Author's response to reviews

Title: A Common Genetic Factor Underlies Hypertension and other Cardiovascular Disorders

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Version: 2 Date: 24 May 2004

PDF covering letter
Dear Mr Hodgkinson,

Thank you for your e-mail of 8th April and for the links to the helpful comments made by the reviewers. As we discussed by e-mail, we are now resubmitting this manuscript to Biomed Central so that it reaches you before 1st June 2004.

Please find below responses to each of the points raised by the reviewers and attached the revised manuscript with highlighted changes. We very much hope this revised manuscript will be found suitable for publication on the BioMed Central website and look forward to hearing your responses.

Yours sincerely,

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In Response to Andreas Wienke

1. comma inserted after (HPT) as requested (highlighted)
2. reference 6 revised and improved: the number of twins remains in the results section and the word 'female' added for clarification (highlighted)
3. the typo AND ("page 1, line 7 from bottom") I cannot find
4. the reviewer requests that numbers be written out in full rather than numerals: this has been done in the methods (highlighted) but seems inappropriate for results and tables
5. prevalences and heritabilities from the other papers have been inserted (highlighted)
6. reference 6 revised and improved (highlighted)
7. Cederlof has been changed to Cederlöf (highlighted)
8. reference 20 is taken from a PhD thesis and has 3 authors (Dutch thesis)
9. reference 21 does not contain a typo: the Pubmed listing is "chromosome 17"
10. reference 22: the typo in "generalisability" has been corrected (highlighted)
11. reference 23: there is no typo in "Snieder"
12. a single blank page has been removed.

Discretionary Revisions

In improving the Twin Register reference, further information about the registry has been provided.(see point 2 above). The details of the analysis and models examined (standard methods) already runs to over a page and three figures: a small amount of further information has been added (highlighted).

In the last section we have already addressed the important point of whether these results pertain to singletons (paragraph 2). We are grateful for the point raised by Andreas Wienke about differences between volunteer and population-based twin registers. The main limitation with volunteer twin registers is that they contain a higher proportion of females and monozygotic twin pairs. It is now more clearly stated that only women were recruited (highlighted) and similar proportions of MZ
and DZ twins were studied. As regards the 'healthy volunteer' effect, we have added a comment to the discussion about this. We do not believe it have biased our results as trait prevalences are similar to population prevalences (inserted and highlighted).

**In Response to Michael Russell**

While we agree that the four phenotypes are "complex diseases or... syndromes" we do not believe that this makes them unsuitable for this kind of study. As this is the first study of its kind, we intentionally 'cast the net wide' in order to include both migraine with and without aura, all forms of hypertension (essential hypertension being much the most prevalent), primary and secondary Raynaud's and coronary disease of all aetiologies. All the syndromes are known to be multifactorial and they are thought polygenic in nature. This broad-brush approach, therefore, would make it less, rather than more likely to detect any underlying genetic component to the phenotypes. We accept that the questionnaire used to detect migraine was indeed validated in a clinic setting but it is based on the widely used International Headache Society criteria and researchers carefully followed the guidelines for ascertaining migraine. It was not possible in this study for physicians to interview twins by telephone to confirm the diagnosis, as has been done in previous studies of migraine.

We agree that the cited papers describing an association between migraine and Raynaud's have a small sample size. However, this finding has been reproduced in several different settings and our own dataset provides strong evidence of an association using a large sample.

Having recognised that the trait ascertainment has some limitations, we disagree that it seems "not interesting" to test a non-population sample as described by the reviewer. As mentioned in the manuscript, we have explored the possibility that the twins differ from the normal population and found little evidence to support this criticism (paper reference 23, Andrew T et al). As mentioned above in response to Andreas Wienke, trait prevalences were in keeping with population studies (added prevalences, highlighted). The limitations we acknowledge make it all the more surprising that the modeling in Mx provided such strong evidence of an underlying common genetic factor.

**In Response to Jane Olson**

A table of descriptive statistics of the phenotypes has been inserted (table 1, highlighted).

We agree that the "crux of the paper is the correlations among the phenotypes" and thank Jane Olsen for suggesting further discussion of this point. We do not believe reporting bias is likely to increase reporting of second conditions in twins having a first condition, except possibly for the co-existence of hypertension with coronary artery disease. We have added discussion of this potential bias (highlighted). In addition, we have previously examined recall of soft tissue rheumatic conditions at different times and compared it to case notes, finding no significant difference (Hakim et al: 1). Further, the manuscript has been criticised on the grounds that the evidence of association between the phenotypes is weak. It seems unlikely that debate
of such a specialist nature would be widely available in the public domain sufficient
to influence twins reporting these conditions.

As far as we know, there are no genome scans or candidate gene association studies
examining all four phenotypes, though we would argue that this study provides the
rationale to perform such work. Discussion of the literature was limited to the
individual traits and their candidate genes for this reason.

Discretionary Revisions

Thank you for pointing out that BMI may be a covariate. We have examined this and
found that it is associated positively with hypertension and migraine, negatively with
Raynaud's and is not associated with coronary artery disease, in our dataset. We have
taken Jane Olson's advice and adjusted for it in the odds ratios of the cross trait
variations (now Table 2). Because it made little difference to the size of the odds
ratios, it was not included in the Mx modeling.

References

1. Hakim AJ, Cherkas LF, Spector TD, MacGregor AJ. Genetic associations between
frozen shoulder and tennis elbow: a female twin study. Rheumatology 2003; 42: 739-
742.