Author's response to reviews

Title: Environmental exposures and their genetic or environmental contribution to depression and fatigue: a twin study in Sri Lanka

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Author's response to reviews: see over

The Editor
BMC Psychiatry

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Dear BMC Psychiatry Editor,

Please find attached the revised version of our article 'Environmental exposures and their genetic or environmental contribution to depression and fatigue: a twin study in Sri Lanka' for your consideration for publication in *BMC Psychiatry*. We have addressed all of the points raised by the reviewers in turn.

Reviewer: Margaret Gatz

This reviewer acknowledged that the body of the manuscript now addresses the issue of the measure of depression being retrospective, but requested that we additionally mention it in the abstract (methods). We have now modified the abstract to draw attention to the lifetime-ever status of the depression assessment, and the possibility of reverse causation. Further, the reviewer requested that we do not refer to "co-occurrence" between depression and fatigue in the discussion, given that the episodes could have been years apart. We have instead refereed to these outcomes occurring in the same individual (p19).

The typo on p20 has been corrected.

Reviewer: Marieke Wichers

No further comments were received.

Reviewer: Yoon-Mi M Hur

1. The reviewer suggested moving Table 1 to the Discussion. We have not done this because it displays empirical findings and so should be in the Results section. However, we have additionally discussed these correlations in the Discussion on p21.

"Also, the environmental exposures correlated with one another to some degree; but rather than appearing to be a generalised effect of poverty, we found evidence of independent environmentally-mediated associations of early school leaving, standard of living and life events with depression in men."

2. The reviewer commented on the high participation rate (91.7%) in the Cotass study, and asked about payment of participants. We have described the compensatory payment (offered after the interview was completed) on p8:

"A payment of 300 Rupees (approximately £1.50) was offered in compensation for participants' time, at the end of the interview (compensatory payment was not mentioned in the information provided prior to the interview). A substantial percentage of the participants refused the payment and instead requested it to be donated back to the research project."

3. The reviewer again requests that we test GE interaction models, given that the sample size of 2000 is not small. While this would be a very interesting set of models, we maintain that we cannot perform these models because the specific details of our data mean they would be underpowered, as described below.

- The three studies mentioned by the reviewer ([1-3]) all used continuous measurements of their phenotype, whilst we used a categorical definition. It has been explained that univariate models using categorical data require substantially larger samples for adequate power [4] in particular where the prevalence of the disorder is low.
- The interaction model for our three categorical environmental exposures would essentially require us to run models that split participants into groups based on exposure, and compare the ACE contributions between exposures (i.e. comparing twin pairs in which both members were exposed, to those in which both members were not exposed). This is an "environment-limitation" model, similar to what is done to compare parameter sizes in male-male pairs to those in female-female pairs. This would lead to small counts in the contingency tables required for the calculation of biserial correlations in a liability threshold model. These small counts are displayed in Table 1. For each environmental exposure, there would be cells with counts of less than 5. The standard advice when using two-by-two contingency tables is that chi-square based tests will be inaccurate if any cell counts is less than 5 [5], and this would affect the fit statistics calculated in SEM. Table 1 pertains to females only (the situation is even worse in men, due to the lower prevalence of depression).
- The fourth exposure, parental care, was measured as a continuous variable, but a GE moderation model is still highly unlikely to have sufficient power. This is because a univariate SEM model of our depression phenotype (without any moderation parameters) could not be calculated due to small numbers in cells among the male participants (e.g. only 4 concordant depressed MZ male pairs and 4 concordant depressed DZ male pairs [6]). This was one of the main reasons we used logistic regression analyses rather than SEM (as described in the letter accompanying the previous submission of this manuscript).

We therefore regret that our sample size is too small to perform the GE interaction models. However, we have now mentioned in the Discussion the studies that show that such interactions exist in other samples where such testing is possible (p 21).

Table 1: Small counts in each cell of contingency tables, if a GE interaction model were to be attempted (females only)

	Groups of twin pairs according to depression status	Counts of twin pairs according to environmental exposures (these figures correspond to cells in contingency tables)					
		Standard of living		**Early school leaving**		**Life events**	
		Both exposed	Both not exposed	Both exposed	Both not exposed	Both exposed	Both not exposed
MZ	Tw1 D Tw2 D	4	18	6	18	10	5
	Tw1 D Tw2 N	0	20	11	14	6	12
	Tw1 N Tw2 D	4	31	18	16	9	16
	Tw1 N Tw2 N	56	264	92	205	45	234
DZ	Tw1 D Tw2 D	2	4	7	1	3	3
	Tw1 D Tw2 N	9	21	9	13	7	9
	Tw1 N Tw2 D	1	16	6	12	3	10
	Tw1 N Tw2 N	31	163	63	115	17	146

MZ = monozygotic; DZ = dizygotic; Tw1 = twin 1; Tw2 = Twin 2; D = depressed; N = not depressed. So, the first row first column refers to a count of 4 twin pairs who have both had depression and both been exposed to poor standard of living.

The manuscript is intended as a full-length article and is not being submitted for publication elsewhere. All authors have read and approved the current version of the manuscript. Contact details for the corresponding author are as follows:

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We look forward to hearing from you.

Yours sincerely,

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5. Cochran WG. **The [chi-squared] test of goodness of fit**. *Annals of Mathematical Statistics* 1952; 25:315–345.

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