PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	CHILDHOOD ADVERSITIES AND ADULT-ONSET ASTHMA: A COHORT STUDY
AUTHORS	Korkeila, Jyrki; Lietzen, Raija; Sillanmaki, Lauri; Rautava, Paivi; Korkeila, Katariina; Kivimaki, Mika; Koskenvuo, Markku; Vahtera, Jussi

VERSION 1 - REVIEW

REVIEWER	Scott, Kate University of Otago, Dunedin, Department of Psychological Medicine
REVIEW RETURNED	14-Jul-2012

GENERAL COMMENTS	This study has been very well done. The associations of childhood adversities with onset of asthma and other health conditions is an area of increasing interest. As the authors note, there are very few prospective studies in this area, especially with baseline information on mental health, a range of other risk factors and objective information about asthma diagnosis. The study therefore makes an important contribution to the topic. There are a couple of issues requiring further information or comment. 1. The main methodological weakness is the low response rate (effectively 37%). This is discussed in the paper and the authors conclude that selection bias "is an unlikely explanation for our findings" on the basis of a non-response analysis in which "there were no significant health-related selective factors among respondents and non-respondents of the survey". It is not clear what they mean by the non-response analysis - this is mentioned but not detailed in the Methods section. Did they actually sample non respondents and get information on baseline indicators eg. mental health status to enable comparisons with survey responders? More detail needs to be provided on this. The second issue is the possibility that the strength of the contribution of psychiatric disorder (as mediator/confounder) to the associations of childhood adversities with asthma onset may have been underestimated. One reason for this is the low response rate as mentioned above - given the tendency for healthier people to be more likely to take part in surveys, it seems probable that the survey sample would under-represent the mentally ill. The second reason is that mental health was only measured at baseline. So all those who had episodes of mental ill-health between baseline and follow up, or prior to the baseline assessment, will be included in the reference group of non-mentally ill for this part of the analysis. This would have the effect of attenuating the association between mental disorders and asthma.

	These issues need to be commented on further in the Discussion section.

REVIEWER	Bartley, Mel University College London, Epidemiology and Public Health
REVIEW RETURNED	24-Jul-2012

GENERAL COMMENTS	This is a well written paper that makes excellent use of the kind of data available from Nordic registers. I have 3 slight concerns. (1). Do I understand that the participants in the study were the stated ages at the time they were recruited? If so this means that they will be remembering their childhood adversities at very different amounts of time subsequent to childhood. So these might be remembered better by some than by others. Also, was the onset of asthma measured subsequent to recruitment or was it taken from register data over the whole life course of all participants? Onet at age 25 might have a different aetiology and risk factors than onset at age 55. (2) The biggest attenuation takes place when mental health varables are entered into the model. It is not clear from the text how the authors regard this in terms of their research question. I would have thought that this could be used as evidence in favour of a psychosocial theory. (3) The childhood adversity items mix material with psychosocial adversities (low income, fear of a family member). Does material hardship play a part in the aetiology of asthma (I am not an expert in this)? Or is the more material item regarded as adding to the burden of psychosocial adversity, which is also quite plausible from e.g. family stress theory.

REVIEWER	Dr John A Burgess Research Fellow Centre for MEGA Epidemiology University of Melbourne I have no competing interests.
REVIEW RETURNED	30-Jul-2012

GENERAL COMMENTS	The authors have set out to examine the relationship between childhood adversity and adult incident asthma in a Finnish cohort derived from the HeSSup study and followed for a period of seven years. The cohort is large and representative of the Finnish population suggesting that the results are likely to be generalizable. The outcome was determined with good objectivity from three large health data bases which, taken together, were likely to capture the incident cases of asthma. The main limitations of the study have been acknowledged by the authors. These limitations include the rather disappointing response rate (40%) to the original survey in 1998 which raises the real possibility of selection bias in terms of exposure. The authors comment that an analysis of the non-responders (as reflectedy by the late responders) showed no difference between responders and non-responders in terms of "health-related factors" but the non-responders were more likely to be users of psycho-pharmaceutical products, perhaps reflecting higher levels of anxiety or depression in turn reflecting more childhood adversity? Perhaps a comment to that effect might be indicated? The other major limitation is the use of participant recall of childhood

	adversity by the adult cohort introducing the possibility of recall bias. The authors have correctly identified this in the discussion as a limitation and I acknowledge that little can be done about the matter other than initiating prospective cohort studies from childhood as the authors indicate, and this is an unlikely enterprise. Cox proportiona hazards analysis has been used to assess the hazard ratios in term of various exposures. I assume that the assumption of proportional hazards was examined and was not violated and if so, a comment to this effect should be included in the statistical analysis section. In the results section, I found the presentation of the change in the hazard ratios consequent upon the inclusion of various confounders a little confusing. Thus on page 16 of 38 in the pdf, lines 28-33, it is stated that the exposure to 3-6 adversities was associated with 1.6 fold (actually 1.62) greater risk of incident asthma and that this was attenuated by 19.4% to 1.50 by demographic information. The change in the hazard ratio is (1.62-1.50)/1.62 which is 7.4% not 19.4%. The value of 19.4% comes from the relative change in the excess hazard (.62-.50)/.62. This is correctly expressed in lines 35-40 as "attenuation of the risk", not attenuation of the hazard ratio. Then in the sentence dealing with the inclusion of all confounding co-variates, it is said again (I believe incorrectly) that the hazard ratio is attenuated by 47% when that figure should be 17.9% (1.62-1.33)/1.62. It is the excess hazard that is attenuated by 47% (.62-.33)/.62. It is a matter of preference but I found the presentation of Table 1 to be unusual in that one must read down the columns to make sense of it. It might be better to present the data so that the reader looks across the rows. Thus in the characteristic "gender", it would be easier to read across the row that among the 8556 men in the cohort, 'n' (x%) experienced 0 adversities, 'n1' (x1%) experienced 1-2 adversities and so on.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Comment 1. & 2. “The main methodological weakness is the low response rate (effectively 37%). This is discussed in the paper and the authors conclude that selection bias "is an unlikely explanation for our findings" on the basis of a non-response analysis in which "there were no significant health-related selective factors among respondents and non-respondents of the survey". It is not clear what they mean by the non-response analysis - this is mentioned but not detailed in the Methods section. Did they actually sample non respondents and get information on baseline indicators eg. mental health status to enable comparisons with survey responders? More detail needs to be provided on this.”

"The second issue is the possibility that the strength of the contribution of psychiatric disorder (as mediator/confounder) to the associations of childhood adversities with asthma onset may have been underestimated. One reason for this is the low response rate as mentioned above - given the tendency for healthier people to be more likely to take part in surveys, it seems probable that the survey sample would under-represent the mentally ill.

Response: This is an excellent remark. We have added in the discussion section a explanation of the process (methodological issues, page 17: “The non-response analysis of the cohort was based on two strategies: 1) comparisons made between early and late responders, and 2) comparisons made between all responders and routine statistical data of the general population. The first analysis showed no significant differences in self-reports of physician-diagnosed illnesses including depression, panic disorder and eating disorder, and the second that there were no indications of selective physical health-related factors. Additionally, the subjects reporting physician-diagnosed panic disorder, heavy alcohol use and use of tranquillizers gave significantly more commonly than others (94.5% vs. 90.9%, respectively) consent to use register-based data [39]. We deemed that a significant bias on important health-related was unlikely. However, it is known from other studies that persons with mental disorders are more likely to be among non-responders. As in the cohort of this study, consent to use register data was likely to compensate for mental disorder bias.”

3. “The second reason is that mental health was only measured at baseline. So all those who had episodes of mental ill-health between baseline and follow up, or prior to the baseline assessment, will be included in the reference group of non-mentally ill for this part of the analysis. This would have the effect of attenuating the association between mental disorders and asthma. These issues need to be commented on further in the Discussion section.”

Response: In the present study the focus was, whether and to what extent a baseline risk factor predicts a later onset of asthma in the case of having childhood adversities. The relationships between, say panic disorder and asthma, are likely to be bidirectional (e.g. ref #20).

We have clarified are initial aims (end of introduction, page 6: 1) It is so far uncertain, whether the association between preceding mental disorder and subsequent asthma could be accounted for by mental disorders, and whether childhood adversities could have an independent influence on incident asthma.”, and 2) “…whether this risk was attributable to mental disorders or behavioral health risk factors at baseline…”

Secondly in the discussion we have added (methodological issues, bottom of page 17): “The associations between asthma and mental disorder symptoms and disorders seem to be bidirectional [20]. Including psychiatric risk factors during the follow-up into our model could have attenuated further the association between asthma and mental health risk factors, but made it more cumbersome to settle on their temporal relationships. The same goes for behavioral risk factors as well.”

Reviewer #2 (1). "Do I understand that the participants in the study were the stated ages at the time they were recruited? If so this means that they will be remembering their childhood adversities at very different amounts of time subsequent to childhood. So these might be remembered better by some than by others. Also, was the onset of asthma measured subsequent to recruitment or was it taken from register data over the whole life course of all participants? One at age 25 might have a different aetiology and risk factors than onset at age 55."

Response:
1. Yes, the subjects were of the stated ages at the time of recruitment.

2. Previous studies indicate that 1) the adversities are better remembered by those with more serious events, and 2) less severe events may be under-reported. This indicates that our findings are not likely to be over-estimates. Secondly, analysis of the use of the same questionnaire used in this study at two time points (1999 and 2003) have yielded reasonable kappa-values (0.56 – 0.90, see page 18). As the point of the reviewer is well taken, we have added on page 18 in the discussion section before

“Conclusions”: “Our findings on the relationships between adversities and incident asthma are not likely to be over-estimates.”

3. The onset of asthma was considered over the whole life course. The age of the subjects was adjusted for (see table 2). All demographic data attenuated the risk by 19,4% (page 13, results).

Reviewer #2 (2) The biggest attenuation takes place when mental health varables are entered into the model. It is not clear from the text how the authors regard this in terms of their research question. I would have thought that this could be used as evidence in favour of a psychosocial theory.

In the introduction we state that childhood adversities are associated with physical illnesses and mental disorders, that mental disorders are associated with asthma. We have clarified are initial aim (page 6): “It is so far uncertain, whether the association between preceding mental disorder and subsequent asthma could be accounted for by mental disorders, and whether childhood adversities could have an independent influence on incident asthma.”

Psychosocial theory is embedded in psychoneuroimmunological models.

Reviewer #2 (3) The childhood adversity items mix material with psychosocial adversities (low income, fear of a family member). Does material hardship play a part in the aetiology of asthma (I am not an expert in this)? Or is the more material item regarded as adding to the burden of psychosocial adversity, which is also quite plausible from e.g. family stress theory.

Response: Low income has been found to be associated with an increased risk of several types of abuse. Material hardship is associated with asthma indicators (e.g. ref # 32 & 49)There is no contradiction between stress theories and psychoneuroimmunological theories, because psychosocial stress is coupled with immunological/hormonal factors.

Reviewer #3

1. The main limitations of the study have been acknowledged by the authors. These limitations include the rather disappointing response rate (40%) to the original survey in 1998 which raises the real possibility of selection bias in terms of exposure. The authors comment that an analysis of the non-responders (as reflectedy by the late responders) showed no difference between responders and non-responders in terms of "health-related factors" but the non-responders were more likely to be users of psycho-pharmaceutical products, perhaps reflecting higher levels of anxiety or depression in turn reflecting more childhood adversity? Perhaps a comment to that effect might be indicated?

Response: See above comments made by reviewer #1, our response to points 1 & 2

2. Reviewer #3: "Cox proportional hazards analysis has been used to assess the hazard ratios in term of various exposures. I assume that the assumption of proportional hazards was examined and was not violated and if so, a comment to this effect should be included in the statistical analysis section."

Response: On page 12, we have added: “The time-dependent interaction terms between any childhood adversity and the logarithm of the follow-up period were all non-significant confirming that the proportional hazard assumptions were justified.”

Reviewer #3: "In the results section, I found the presentation of the change in the hazard ratios consequent upon the inclusion of various confounders a little confusing. Thus on page 16 of 38 in the pdf, lines 28-33, it is stated that the exposure to 3-6 adversities was associated with 1.6 fold (actually 1.62) greater risk of incident asthma and that this was attenuated by 19.4% to 1.50 by demographic

information. The change in the hazard ratio is (1.62-1.50)/1.62 which is 7.4% not 19.4%. The value of 19.4% comes from the relative change in the excess hazard (.62-.50)/.62. This is correctly expressed in lines 35-40 as "attenuation of the risk", not attenuation of the hazard ratio. Then in the sentence dealing with the inclusion of all confounding co-variates, it is said again (I believe incorrectly) that the hazard ratio is attenuated by 47% when that figure should be 17.9% (1.62-1.33)/1.62. It is the excess hazard that is attenuated by 47% (.62-.33)/.62."

Response: The reviewer is quite right. This is a lapse on our part. We have replaced the “attenuation of hazard ratio” with “attenuation of excess hazard”. In the discussion we originally used “excess”.

Reviewer #3: "It is a matter of preference but I found the presentation of Table 1 to be unusual in that one must read down the columns to make sense of it. It might be better to present the data so that the reader looks across the rows. Thus in the characteristic "gender", it would be easier to read across the row that among the 8556 men in the cohort, 'n' (x%) experienced 0 adversities, 'n1' (x1%) experienced 1-2 adversities and so on."

Response: We agree that this is a matter of taste and our taste seems to be different from that of the reviewer.

VERSION 2 – REVIEW

REVIEWER	Kate Scott University of Otago New Zealand
REVIEW RETURNED	07-Sep-2012

GENERAL COMMENTS	The authors have addressed my comments satisfactorily.