate the situation described by the reviewer. Measures of dietary intake such as food frequency questionnaires, food diaries and 24-hour recalls, will have components of bias and attenuation compared to the true intake (along with the more problematic person-specific biases). As you would expect, the bias and attenuation components add an additional source of error that leads to bias under all simulated situations. However, given a suitable instrument for validation (e.g. biomarker) measured without bias / attenuation, but with a simple random error, regression calibration can still be used. We have added some discussion on this (page 14 ii).

Minor essential revisions.

1) We accept that it was inappropriate to say that food diaries and 24-hour recalls measure diet “very precisely”. What we meant was that they may be more precise
than food frequency questionnaires, but cover a very short period of time, so are imprecise when used to infer long-term intake. We have modified the text accordingly (page 3).
We would like to thank the reviewer for his very detailed comments and advice. We address each point in turn.

General

The first reviewer encouraged an even broader interpretation than we have made, whilst this reviewer has urged a more cautious interpretation. We have tried to satisfy both viewpoints by specifying the situations in which our results hold more carefully and giving a little more theoretical reasoning behind them. This will hopefully allow the informed reader to decide the extent to which our results are applicable to any particular situation.

Major compulsory revisions.

1)  
   a) We have added the theoretical explanation for our findings (pages 10 and 15).

   b) To maintain the focus of our paper on the topic of gene-environment interactions, we have opted not to extend our simulations to the more complicated models including gene-confounder interactions. Instead, we have included a brief discussion of that situation (page 15 iii).

   c) As suggested, we have included discussion of other situations in which confounder measurement error matters (pages 14 and 15).

   d) We agree that our conclusions are only appropriate in the context described and we have rephrased our conclusions accordingly to avoid misinterpretation (page 14, 15 and 16).

2)  
   a) As suggested, we have included more explanation of our findings in terms of subgroups (bottom of page 15).

   b) We agree that our results assume that genotype is independent of the exposure and confounder, and we have included the additional point that this includes independence from the exposure variance and exposure error variance (page 14 i).

3)  
   a) We have corrected the text of the abstract as suggested (abstract).

   b) We agree with the reviewer’s caution on interpreting the main effects in the presence of interaction. We have now defined what we mean by main effect in this setting (page 8), but for the purposes of this paper we prefer the usual approach of comparison with a referent category rather than with an average effect over the two categories. Our main focus is on the interaction term itself.
4) We agree that the term “power” here is inappropriate and have rephrased the text accordingly throughout the text, and included a brief explanation (page 9).

5) The reason is because standard regression calibration is not actually appropriate in this situation and our suggested solution was left for a later paper. Please see our response to Robert Lyles’ comment on scenario 2. We have re-analysed the example using our adapted regression calibration and updated table 4 and the accompanying text accordingly (page 8, table 4).

Minor essential revisions.

6) We now state this assumption more explicitly (page 14 i and page 16).

7) We have removed this phrase (page 6).

8) We have corrected the order the FFQs are introduced (bottom page 7).

9) The reliability ratios were based on the covariance matrix and measurement error matrix from the (multivariable) regression calibration. I have clarified this in the text and hope it answers the reviewer’s point (page 11).

10) We have rephrased this (page 11).

11) We have corrected this (table 3).

Discretionary revisions.

12) The Monte Carlo error is low and we have now included this in the text (page 10, tables 1-3).