Author's response to reviews

Title: Interplay between heritability of smoking and environmental conditions? A comparison of two birth cohorts

Authors:

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Version: 2 Date: 18 April 2011

Author's response to reviews: see over
Reviewer's report
Title: Interplay between heritability of smoking and environmental conditions? A comparison of two birth cohorts
Version: 1 Date: 15 March 2011
Reviewer: Jason J.D. Boardman

BMC: Interplay between heritability of smoking and environmental conditions
This is an interesting paper that builds on a body of work examining cohort variation in biometric estimates for smoking onset. The extension to this cohort is new and the use of data from the Netherlands is also important. It is a fairly basic set of analyses and they find comparable heritability estimates for both cohorts. Based on this evidence they suggest that the genetic influences on smoking are not susceptible to changes in the smoking environments for the two cohorts and thus, this environmental factor may not be relevant to the GxE research on smoking.

I have two main issues:

1. They need to be very clear that this is not a replication of Boardman, Kendler, or Heath, per se. These are two very different cohorts in very different social contexts. Moreover, it would be useful to provide some tentative speculation about why they might not have seen the same results.

We now discuss the three papers more comprehensively and compare their results with ours more systematically (discussion page 11-12).

2. Very little is made of the theoretical reasons for why they would expect gender differences for this cohort in this context. This is potentially very interesting but it gets lost as a modeling exercise rather than a scientific question. The environmental terms for women are very different from those of men. This needs to be discussed.

For the present study, our main aim was to explore cohort differences in genetic architecture (within sex) because the prevalence of smoking decreased with time. We agree with the reviewer that gender differences are potentially interesting and we added some sentences about this issue to the discussion, page 14.

3. There is not enough information provided about the models. Typically researchers provide model fit statistics (AIC/BIC/-2LL, etc.) for the different models (A, AE, ADE, etc.). This is simply one univariate model and based on the confidence intervals, I would imagine that they could drop the C estimate for the latter cohort. If my back of the envelope estimates are correct, most of this .06 (for men) would go to the A term and you’d have evidence for a higher heritability in the most recent cohort. Given that this is such a short window of time compared to the other studies, this change is reasonable and it is in line with Boardman but not Kendler. This is worth investigating more thoroughly.

We agree with the reviewer, and we added a table with model fitting results (Table 4).
The reviewer suggest that the C estimate for men in the 2009-10 cohort could be dropped. Our main question was whether there were cohort differences, so we first compared the cohorts. The estimates for A, C and E were not significantly different in both cohorts (within sex). Because the cohorts were not significantly different we combined the data (generating more power) and then tested for sex difference in genetic architecture. We used a p-value threshold of 0.01 and formally equalizing ACE for men and women did not deteriorate the fit of the model (P=.0195). However, we discuss that this test is borderline significant (discussion, page 14). Next we tested whether A or C could be dropped from the model, but this caused a significant deterioration of the model (see table 4).

4. Much more information needs to be provided about the design of the study.

We added information on the design of the study to the Method section page 5 (general info on NTR) and on page 7 (twin model/genetic analyses).

5. Some have made a case that regular smoking only makes sense as an outcome when you consider that people have to try it first. There are comparable multinomial models that can be assessed in which never, tried but stopped, tried and progressed to smoking can be assessed. There are different genetic factors that are linked to initiation (novelty seeking, etc.) versus dependence (nicotine metabolism, etc.). More could be made of this fairly simple dependent variable.

We agree with the suggestion of the reviewer that measures like nicotine dependence have to be explored in bivariate models including smoking initiation since the genetic liability for nicotine dependence is unknown in subjects who never started to smoke. In the present study we used data on smoking initiation (did you ever smoke) in a rather young sample (18-25) because we were interested in the genetic architecture of the uptake of smoking since we noticed that the prevalence of smoking largely decreased in the past 15 years (as a consequence of policy changes). We agree that it would be interesting to study cohort differences for other phenotypes as well, as we discuss on page 14.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being Published
Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer's report
Title: Interplay between heritability of smoking and environmental conditions? A comparison of two birth cohorts
Version: 1 Date: 11 March 2011
Reviewer: Nick G Martin

Reviewer's report:
This is a highly interesting paper that makes use of a policy change towards smoking in the past 20 years to explore genotype-environment interaction. A rich dataset of twin data collected 1993-1995 and in 2009-2010 on 2 large birth cohorts was available (twins received the same questions about smoking in the 2 surveys).

A clear decrease in smoking prevalence was observed. Is this decrease comparable to what is seen in the Dutch population in general?

Yes, this decrease is comparable to what is seen in the Dutch population in general. We mention this in the discussion on page 11:

*The observed decrease is in line with other studies in the Netherlands (a decrease of smoking from 38% to 30% for man and from 30% to 26% for women, from 1991 to 2009, www.stivoro.nl).*

Also could the authors comment on how representative their samples are? (how were they ascertained)?

A sentence on the design of the NTR including a reference to a paper that describes the NTR more thoroughly was added to the method section, page 6. We also refer to 2 papers that show that the non-response bias in the NTR sample is rather small (method, page 6).

The main outcome of the GxE interaction analyses was that the heritability was the same in both cohorts. This is a remarkable finding; are there any comparable results (for other phenotypes that show changes in prevalence over the past 20 or 30 years?)

On page 11/12, we discuss other studies exploring the heritability in cohorts with different prevalence for smoking but those studies have a different social context, and none of the studies used data of 2 cohorts with the same age, but measured 15 years apart (like our study).

As far as we know, there are no comparable results for other phenotypes. We did explore this phenomenon for alcohol in our own data and we added a sentence to the discussion (page 13) regarding this result:

*In the data of the NTR, we observed a change in the prevalence of alcohol use in the past 15 years (an increase instead of a decrease). The heritability for alcohol use (alcohol initiation, frequency and quantity) was stable over the cohorts [28]. Those results are in line with our results on smoking initiation and suggest that changes in environmental factors causing a change in prevalence not automatically lead to change in the genetic architecture.*

I recommend immediate publication

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests
FURTHER REQUESTS:

1. We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional copyediting service. It is important that the quality of language is of a high standard so that the case can be clearly understood and fairly assessed by the referees.

If you wish to use a professional editing service, BioMed Central recommends Edanz; please contact Edanz directly to make arrangements for editing, and for pricing and payment details. Note that use of an editing service is not a guarantee of acceptance for publication.

We carefully checked the language in the paper.

2. The Editors would also like to request you to document the manuscript whether the data used for the study was publicly available, otherwise we require the name of ethics committee which approved it.

The data originate from the data collection of the Netherlands Twin Register. All the NTR-work with human subjects is reviewed by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam, an Institutional Review Board (IRB) certified by the US Office of Human Research Protections (IRB number IRB-2991 under Federal wide Assurance-3703; IRB/institute code NTR 03-180).

We added this sentence to the method section, page 6.