PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.
AUTHORS	Hammerton, Gemma; Harold, Gordon; Thapar, Anita; Thapar, Ajay

VERSION 1 - REVIEW

REVIEWER	Peter G. Kaufmann Ph.D. Deputy Chief, Clinical Applications and Prevention Branch Division of Cardiovascular Sciences National Heart, Lung, and Blood Institute USA I have no competing interests to report.
REVIEW RETURNED	08-Jul-2013

THE STUDY	Depression and blood pressure in high-risk children and adolescents. Using data from two independent cohorts the authors report a relationship between systolic blood pressure and depressive disorder in children with a parental history of depressive disorder. The quality of this study is difficult to assess due to inconsistent use of terminology used for depressive disorder and inconsistent description of the methods used for ascertaining depression. In Methods, page 4 line 16, authors refer to two episodes of DSM-IV MDD, presumably of one of the parents. In line 43 the DSM-IV diagnosis clearly refers to the children. However, beginning with line 50, reference is made to psychiatric data collected from parents and children by “semi-structured research diagnostic interviews” (presumably CAPA) and “from self-completed questionnaires.” Were both of these sources of ascertaining MDD? Page 6 line 29 refers to Childrens’ “depressive disorder at age 15 years” presumably by use of DAWBA. On page 9, line 51, 18 children reported depressive disorder at age 15 (Also see similar terminology on page 13, line 54). Was this based on DAWBA, or by other self-report? Since DAWBA as described previously ascertains depressive symproms for the previous month, does page 9 line 51 refer to a one-month incidence/prevalence or for the entire 15th year? Moreover, since CAPA as used in the EPAD sample ascertains depression for the previous 3-month period, were the rates using different instruments adjusted accordingly? The rate of MDD using DAWBA would seem to be proportionately higher than perhaps reported. On page 6, line 52 etc it is stated that parent and child diagnoses were combined (using an either/or approach). This reader can surmise the intended meaning of the statement, but it remains unclear what proportion of diagnoses of childrens’ depression were based on parents vs., children. In short, it is difficult to follow exactly which values, derived from which methods, were used to diagnose depression in children. Similar uncertainties exist regarding the diagnosis of depression in

	the ALSPAC cohort. Page 6 line 50 – "reviewed by two senior …" Of what did these reviews consist? Review of the scoring by the CAPA interviewers? Independent interview of children and/or parents? How many CAPA (and DAWBA) interviewers were used? How were they trained, certified, monitored? The diagnostic interview by CAPA can yield a diagnosis of MDD as well as of dysthymia. Was the association between dysthymia and blood pressure the same, or at least in the same direction, as the association between MDD and blood pressure? Familial aggregation of blood pressure has been reported in some studies (Fuentes et al 2000; Burke et al 1991 – CARDIA); Other studies have reported an association between low blood pressure and depression in adults. Adjusting for parental blood pressure in these analyses may be as important as adjusting for weight of the child. Are parental blood pressures available? If not, this should be discussed as a limitation of the study. Figures 2 and 3 show % new onset depressive disorder in EPAD and ALSPAC samples, by blood pressure quintiles. It would be informative to know the BP ranges for each of the quintiles. It would be informative to have new onset depression reported for the replication sample, high risk ALSPAC children, using BP ranges identical to the EPAD quintiles. The finding that in the absence of maternal depression children with high blood pressure showed the highest percentage of depressive disorder should be discussed with respect to mechanisms. The demographic characteristics of children and parents should be reported in the manuscript, not as supplemental material.
RESULTS & CONCLUSIONS	It is difficult to judge whether the research questions has been answeered adequately, as questions remain aboiut the measures employed, as discussed in the previous section. This affects the credibility of the results and data, as well as the presentation.

REVIEWER	Karen A. Matthews, PhD Distinguished Professor of Psychiatry Professor of Epidemiology and Psychology University of Pittsburgh USA The reviewer has no conflicts of interest to disclose.
REVIEW RETURNED	08-Jul-2013

GENERAL COMMENTS	This paper investigates the association between BP and depression onset in a sample of children with a parental history of recurrent major depression. It reports that low SBP leads to onset of depression in these children and then in a second epidemiological study finds the same pattern using different instruments. The fact that the pattern is similar in the two studies is noteworthy. What is missing is a reasonable explanation as to why this pattern might occur and the clinical implications of these findings. The paper is couched in the adult epidemiological literature, which has found inconsistent relationships for depression as a predictor of hypertension. It is difficult to understand how these findings help to explain those results. It would also be worthwhile to reanalyze the data and standardize the BP data within age/gender/height groups as this is the more

	standard way of examining BP data in pediatric samples. I would also find it helpful to test for gender interactions as the findings may be due to the females, not the males, given the incident depression data reported.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Depression and blood pressure in high-risk children and adolescents.
Using data from two independent cohorts the authors report a relationship between systolic blood pressure and depressive disorder in children with a parental history of depressive disorder. The quality of this study is difficult to assess due to inconsistent use of terminology used for depressive disorder and inconsistent description of the methods used for ascertaining depression.

We agree that there had been some inconsistencies in terminology and descriptions and the Methods section has been extensively revised to address this (see individual points below)

In Methods, page 4 line 16, authors refer to two episodes of DSM-IV MDD, presumably of one of the parents.

Yes using the SCAN (Schedules for Clinical Assessment in Neuropsychiatry) interview. We have clarified this in manuscript (Page 4 line 58)

In line 43 the DSM-IV diagnosis clearly refers to the children. However, beginning with line 50, reference is made to psychiatric data collected from parents and children by “semi-structured research diagnostic interviews” (presumably CAPA) and “from self-completed questionnaires.” Were both of these sources of ascertaining MDD?

The diagnosis of Major Depressive disorder in the children was solely based on interview data (using CAPA for the original sample and DAWBA in the replication sample). This has been clarified and expanded in the text (Page 4 line 68, page 5 line 81, page 7 and page 9).

Page 6 line 29 refers to Childrens’ “depressive disorder at age 15 years” presumably by use of DAWBA. On page 9, line 51, 18 children reported depressive disorder at age 15 (Also see similar terminology on page 13, line 54). Was this based on DAWBA, or by other self-report?

The DAWBA interview.

Since DAWBA as described previously ascertains depressive symptoms for the previous month, does page 9 line 51 refer to a one-month incidence/prevalence or for the entire 15th year? Moreover, since CAPA as used in the EPAD sample ascertains depression for the previous 3-month period, were the rates using different instruments adjusted accordingly? The rate of MDD using DAWBA would seem to be proportionately higher than perhaps reported.

We agree that the DAWBA rates would probably be higher. The problem of different psychiatric interviews using different ascertainment periods is recognised as a problem for studies on prevalence and cannot be easily adjusted for. However for this paper we focused on association rather than prevalence and moreover the replication of our findings in a different dataset using the DAWBA may lead to a more conservative result (as depression prevalence may be proportionately lower) which would strengthen rather than weaken the conclusions. It also suggests the findings are related to the depression construct rather than instrument specific.

On page 6, line 52 etc it is stated that parent and child diagnoses were combined (using an either/or approach). This reader can surmise the intended meaning of the statement, but it remains unclear what proportion of diagnoses of childrens' depression were based on parents vs., children.

Using both parent and child reports of the child's psychopathology is standard child psychiatric practice - in clinics and in research. In the EPAD sample, overall 46% of the diagnoses came from child report, 38% came from parent report and the remainder were reported by both parent and child, this information has not been added into the manuscript but we can add it in if it would help to clarify this. We emphasise that ALL diagnoses were also reviewed by two clinical child and adolescent psychiatrists.

In short, it is difficult to follow exactly which values, derived from which methods, were used to diagnose depression in children. Similar uncertainties exist regarding the diagnosis of depression in the ALSPAC cohort.

We have revised the Methods to make this clearer, both for the CAPA interview (Page 7) and for the DAWBA interview (Page 9)

Page 6 line 50 – "reviewed by two senior …" Of what did these reviews consist? Review of the scoring by the CAPA interviewers?

This has been clarified in the text (Page 7 to 8). The two senior child psychiatrists met weekly with the team to review CAPA scoring, to review all diagnoses. All quality control measures that would be used in epidemiological and clinical studies in child psychiatry were used.

Independent interview of children and/or parents?

Yes. The text has been revised to clarify this (Page 7 line 111 and page 8 line 121).

How many CAPA (and DAWBA) interviewers were used? How were they trained, certified, monitored?

In the original study, there were 2 interviewers per family and 3 teams of 2 interviewers. All were trained for 2 weeks and monitored for one month before being allowed out into the field and then supervised weekly. Details of training, certification and monitoring have been added to the text for the original study (Page 7-8) as well as further details about the DAWBA process (Page 9)

The diagnostic interview by CAPA can yield a diagnosis of MDD as well as of dysthymia. Was the association between dysthymia and blood pressure the same, or at least in the same direction, as the association between MDD and blood pressure?

Numbers with dysthymia were too small to look at this -only 4 individuals have dysthymia across whole study and this information not available for ALSPAC. Analyses were rerun in the original sample for new onset mood disorder and results were unchanged (this measure includes an additional 14 children (dysthymia, adjustment disorder, depressive disorder not otherwise specified, bipolar and cyclothymia). This has been added to the text (primary diagnoses of those with a new onset mood disorder listed on page 12 line 238)

Familial aggregation of blood pressure has been reported in some studies (Fuentes et al 2000; Burke et al 1991 – CARDIA); Other studies have reported an association between low blood pressure and depression in adults. Adjusting for parental blood pressure in these analyses may be as important as

adjusting for weight of the child. Are parental blood pressures available? If not, this should be discussed as a limitation of the study.

We have now obtained further information from ALSPAC and have adjusted for maternal blood pressure in pregnancy in ALSPAC and results remain unchanged. This additional adjustment has been added to the manuscript (Page 13 line 258). Unfortunately parental blood pressure was not available in the original EPAD study.

Figures 2 and 3 show % new onset depressive disorder in EPAD and ALSPAC samples, by blood pressure quintiles. It would be informative to know the BP ranges for each of the quintiles. It would be informative to have new onset depression reported for the replication sample, high risk ALSPAC children, using BP ranges identical to the EPAD quintiles.

Quintiles in figures are created using standardised blood pressure therefore ranges will be z scores rather than a specific range for systolic blood pressure. See graph (in response to decision letter supplementary file in file upload section) using same standardised cut offs (displayed on x axis) in both samples (using EPAD quintile cut offs). However, the above graph would need to be interpreted with caution as only one child with depression was in the highest quintile.

The finding that in the absence of maternal depression children with high blood pressure showed the highest percentage of depressive disorder should be discussed with respect to mechanisms.

We have added in some more discussion of possible mechanisms. However given the very limited research on this topic the need for further research has been highlighted.

The demographic characteristics of children and parents should be reported in the manuscript, not as supplemental material.

This has been added to the manuscript (Table on Page 11).

It is difficult to judge whether the research questions has been answered adequately, as questions remain about the measures employed, as discussed in the previous section. This affects the credibility of the results and data, as well as the presentation.

We hope that our responses regarding measures have satisfactorily clarified the situation.

Reviewer 2

This paper investigates the association between BP and depression onset in a sample of children with a parental history of recurrent major depression. It reports that low SBP leads to onset of depression in these children and then in a second epidemiological study finds the same pattern using different instruments. The fact that the pattern is similar in the two studies is noteworthy.

This was what we found very persuasive.

What is missing is a reasonable explanation as to why this pattern might occur and the clinical implications of these findings. The paper is couched in the adult epidemiological literature, which has found inconsistent relationships for depression as a predictor of hypertension. It is difficult to understand how these findings help to explain those results.

We agree that this would be important to discuss and have added in some more discussion of possible mechanisms (page 18-19). However there is very limited scientific literature examining this

issue and we have highlighted the need for further research.

It would also be worthwhile to reanalyze the data and standardize the BP data within age/gender/height groups as this is the more standard way of examining BP data in pediatric samples.

As suggested we have standardised systolic blood pressure by age, gender and height and rerun analyses in the ALPSAC sample. All results remain similar.
Association between systolic blood pressure at age 12 years and depressive disorder at age 15 years, whilst adjusting for weight in the ALSPAC selected sample of offspring with recurrently depressed parents: OR = .49, 95% CI .26 to .92; p=.027. Association between systolic blood pressure at age 12 years and depressive disorder at age 15 years, whilst adjusting for weight in the ALSPAC unselected sample: OR = 1.02, 95% CI .77 to 1.34; p=.907. We have not included this information in the manuscript (as the same analysis was not felt to be appropriate for the high risk sample –see below). But will include this if requested. In the original study (EPAD), given the wide age range of the participants, we feel that standardising for height as well as age would lead to misleading results given that children vary considerably on stage of pubertal development at a given age, which not only affects height but has an important influence on depression but these influences are likely not to be concurrent (Thapar et al, 2012 Lancet). For children who are post-pubertal we agree that standardising for height would be appropriate. We have run some additional analyses. We created a standardised systolic blood pressure based on age, gender and height in the original study and examined the association with depression in those children that have already gone through puberty (i.e. late and post puberty) and the results are in the same direction, but non-significant but we feel this is likely to be because the sample size is very small (only 12 have depression in this group):OR = .59, 95% CI .32 to 1.09; p=.091. Therefore we have not currently changed the manuscript. However, pattern of results looks similar using whole EPAD sample and systolic blood pressure standardised by age, gender and height (see graph in response to decision letter supplementary file in file upload section)

I would also find it helpful to test for gender interactions as the findings may be due to the females, not the males, given the incident depression data reported.

We agree that this is potentially important but, as we have reported in the manuscript the gender interaction term was not significant (Page 12 line 242 and page 13 line 259). We have carried out a more detailed analysis which indicates some possible differences by gender but given larger numbers of depression in girls, we cannot exclude lack of power for the analyses in boys as having a role. This would need further research.
EPAD:
Interaction: OR = 1.15, 95% CI .45 to 2.99; p=.769
Females (n=19): OR = .68, 95% CI .43 to 1.06; p=.091
Males (n=5): OR = .68, 95% CI .28 to 1.65; p=.390
ALSPAC:
Interaction: OR = .42, 95% CI .15 to 1.19; p=.102
Females (n=13): OR = .38, 95% CI .19 to .77; p=.007
Males (n=5): OR = .84, 95% CI .31 to 2.28; p=.729

VERSION 2 – REVIEW

REVIEWER	Peter G. Kaufmann Ph.D. Deputy Chief Clinical Applications and Prevention Branch Division of Cardiovascular Sciences National Heart, Lung, and Blood Institute

	USA I have no competing interests to report.
REVIEW RETURNED	

THE STUDY	These data seem contrary to the "vascular depression" hypothesis in adults, in which elevated blood pressure is related to depression (e.g., see "The vascular depression hypothesis: mechanisms linking vascular disease with depression" - Taylor, Aizenstein and Alexopoulos, Molecular Psychiatry, 2013). Authors may wish to comment on this in their discussion.
RESULTS & CONCLUSIONS	Under Initial analyses in EPAD high-risk sample a statement is made that "Lower systolic blood pressure at baseline significantly predicted new onset depressive disorder (OR = .65, 95% CI .44 to .96; p=.029) when adjusting for child's weight at baseline." The cited OR, if correct, actually means the opposite – low SBP is protective against depression. Under Replication in ALSPAC dataset… there is a similar statement, with OR given as .48 – is this correct? Figures 2 and 3 do support the narrative statements but the OR seems to be the inverse of what it should be, or the OR may be 1.65 and 1.48, respectively. RE: Sensitivity and specificity. The sensitivity and specificity for SBP as a predictor of incident depression were given as 63% and 66% for the high risk EPAD sample and similar values of 61 % and 61 % for the ALSPAC replication sample, for the selected SBP cut off values. The false positive rate (computed as 1-specificity) for the EPAD sample would then be 34% and for the ALSPAC sample 37%, which is a very high error rate. The implications for such a high error rate in predicting depression are somewhat daunting. Perhaps the cut offs should be reconsidered, and the issue of error rates addressed in the Discussion.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

These data seem contrary to the "vascular depression" hypothesis in adults, in which elevated blood pressure is related to depression (e.g., see "The vascular depression hypothesis: mechanisms linking vascular disease with depression" - Taylor, Aizenstein and Alexopoulos, Molecular Psychiatry, 2013). Authors may wish to comment on this in their discussion.

We are grateful to the reviewer for bringing this interesting paper (Taylor et. al, 2013) to our attention. However this paper primarily refers to "geriatric depressive syndromes" and this together with most scientific literature to date refers to adult populations. As noted in the above paper there are considerable age-related vascular changes. It is for this reason we want to focus on children prior to the establishment of hypertensive disease as associations may likely show developmental changes. We have added comments on this in the discussion (page 18, line 369-374).

Under Initial analyses in EPAD high-risk sample a statement is made that "Lower systolic blood pressure at baseline significantly predicted new onset depressive disorder (OR = .65, 95% CI .44 to .96; p=.029) when adjusting for child's weight at baseline." The cited OR, if correct, actually means the opposite – low SBP is protective against depression. Under Replication in ALSPAC dataset… there is a similar statement, with OR given as .48 – is this correct? Figures 2 and 3 do support the

narrative statements but the OR seems to be the inverse of what it should be, or the OR may be 1.65 and 1.48, respectively.

The predictor variable, systolic blood pressure, is measured on a continuous scale, with a higher value representing higher blood pressure. Therefore, in this context, an odds ratio of below 1 means that as blood pressure increases, risk for future depression decreases. We do note, however, that this could cause confusion for readers as an odds ratio of below 1 would normally represent a protective rather than risk factor, so we have clarified this information in results section (page 12, line 233-236 & page 13, line 256-259).

RE: Sensitivity and specificity. The sensitivity and specificity for SBP as a predictor of incident depression were given as 63% and 66% for the high risk EPAD sample and similar values of 61 % and 61 % for the ALSPAC replication sample, for the selected SBP cut off values. The false positive rate (computed as 1-specificity) for the EPAD sample would then be 34% and for the ALSPAC sample 39%, which is a very high error rate. The implications for such a high error rate in predicting depression are somewhat daunting. Perhaps the cut offs should be reconsidered, and the issue of error rates addressed in the Discussion.

We agree that these false positive rates in both EPAD and ALSPAC seem high and we have added a line into the discussion to comment on this (page 19, line 402-403). Our aim is not however to use blood pressure as a screening tool for depression. Our only reason for using a cut point was to be able to establish what is meant by low blood pressure and for this we used a ROC curve technique to maximise both sensitivity and specificity (we aimed for both of these to be >0.60) (we have clarified this on page 15, line 293-94). Moreover some of the “false positives” will have sub-threshold levels of depression symptoms and are likely to develop depression in the future (Fergusson et al, 2005; Johnson et al, 2009). Therefore we have not currently changed the results section of the manuscript but have clarified why we selected these cut points in the discussion (page 19, Lines 403-407).