Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003206
Article Type:	Research
Date Submitted by the Author:	10-May-2013
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Cardiovascular medicine
Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Hypertension < CARDIOLOGY

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Abstract

Objective – To examine the relationship between blood pressure and depressive disorder in children and adolescents at high-risk for depression.

Design – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study of offspring of parents with recurrent depression and an on-going birth cohort for replication.

Setting – Community based studies.

Participants – High-risk sample includes 281 families where children were aged 9-17 years at baseline and 10-19 years at the final data point. Replication cohort includes 4830 families where children were aged 11-14 years at baseline and 14-17 years at follow up and a subsample of 612 families with mothers that had reported recurrent depression.

Main outcome measures – High-risk sample: new onset DSM-IV defined depressive disorder using the Child and Adolescent Psychiatric Assessment (CAPA). Replication sample: DSM-IV defined depressive disorder using the Development and Wellbeing Assessment (DAWBA).

Results – Blood pressure was standardised for age and gender to create standard deviation scores and child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and future depression was also found in the replication cohort in those children whose mothers had experienced recurrent depression in the past.

Conclusion – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of parents with depression. Further studies are needed to investigate how this association arises.

Key words

Depression; Blood Pressure; ALSPAC; Adolescent; Cohort Studies

Article focus:

- To examine the relationship between blood pressure and future depressive disorder in adolescents at high-risk for depression.

Key messages

- Low systolic blood pressure predicts future depressive disorder in adolescent offspring of parents with recurrent depression.

Strength and Limitations

- Replication of findings in two independent cohort studies, one a high risk sample and one a population based cohort.
- Mechanism by which low blood pressure is linked to depression risk needs further investigation.

Introduction

The two leading causes of death and disability in the developed world are major depressive disorder and cardiovascular disease. The association between depression and cardiovascular disease is well established in adults,[1] although the mechanisms by which it arises are still not clear. It has been suggested that these links reflect early associations between depression and cardiovascular risk factors. High blood pressure is an important cardiovascular risk factor and it has also been linked to depression in adults in some studies.[2] Other studies, however, have found the converse. They suggest that depression is associated with low blood pressure and that it is only depression treated with certain antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the findings are inconsistent, with some studies finding depression as a predictor of either high blood pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure predicting depression.[6]

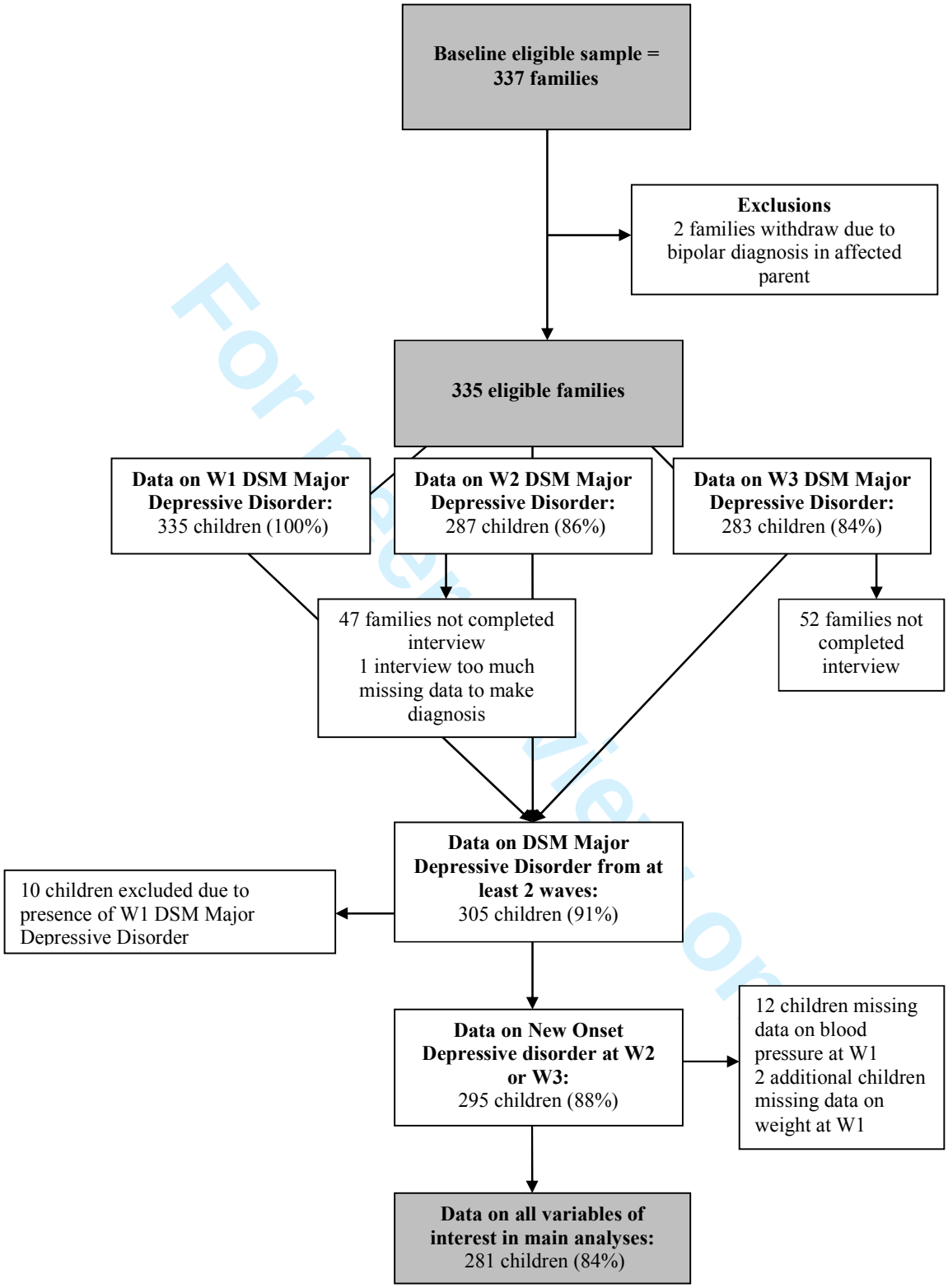
Although both depression and the early indicators of cardiovascular disease have been found to have onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger populations. In this study, the main aim was to investigate the relationship between blood pressure and subsequent first onset depressive disorder in a prospective cohort of children and adolescents at high risk of depression. The secondary aim was to replicate findings in an independent cohort.

Method

Data were derived from a prospective longitudinal study of offspring of parents with recurrent depression–'The Early Prediction of Adolescent Depression (EPAD) study'. At baseline, the sample included 337 families (315 mothers and 22 fathers) that were recruited from general practices across South Wales, by writing to eligible families, and from a database of individuals with previously identified unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test the main hypotheses of the original project whilst allowing detailed assessments at each time point. The presence of least two episodes of DSM-IV major depressive disorder was confirmed at baseline interview. The youngest child within the age range of 9 to 17 years was selected for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to and currently living with the affected parent. Additional exclusion criteria included children with moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the study because the depressed parent had been diagnosed as suffering from bipolar disorder since the wave 1 assessment. Parents and offspring were assessed independently by two trained research psychologists on three occasions over the course of the study which began in April 2007 and finished in April 2011. The average time between the baseline and second assessment was 16.2 months and between the second and third assessment was 12.5 months. Further details on the sample characteristics and methodology have been described previously.[9]

For the main analyses, 30 families were excluded because they had not completed at least two waves of data. A further 10 children were excluded from main analyses when the outcome variable used was 'new onset depressive disorder' in the child as they had had a baseline diagnosis of DSM-IV major depressive disorder. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not been completed at baseline either because there had been a fault in the equipment or the child had refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data were collected from parents and children via semi-structured research diagnostic interviews and blood pressure and weight were assessed by the interviewer. Additional data were also collected from parents and children from self-completed questionnaires that were mailed to the families two weeks before their interview. Ethical approval for the study was obtained from the Multi-centre Research Ethics Committee for Wales.

Figure 1



Flow chart of retention at each assessment in the EPAD sample

Data were also utilised from a birth cohort study 'The Avon Longitudinal Study of Parents and Children (ALSPAC)' to allow replication of findings from the first high-risk sample. The cohort was set up to examine genetic and environmental determinants of health and development.[10] The initial cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date of delivery between 1st April 1991 and 31st December 1992 (www.alspac.bris.ac.uk). All pregnant women resident in three health districts in the old administrative county of Avon who had an estimated delivery between the above dates were eligible to participate. In addition, pregnant women that had migrated into the catchment area before the point of delivery were eligible. Recruitment was carried out by attempting to make contact with eligible women through ALSPAC staff visiting community locations and through using antenatal and maternity health services and media information to encourage contact and promote the study.[10] The parents completed regular postal questionnaires concerning their child's health and development since birth. The children have completed questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and 2315 males; age range: 11-14 years; mean age = 12.8 years) and depressive disorder at age 15 years (age range: 14-17 years; mean age = 15.4 years). Main analyses focused on the sample of children with mothers that had reported recurrent depression, 612 children were included in these analyses (347 females and 265 males). Ethical approval for the study was obtained from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

Measures

EPAD study:

Major depressive disorder and depression symptoms – Parent and child versions of the Child and Adolescent Psychiatric Assessment (CAPA),[11] were used at each assessment to assess the presence of a major depressive disorder in the child over the preceding three months. The parent and child versions were completed independently. Child diagnoses were made using DSM-IV criteria, based on CAPA symptoms. All those meeting diagnostic criteria and subthreshold cases were reviewed by two senior child and adolescent psychiatrists. Parent and child reported diagnoses were combined (using an either/or approach) to generate DSM-IV diagnoses. The total number of DSM-IV major depression symptoms was also computed from the parent and child CAPA.

New onset major depressive disorder - The presence of a new onset major depressive disorder at either the second or third assessment was defined by excluding children that had a baseline diagnosis of DSM-IV major depressive disorder.

Blood pressure –An Omron 705IT sphygmomanometer was used to measure blood pressure at each assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were measured using standardised guidelines set out by the American Heart association.[12] At least two readings were taken at least one minute apart using the right arm. When the difference between two readings was 5mmHg or less an average was taken.

Weight and other potential confounders – Weight was considered to be a confounder of the relationship between blood pressure and depression due to its potential association with both.[13, 14] Interviewers measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also examined whether the results were affected by the presence of physical health problems (parent reported), any medication use (child or parent reported) and using body mass index (BMI) instead of weight.

ALSPAC:

Maternal history of recurrent depression – Mothers completed regular questionnaires from pregnancy to when the child was aged 12 years including the questions 'Have you had depression in the last year/ last two years/ since your child was born/ever'. The mother was also asked 'Have you ever had severe depression' on three occasions over this time period. Families were included in the subsample of recurrently depressed mothers if the mother had reported having depression on at least two separate occasions, and if at least one of these occasions was reported as being severe. These criteria were used to create a subsample that was as similar as possible to the primary high-risk sample.

Child depressive disorder – Parent versions of the Development and Wellbeing Assessment (DAWBA),[15] were used at the assessment when the target age of the children was 13 years and child versions of the DAWBA were used at the assessment when the target age of the children was 15 years to assess the presence of a depressive disorder over the preceding month. DSM-IV diagnoses of

depression were generated at each time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV diagnosis of depression (see www.DAWBA.com for more information). Each individual is assigned one of six probability bands, and the top two levels were used as a computer generated DAWBA diagnosis.[16]

Blood pressure – Systolic and diastolic blood pressure were measured at the clinic assessments when the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

Weight and BMI – Interviewers measured the weight and height of the children in light clothing and without shoes at the clinic assessments when the target ages of the children was 12 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then calculated (kg/m²).

Statistical methods

Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the high-risk sample and then in the replication cohort using the subsample of children with mothers that have experienced recurrent depression in the past. Next, regression analyses were performed to examine the association between blood pressure and depression in the high-risk sample and then in the subsample from the replication cohort. Logistic regression analyses were used when the dependent variable was dichotomous and ordinary least squares linear regression analysis was used when the dependent variable was continuous. Continuous outcome data that were not normally distributed were transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship between systolic blood pressure and future depressive disorder was examined by investigating the percentage of children with future depressive disorder by blood pressure quintiles, again in both samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. Lastly, the association between systolic blood pressure and future depressive disorder was investigated in the general population by using the entire ALSPAC sample and the presence of a multiplicative interaction between maternal depression and systolic blood pressure on future depressive disorder was examined. Listwise deletion was used to deal with missing data in all analyses and data were analysed using SPSS (v20).**Results**

For demographic comparability of samples see supplementary material (online publication only).

Descriptives from EPAD high-risk sample

Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at baseline. Systolic blood pressure at baseline was significantly correlated with age (r=.23, p<.001), but diastolic blood pressure was not (r=.02, p=.728). Systolic blood pressure was thus standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. Standardised scores were calculated using the 2007 blood pressure centiles for Great Britain.[17] Mean blood pressures for each age group in this sample were generally higher than population norms.[17, 18] Systolic blood pressure at baseline was significantly associated with weight (r=.25, p<.001), but diastolic blood pressure was not (r=.07, p=.236). Given this finding all analyses with systolic blood pressure are reported controlling for weight.

Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder (8.54%).

Descriptives from ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic (r=.45, p<.001) and diastolic blood pressure (r=.18, p<.001), therefore all results are reported controlling for weight.

Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder at age 15 (2.94%).

Initial analyses in EPAD high-risk sample

Logistic regression analyses were performed to investigate the association between blood pressure and new onset depressive disorder in the EPAD sample. 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. Diastolic blood pressure at baseline did not significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01; p=.120).

Results remained the same when the outcome was expanded to include the new onset of any mood disorder including major depressive disorder, dysthymia, cyclothymia, bipolar disorder and adjustment disorder with depressed mood. Results also remained similar when separately adjusting for medication use and physical health problems in the child and when adjusting for BMI instead of weight. The association was not significantly moderated by gender (p=.769).

Given few adolescents developed new onset depressive disorder, the analysis was repeated using total depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome, and again controlling for weight, showed significant association (β = -.13; p=.040).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This was non-significant (β = -.05; p =.412). Given the low number of individuals with depressive disorder at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again the results were non-significant (β = -.07; p = .286).

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Logistic regression analyses were undertaken in the replication sample. Lower systolic blood pressure at age 12 significantly predicted depressive disorder at age 15 (OR = .48, 95% CI .27 to .85; p=.012), however, diastolic blood pressure did not (OR = .98, 95% CI .93 to 1.05; p=.597). Results remained similar when adjusting for BMI instead of weight. The association was not significantly moderated by gender (p=.102).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood

pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant (β = -.04; p = .378).

Relationship between blood pressure and depressive disorder in high-risk EPAD sample

To further investigate the relationship between systolic blood pressure and depressive disorder in the EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 2

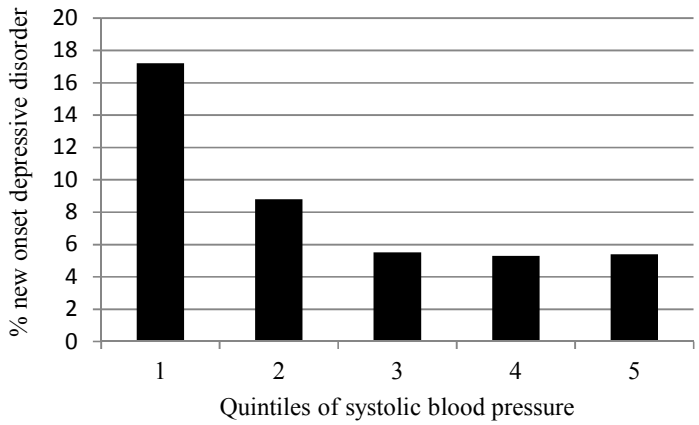


Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of systolic blood pressure at baseline in the EPAD sample

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

To further investigate the relationship between systolic blood pressure and depression in the replication sample, blood pressure was split into quintiles to examine the percentage of children with depression at age 15 by blood pressure categories and the linearity of the relationship.

As can be seen in Figure 3, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 3

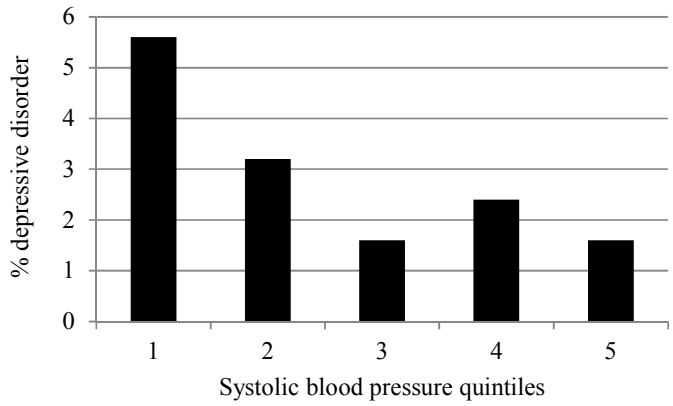


Figure to show percentage of children with depressive disorder at age 15 years by quintiles of systolic blood pressure at age 12 years in the ALSPAC sample

Analyses so far have highlighted a significant association between lower systolic blood pressure and future depression in two different samples of offspring of parents with recurrent depression. Next, ROC analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. A cut off point of below 0.025 standard deviations above the mean using the 2007 blood pressure centiles for Great Britain[17] showed a sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12 year old girl). A cut off point of below 0.485 standard deviations below the mean using the 2007 blood pressure centiles for Great Britain[17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the association between low blood pressure and future depressive disorder using each of the cut offs identified in each sample (Table 1).

Table 1

	OR (95% CI)[1]

	Optimal cut off in EPAD sample (< .025)	Optimal cut off in ALSPAC sample (< -.485)
EPAD sample	3.13 (1.30, 7.53)	3.43 (1.45, 8.13)
ALSPAC sample	3.00 (.93, 9.71)	3.62 (1.23, 10.65)

[1]Adjusted for child weight at W1

Association between low blood pressure and future depressive disorder in the EPAD and ALSPAC samples using the optimal cut off for low blood pressure identified in each sample using ROC curve analysis

From these analyses it seems a cut off for low systolic blood pressure for children aged 12 years lies between 108 and 113mmHg.

Lastly, supplementary analyses were performed to examine the association between blood pressure and future depression in the general population using the entire ALSPAC sample.

Supplementary analyses using entire ALSPAC sample:

1) **Testing the relationship between depressive disorder and blood pressure in the general population (not limiting analysis to those adolescents with a parental history of recurrent depression)**

Descriptives

Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.44$, $p<.001$) and diastolic blood pressure ($r=.19$, $p<.001$), therefore all results are reported controlling for weight.

Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder at age 15 (1.55%).

Preliminary analyses

Logistic regression analyses were performed to investigate the association between blood pressure and depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .76 to 1.27; p=.875). Diastolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04; p=.604).

2) **Examining whether a history of recurrent maternal depression moderated the relationship between systolic blood pressure and depression**

Logistic regression analyses were then performed to test if recurrent maternal depression moderated the relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic blood pressure and maternal recurrent depression were centred to convert them to their deviation form to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95% CI .27 to .89; p=.019).

Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal depression was present, children with low blood pressure showed the highest percentage of depressive disorder. However, when recurrent maternal depression was not present, children with high blood pressure showed the highest percentage of depressive disorder.

Figure 4

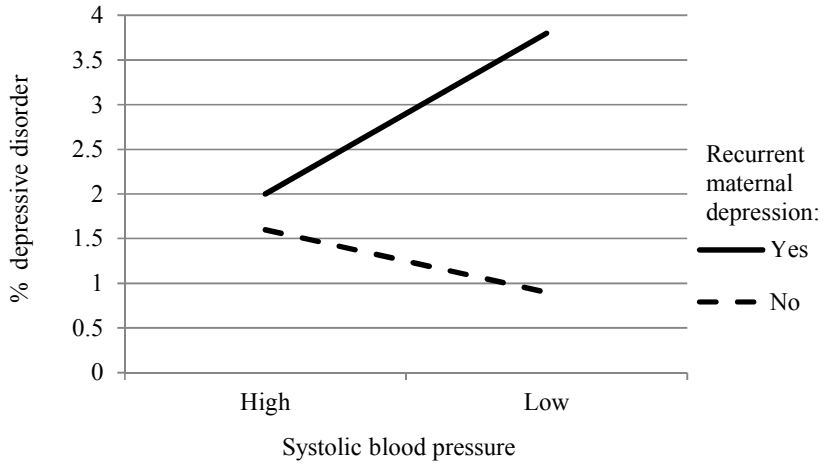


Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low' systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample

Discussion

In this study we found that lower systolic blood pressure significantly predicted future new onset depressive disorder amongst a sample of children and adolescents at high risk of developing depression because of a parental history of recurrent depression. This finding was replicated in a large community based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression (replication sample). When investigating this relationship in more detail, it seemed that those with the lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut off value for systolic blood pressure in 12 year old children was identified as being within the range of 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort (ALSPAC), the association between blood pressure and major depressive disorder was no longer significant. There was no evidence for an association in the opposite direction (depression predicting future blood pressure levels) either in the study sample or in the replication cohort nor was there an association between diastolic blood pressure and future depression in either dataset.

In our study low systolic blood pressure significantly predicted depressive disorder in adolescent offspring of individuals with recurrent depressive disorder but not in adolescents from the general population. There have been no previously published longitudinal studies examining the relationship between blood pressure and depression in children from the general population or children at high-risk of depression. In adults, findings have been mixed but links between low blood pressure and depression have been noted. These have not only been noted cross-sectionally in adults,[19] but a study on elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] In adolescents who did not have a parent with recurrent depressive disorder, higher blood pressure showed some association with a higher risk of future depressive disorder. This may be one explanation of some of the mixed findings in previous studies. The mechanism by which low blood pressure might precede depression for adolescent offspring of individuals with recurrent depressive disorder is unclear. For adults in certain countries (such as Germany) it seems accepted that chronic low blood pressure is associated with mood problems (the “hypotensive syndrome”). This consists of somatic symptoms such as tiredness, dizziness and headaches with occasionally some minor psychiatric symptoms such as anxiety and depression,[20] with the rationale that the somatic symptoms are unpleasant to live with and therefore may lead to low mood and feelings of depression in the subject.[3] Another possible explanation is that low blood pressure is an epiphenomenon, and that a common set of risk factors or

biological mechanism,[21] may explain the link between low blood pressure and mood disorder. Why this finding is limited to children of parents with a history of recurrent depression is unclear. Some animal studies have shown that early life stress (such as maternal deprivation in rats during postnatal days) has long-term effects on brain function and biology with implications for the development of depression or vulnerability to stress later in life.[22] Therefore the results from the current study could be explained by blood pressure being an initial manifestation of response to adversity and depression a later manifestation. However no empirical evidence for such an association has been found.

Strengths and Limitations

This is the first study we are aware of to report on the longitudinal relationship between blood pressure and depressive disorder in adolescents, an important period for the onset of depression. In the main sample, children and adolescents were followed up at three points over a four year period with a high retention rate of over 80%. A similar pattern of results was found in a large community based cohort study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples, diagnoses were systematically ascertained using interview and blood pressure readings were measured according to standardised protocol. In addition, potential confounders of the relationship were taken account of. There were also possible limitations of the study. Blood pressures were measured using an electronic device which uses an oscillometric technique rather than the auscultatory technique that most population norms are based on and it has been noted that these readings are not equivalent. However there is a lack of consensus as to whether using different methods leads to any systematic bias and inaccuracies seem more related to not using a standardised technique rather than the instrument.[23] In addition, the cut off values identified in the high risk and replication samples differed slightly. This may have been because of differences in measurement techniques in the two studies. These results need to be replicated in other samples in order to establish more precise cut off for low systolic blood pressure. Despite being a high-risk sample, the number of children with depressive disorder was small and many of the sample had not been though the age of maximum risk for developing a depressive disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of children with depressive disorder was also low in the replication sample, partly because only a self-report measure of depressive disorder was available at age 15, and partly because of selective attrition over time. Previous studies have reported that although attrition has affected prevalence rates of

depression in the mother and internalising disorders in the children, the associations between risks and outcomes remained intact, although conservative estimates of the likely true effects.[24, 25] Lastly, the subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe group as maternal self-report of depression was used as opposed to defining episodes of depression using DSM-IV criteria as was done in the main dataset.

In summary, in our study of adolescents at high risk of depression we found that low blood pressure was associated with major depressive disorder. This finding was replicated in an independent cohort. Future research is needed using different populations to confirm this relationship as it is a novel finding and to investigate the mechanisms by which the relationship between low blood pressure and depressive disorder in children at risk for depression may arise.

Acknowledgments

Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable Trust and the National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship.

We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for their help with recruiting them and the whole EPAD team. We thank the other investigators involved in the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar, Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules Thorn Charitable Trust.

Conflict of interest

None of the authors have conflict of interest/financial disclosures.

Role of funding source

Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors (AKT). The funders had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the paper for publication.

Contributorship

Ms Gemma Hammerton (jointly designed the paper and the analysis, carried out the analysis, jointly drafted and revised the paper), Professor Anita Thapar (helped with initial conception of the study and with study design, critically revised the draft for important intellectual content), Professor Gordon Harold,(advised on analysis of the paper, critically revised the paper) Dr Ajay Thapar (conception of the paper, jointly designed the study and analysis, joint initial drafting and revising the paper). All authors approved the final version prior to submission of the paper. Dr Ajay Thapar is the guarantor.

Data sharing

No additional data available.

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Supplementary material for online publication only

Demographic comparability of the EPAD high-risk sample, the ALSPAC subsample of children with mothers that have experienced recurrent depression and the whole ALSPAC sample

In the EPAD sample, the mother and father questionnaires completed at baseline were used to assess maternal education and highest parental social class. In the ALSPAC sample, the mother and father questionnaires completed during pregnancy were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels, degree or postgraduate qualification). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

Table 2 shows that the three samples are comparable on a range of demographics (child age, gender, maternal education and parental social class).

Table 2

	EPAD (n=281)	**ALSPAC** (subsample of depressed mothers; n=612)	**ALSPAC** (whole sample; n=4830)
Child age: mean (sd)	12.4 (2.0)	12.8 (0.2)	12.8 (0.2)
Child gender (% female)	58.4	56.7	52.1
Maternal education (% higher education)	51.9	44.3	47.2
Parental social class (% non-manual)	74.0	84.1	87.7

Demographics at baseline in the EPAD sample, ALSPAC subsample of depressed mothers and the whole ALSPAC sample

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **page 4 & 6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **page 4 & 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **page 4 & 6**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **pages 6, 7 & 9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **pages 6, 7 & 8**
Bias	9	Describe any efforts to address potential sources of bias **page 3, pages 7, 9, 10 (addressing confounders), and pages 17**
Study size	10	Explain how the study size was arrived at **pages 4, 5 & 6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **pages 6, 7 & 8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **pages7, 8, 9 & 10**
		(*b*) Describe any methods used to examine subgroups and interactions **pages 8 & 14**
		(*c*) Explain how missing data were addressed **page 8**
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **pages 8, 10 & 11**
Results		

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **pages 4, 5 & 6**
		(b) Give reasons for non-participation at each stage **pages 4, 5 & 6**
		(c) Consider use of a flow diagram **page 5**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **page 9, 13 & web only material**
		(b) Indicate number of participants with missing data for each variable of interest **pages 4, 5 & 6**
		(c) Summarise follow-up time (eg, average and total amount) **page 4**
Outcome data	15*	Report numbers of outcome events or summary measures over time **page 9**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **pages 6, 9 & 10**
		(*b*) Report category boundaries when continuous variables were categorized **page 11 & 12**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **pages 10-15**
Discussion		
Key results	18	Summarise key results with reference to study objectives **page 16**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **pages 17 & 18**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **page 16**
Generalisability	21	Discuss the generalisability (external validity) of the study results **pages 16 & 17**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **page 19**

*Give information separately for exposed and unexposed groups. **n/a**

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ open

Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003206.R1
Article Type:	Research
Date Submitted by the Author:	25-Jul-2013
Complete List of Authors:	Hammerton, Gemma; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences Harold, Gordon; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences Thapar, Anita; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences Thapar, Ajay; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Cardiovascular medicine
Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Hypertension < CARDIOLOGY

Title: Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Abstract

Objective – To examine the relationship between blood pressure and depressive disorder in children and adolescents at high-risk for depression.

Design – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study of offspring of parents with recurrent depression and an on-going birth cohort for replication.

Setting – Community based studies.

Participants – High-risk sample includes 281 families where children were aged 9-17 years at baseline and 10-19 years at the final data point. Replication cohort includes 4830 families where children were aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring with mothers that had reported recurrent depression.

Main outcome measures –New onset DSM-IV defined depressive disorder in the offspring using established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the replication sample.

Results – Blood pressure was standardised for age and gender to create standard deviation scores and child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and future depression was also found in the replication cohort in the second subset of high-risk children whose mothers had experienced recurrent depression in the past.

Conclusion – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of parents with depression. Further studies are needed to investigate how this association arises.

Key words

Depression; Blood Pressure; ALSPAC; Adolescent; Cohort Studies

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Article focus:

- To examine the relationship between blood pressure and future depressive disorder in adolescents at high-risk for depression.

Key messages

- Low systolic blood pressure predicts future depressive disorder in adolescent offspring of parents with recurrent depression.

Strength and Limitations

- Replication of findings in two independent cohort studies, one a high risk sample and one a population based cohort.
- Mechanism by which low blood pressure is linked to depression risk needs further investigation.

Introduction

The two leading causes of death and disability in the developed world are depression and cardiovascular disease. The association between depression and cardiovascular disease is well established in adults,[1] although the mechanisms by which it arises are still not clear. It has been suggested that these links reflect early associations between depression and cardiovascular risk factors. High blood pressure is an important cardiovascular risk factor and it has also been linked to depression in adults in some studies.[2] Other studies, however, have found the converse. They suggest that depression is associated with low blood pressure and that it is only depression treated with certain antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the findings are inconsistent, with some studies finding depression as a predictor of either high blood pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure predicting depression.[6]

Although both depression and the early indicators of cardiovascular disease have been found to have onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger populations. In this study, the main aim was to investigate the relationship between blood pressure and subsequent first onset episode of depression in a prospective cohort of children and adolescents at high risk of depression. The secondary aim was to replicate findings in an independent cohort.

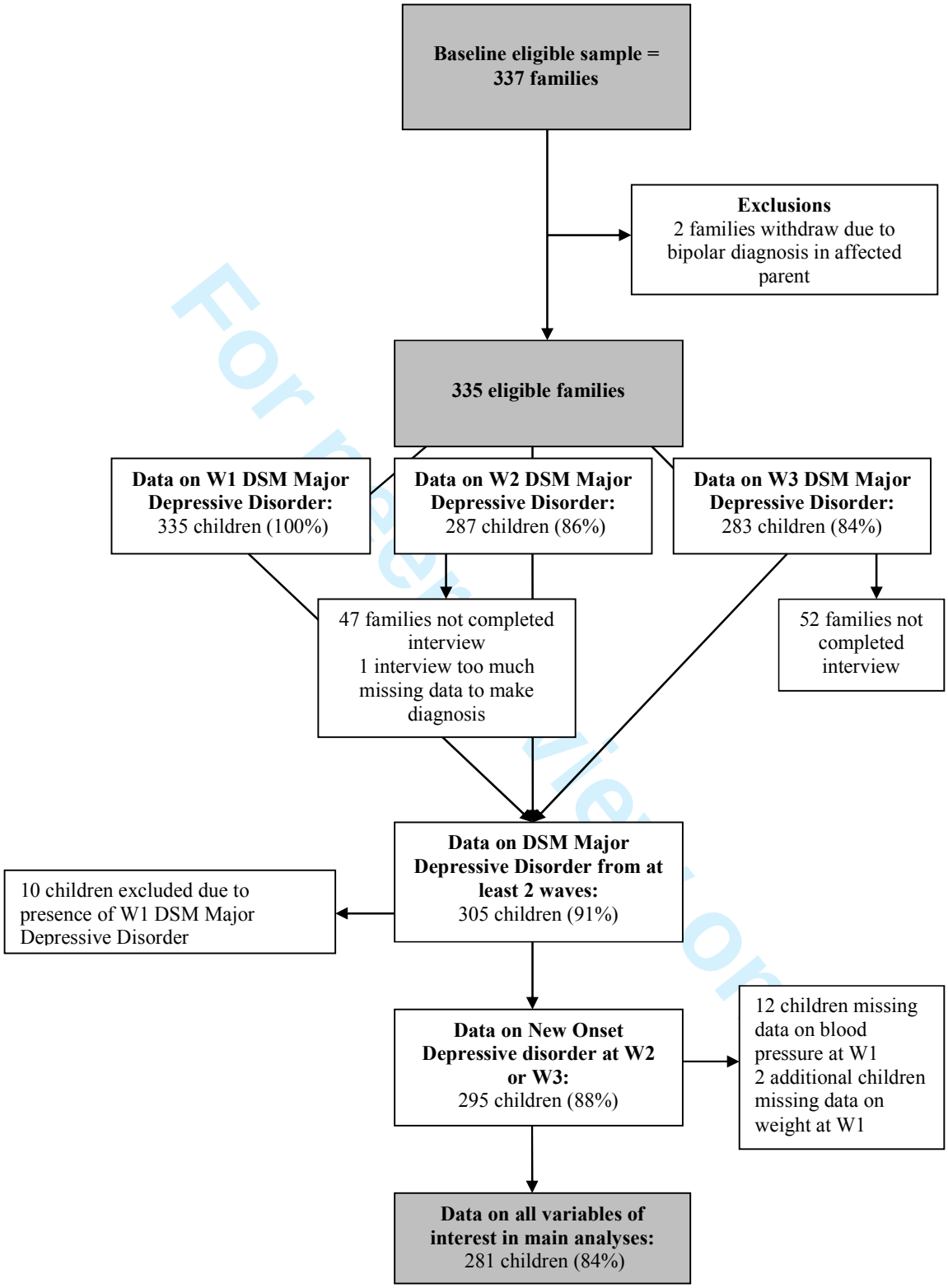
Method

Data were derived from a prospective longitudinal study of offspring of parents with recurrent depression–'The Early Prediction of Adolescent Depression (EPAD) study'. At baseline, the sample included 337 families (315 mothers and 22 fathers) that were recruited from general practices across South Wales, by writing to eligible families, and from a database of adults with previously identified unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test the main hypotheses of the original project whilst allowing detailed assessments at each time point. Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to and currently living with the affected parent. Additional exclusion criteria included children with moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the study because the depressed parent had been diagnosed as suffering from bipolar disorder since the wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed using age-appropriate standard research diagnostic interviews independently by two trained research psychologists on three occasions over the course of the study which began in April 2007 and finished in April 2011. The average time between the baseline and second assessment was 16.2 months and between the second and third assessment was 12.5 months. Further details on the sample characteristics and methodology have been described previously.[9]

For the main analyses, 30 families were excluded because they had not completed at least two waves of data. A further 10 children were excluded from main analyses because they already met criteria for DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not been completed at baseline either because there had been a fault in the equipment or the child had refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data were collected from parents and children via semi-structured research diagnostic interviews and blood

pressure and weight were assessed by the interviewer. Additional data on physical health problems, maternal education and social class were collected from parents and children from self-completed questionnaires that were mailed to the families two weeks before their interview. Ethical approval for the study was obtained from the Multi-centre Research Ethics Committee for Wales.

Figure 1



Flow chart of retention at each assessment in the EPAD sample

Data were also utilised from a birth cohort study 'The Avon Longitudinal Study of Parents and Children (ALSPAC)' to allow replication of findings from the first high-risk sample. The cohort was set up to examine genetic and environmental determinants of health and development.[10] The initial cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date of delivery between 1st April 1991 and 31st December 1992 (www.alspac.bris.ac.uk). All pregnant women resident in three health districts in the old administrative county of Avon who had an estimated delivery between the above dates were eligible to participate. In addition, pregnant women that had migrated into the catchment area before the point of delivery were eligible. Recruitment was carried out by attempting to make contact with eligible women through ALSPAC staff visiting community locations and through using antenatal and maternity health services and media information to encourage contact and promote the study.[10] The parents completed regular postal questionnaires concerning their child's health and development since birth. The children have completed questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range: 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children whose mothers had experienced recurrent depression (at least two episodes); 612 children were included in these analyses (347 females and 265 males). Ethical approval for the study was obtained from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

Measures

EPAD study:

Assessment of depression in the offspring of parents with recurrent depression

The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic interview that has high reliability and that is used to assess children's psychiatric symptoms [11]. Parents are asked about their children's psychopathology and children are independently interviewed using the interview schedules (parent and child versions). The presence of any given symptom has to be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

selected recordings at each time point (10 parent report and 10 child report) and through weekly supervision by an academic clinician with extensive experience in using the interview. Average agreement between raters for DSM-IV psychiatric disorder was excellent (κ =0.92), as was average agreement for depression symptoms (κ =0.93). CAPA was used at each assessment and assesses the presence of a major depressive disorder in the child over the preceding three months. The parent and child versions were completed independently, with interviews conducted in separate rooms where possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of DSM-IV major depressive disorder symptoms was also computed from the CAPA.

New onset major depressive disorder - The presence of a new onset DSM-IV diagnosis of major depressive disorder at either the second or third assessment was defined by excluding children that had a baseline diagnosis of DSM-IV major depressive disorder.

Blood pressure –An Omron 705IT sphygmomanometer was used to measure blood pressure at each assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were measured using standardised guidelines set out by the American Heart association.[12] At least two readings were taken at least one minute apart using the right arm. When the difference between two readings was 5mmHg or less an average was taken.

Weight and other potential confounders – Weight was considered to be a confounder of the relationship between blood pressure and depression due to its potential association with both.[13, 14] Interviewers measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also examined whether the results were affected by the presence of physical health problems (parent reported), any medication use (child or parent reported) and using body mass index (BMI) instead of weight.

Demographics – The mother and father questionnaires completed at baseline were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels, degree or postgraduate qualification). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

ALSPAC:

Maternal history of recurrent depression – Mothers completed regular questionnaires from pregnancy to when the child was aged 12 years including the questions 'Have you had depression in the last year/ last two years/ since your child was born/ever'. The mother was also asked 'Have you ever had severe depression' on three occasions over this time period. Research diagnostic interview generated psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data set thus had to be defined where mother had reported having depression on at least two separate occasions, and if at least one of these occasions was reported as being severe. These criteria were used to create a subsample that was as similar as possible to the primary high-risk sample.

Child depressive disorder – Parent reports on their child's symptoms were obtained using a structured diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA, has been used widely for large scale population studies. The parent-rated DAWBA was completed when the target age of the children was 13 years. Children were directly interviewed using the DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV diagnosis of depression and generates diagnoses (see www.DAWBA.com for more information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part of the ALSPAC data collection process. [16]

Blood pressure – Systolic and diastolic blood pressure were measured at the clinic assessments when the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

Weight and other potential confounders – Interviewers measured the weight and height of the children in light clothing and without shoes at the clinic assessments when the target age of the children was 12 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then calculated (kg/m²). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal medical records.

Demographics – The mother and father questionnaires completed during pregnancy were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels or degree). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

Statistical methods

Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the high-risk sample and then in the replication cohort using the subsample of children with mothers that have experienced recurrent depression in the past. Next, regression analyses were performed to examine the association between blood pressure and depression in the high-risk sample and then in the subsample from the replication cohort. Logistic regression analyses were used when the dependent variable was dichotomous and ordinary least squares linear regression analysis was used when the dependent variable was continuous. Continuous outcome data that were not normally distributed were transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship between systolic blood pressure and future depressive disorder was examined by investigating the percentage of children with future depressive disorder by blood pressure quintiles, again in both samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. Lastly, the association between systolic blood pressure and future depressive disorder was investigated in the general population by using the entire ALSPAC sample and the presence of a multiplicative interaction between maternal depression and systolic blood pressure on future depressive disorder was examined. Listwise deletion was used to deal with missing data in all analyses and data were analysed using SPSS (v20).**Results**

Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent depression), the ALSPAC replication subsample of children with mothers that have experienced recurrent depression and the whole ALSPAC sample

Table 1 shows that the three samples are comparable on a range of demographics (child age, gender, maternal education and parental social class).

Table 1

	EPAD (n=281)	**ALSPAC** (subsample of offspring of recurrently depressed mothers; n=612)	**ALSPAC** (whole sample; n=4830)
Child age: mean (sd)	12.4 (2.0)	12.8 (0.2)	12.8 (0.2)
Child gender (% female)	58.4	56.7	52.1
Maternal education (% higher education)	51.9	44.3	47.2
Parental social class (% non-manual)	74.0	84.1	87.7

Demographics at baseline in the EPAD sample, ALSPAC subsample of offspring of recurrently depressed mothers and the whole ALSPAC sample

Descriptives from EPAD high-risk sample

Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at baseline. Systolic blood pressure at baseline was significantly correlated with age (r=.23, p<.001), but diastolic blood pressure was not (r=.02, p=.728). Systolic blood pressure was thus standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable.[17] Mean blood pressures for each age group in this sample were generally higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated with weight (r=.25, p<.001), but diastolic blood pressure was not (r=.07, p=.236). Given this finding all analyses with systolic blood pressure are reported controlling for weight.

Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder (8.54%).

Descriptives from ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.45$, $p<.001$) and diastolic blood pressure ($r=.18$, $p<.001$), therefore all results are reported controlling for weight.

Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at age 15 (2.94%).

Initial analyses in EPAD high-risk sample

Logistic regression analyses were performed to investigate the association between blood pressure and new onset depressive disorder in the EPAD sample of children. 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. Diastolic blood pressure at baseline did not significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01; p=.120).

Results remained the same when the outcome was expanded to include the new onset of more broadly defined mood-related diagnoses (primary diagnosis: major depressive disorder n=22, dysthymia n=1, cyclothymia n=1, bipolar disorder n=3, adjustment disorder with depressed mood n=4 and depressive disorder not otherwise specified n=5). Results also remained similar when separately adjusting for medication use and physical health problems in the child and when adjusting for BMI instead of weight. The association was not significantly moderated by gender (p=.769).

Given few adolescents developed new onset depressive disorder, the analysis was repeated using total depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome, and again controlling for weight, showed significant association ($\beta = -.13$; p=.040).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This was non-significant (β = -.05; p =.412). Given the low number of individuals with depressive disorder at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again the results were non-significant (β = -.07; p = .286).

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Logistic regression analyses were undertaken in the replication sample. Lower systolic blood pressure at age 12 significantly predicted depressive disorder at age 15 (OR = .48, 95% CI .27 to .85; p=.012), however, diastolic blood pressure did not (OR = .98, 95% CI .93 to 1.05; p=.597). Results remained similar when adjusting for BMI instead of weight and when additionally adjusting for maternal systolic blood pressure in pregnancy. The association was not significantly moderated by gender (p=.102).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant (β = -.04; p = .378).

Relationship between blood pressure and depressive disorder in high-risk EPAD sample

To further investigate the relationship between systolic blood pressure and depressive disorder in the EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 2

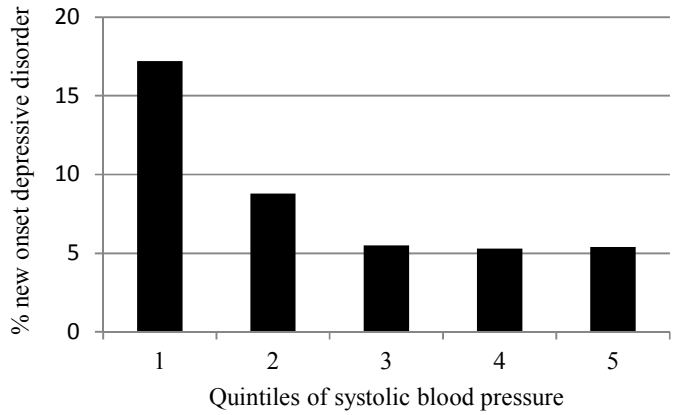


Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of systolic blood pressure at baseline in the EPAD sample

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

To further investigate the relationship between systolic blood pressure and depression in the replication sample, blood pressure was split into quintiles to examine the percentage of children with depression at age 15 by blood pressure categories and the linearity of the relationship.

As can be seen in Figure 3, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 3

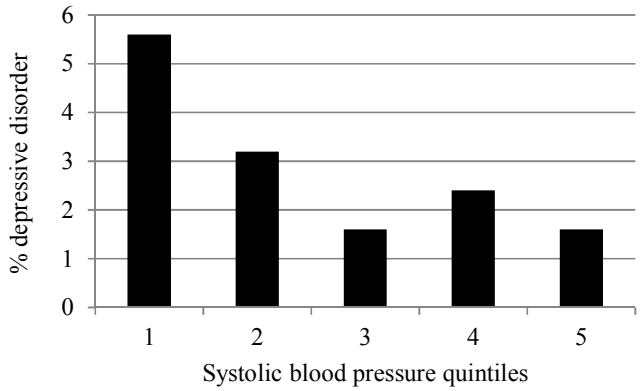


Figure to show percentage of children with depressive disorder at age 15 years by quintiles of systolic blood pressure at age 12 years in the ALSPAC sample

Analyses so far have highlighted a significant association between lower systolic blood pressure and future depression in two different samples of offspring of parents with recurrent depression. Next, ROC analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. A cut off point of below 0.025 standard deviations above the mean using standardised systolic blood pressure [17] showed a sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the association between low blood pressure and future depressive disorder using each of the cut offs identified in each sample (Table 2).

Table 2

	OR (95% CI)[1]	
	Optimal cut off in EPAD sample (< .025)	Optimal cut off in ALSPAC sample (< -.485)
EPAD sample	3.13 (1.30, 7.53)	3.43 (1.45, 8.13)
ALSPAC sample	3.00 (.93, 9.71)	3.62 (1.23, 10.65)

[1]Adjusted for child weight at W1

Association between low blood pressure and future depressive disorder in the EPAD and ALSPAC samples using the optimal cut off for low blood pressure identified in each sample using ROC curve analysis

From these analyses it seems a cut off for low systolic blood pressure for children aged 12 years lies between 108 and 113mmHg.

Lastly, supplementary analyses were performed to examine the association between blood pressure and future depression in the general population using the entire ALSPAC sample.

Supplementary analyses using entire ALSPAC sample:

1) **Testing the relationship between depressive disorder and blood pressure in the general population (not limiting analysis to those adolescents with a parental history of recurrent depression)**

Descriptives

Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.44$, $p<.001$) and diastolic blood pressure ($r=.19$, $p<.001$), therefore all results are reported controlling for weight.

Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last month at age 15 (1.55%).

Preliminary analyses

Logistic regression analyses were performed to investigate the association between blood pressure and depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .76 to 1.27; p=.875). Diastolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04; p=.604).

2) **Examining whether a history of recurrent maternal depression moderated the relationship between systolic blood pressure and depression**

Logistic regression analyses were then performed to test if recurrent maternal depression moderated the relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic blood pressure and maternal recurrent depression were centred to convert them to their deviation form to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95% CI .27 to .89; p=.019).

Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal depression was present, children with low blood pressure showed the highest percentage of depressive disorder. However, when recurrent maternal depression was not present, children with high blood pressure showed the highest percentage of depressive disorder.

Figure 4

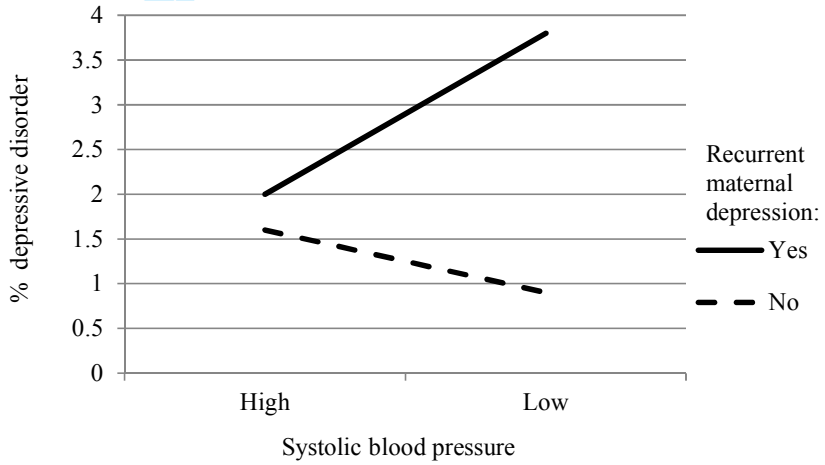


Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low' systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample

Discussion

In this study we found that lower systolic blood pressure significantly predicted future new onset depressive disorder amongst a sample of children and adolescents at high risk of developing depression because of a parental history of recurrent depression. This finding was replicated in a large community based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression (replication sample). When investigating this relationship in more detail, it seemed that those with the lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut off value for systolic blood pressure in 12 year old children was identified as being within the range of 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort (ALSPAC), the association between blood pressure and major depressive disorder was no longer significant. There was no evidence for an association in the opposite direction (depression predicting future blood pressure levels) either in the study sample or in the replication cohort nor was there an association between diastolic blood pressure and future depression in either dataset.

In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive disorder was slightly higher than population norms, it was those whose blood pressure was lower who were at most risk of developing depressive disorder. This was not true in adolescents from the general population. There have been no previously published longitudinal studies examining the relationship between blood pressure and depression in children from the general population or children at high-risk of depression. In adults, findings have been mixed but links between low blood pressure and depression have been noted. These have not only been noted cross-sectionally in adults,[19, 20] but a study on elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] In adolescents who did not have a parent with recurrent depressive disorder, higher blood pressure showed some association with a higher risk of future depressive disorder. Given the limited scientific literature on this topic the mechanisms by which low blood pressure might precede depression for adolescent offspring of individuals with recurrent depressive disorder are unclear and we can at present only speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or environmental) that contribute to both lower blood pressure and depression that are especially enriched in those offspring most at risk of developing depressive disorder in the near future. Another possibility is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major

depressive disorder. There is strikingly limited research on biological links between early mental health problems and physical health as well as on autonomic system function in young people who are familially vulnerable to depression [21]. Our findings highlight the need for further research on links between mental and physical health in young people.

Strengths and Limitations

This is the first study we are aware of to report on the longitudinal relationship between blood pressure and depressive disorder in adolescents, an important period for the onset of depression. In the main sample, children and adolescents were followed up at three points over a four year period with a high retention rate of over 80%. A similar pattern of results was found in a large community based cohort study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples, diagnoses were systematically ascertained using interview and blood pressure readings were measured according to standardised protocol. In addition, potential confounders of the relationship were taken account of. There were also possible limitations of the study. Blood pressures were measured using an electronic device which uses an oscillometric technique rather than the auscultatory technique that most population norms are based on and it has been noted that these readings are not equivalent. However there is a lack of consensus as to whether using different methods leads to any systematic bias and inaccuracies seem more related to not using a standardised technique rather than the instrument.[22] In addition, the cut off values identified in the high risk and replication samples differed slightly. This may have been because of differences in measurement techniques in the two studies. These results need to be replicated in other samples in order to establish more precise cut off for low systolic blood pressure. Despite being a high-risk sample, the number of children with depressive disorder was small and many of the sample had not been though the age of maximum risk for developing a depressive disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of children with depressive disorder was also low in the replication sample, partly because only a self-report measure of depressive disorder was available at age 15, and partly because of selective attrition over time. Previous studies have reported that although attrition has affected prevalence rates of depression in the mother and internalising disorders in the children, the associations between risks and outcomes remained intact, although conservative estimates of the likely true effects.[23, 24] Lastly, the subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe

group as maternal self-report of depression was used as opposed to defining episodes of depression using DSM-IV criteria as was done in the main dataset.

In summary, in our study of adolescents at high risk of depression we found that low blood pressure was associated with major depressive disorder. This finding was replicated in an independent cohort. Future research is needed using different populations to confirm this relationship as it is a novel finding and to investigate the mechanisms by which the relationship between low blood pressure and depressive disorder in children at risk for depression may arise.

Acknowledgments

Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable Trust and the National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship.

We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for their help with recruiting them and the whole EPAD team. We thank the other investigators involved in the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar, Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules Thorn Charitable Trust.

Conflict of interest

None of the authors have conflict of interest/financial disclosures.

Role of funding source

Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors (AKT). The funders had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the paper for publication.

Contributorship

Ms Gemma Hammerton (jointly designed the paper and the analysis, carried out the analysis, jointly drafted and revised the paper), Professor Anita Thapar (helped with initial conception of the study and with study design, critically revised the draft for important intellectual content), Professor Gordon Harold,(advised on analysis of the paper, critically revised the paper) Dr Ajay Thapar (conception of the paper, jointly designed the study and analysis, joint initial drafting and revising the paper). All authors approved the final version prior to submission of the paper. Dr Ajay Thapar is the guarantor.

Data sharing: no additional data available.

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Title: Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Abstract

Objective – To examine the relationship between blood pressure and depressive disorder in children and adolescents at high-risk for depression.

Design – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study of offspring of parents with recurrent depression and an on-going birth cohort for replication.

Setting – Community based studies.

Participants – High-risk sample includes 281 families where children were aged 9-17 years at baseline and 10-19 years at the final data point. Replication cohort includes 4830 families where children were aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring with mothers that had reported recurrent depression.

Main outcome measures –New onset DSM-IV defined depressive disorder in the offspring using established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the replication sample.

Results – Blood pressure was standardised for age and gender to create standard deviation scores and child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and future depression was also found in the replication cohort in the second subset of high-risk children whose mothers had experienced recurrent depression in the past.

Conclusion – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of parents with depression. Further studies are needed to investigate how this association arises.

Key words

Depression; Blood Pressure; ALSPAC; Adolescent; Cohort Studies

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Article focus:

- To examine the relationship between blood pressure and future depressive disorder in adolescents at high-risk for depression.

Key messages

- Low systolic blood pressure predicts future depressive disorder in adolescent offspring of parents with recurrent depression.

Strength and Limitations

- Replication of findings in two independent cohort studies, one a high risk sample and one a population based cohort.
- Mechanism by which low blood pressure is linked to depression risk needs further investigation.

Introduction

The two leading causes of death and disability in the developed world are depression and cardiovascular disease. The association between depression and cardiovascular disease is well established in adults,[1] although the mechanisms by which it arises are still not clear. It has been suggested that these links reflect early associations between depression and cardiovascular risk factors. High blood pressure is an important cardiovascular risk factor and it has also been linked to depression in adults in some studies.[2] Other studies, however, have found the converse. They suggest that depression is associated with low blood pressure and that it is only depression treated with certain antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the findings are inconsistent, with some studies finding depression as a predictor of either high blood pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure predicting depression.[6]

Although both depression and the early indicators of cardiovascular disease have been found to have onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger populations. In this study, the main aim was to investigate the relationship between blood pressure and subsequent first onset episode of depression in a prospective cohort of children and adolescents at high risk of depression. The secondary aim was to replicate findings in an independent cohort.

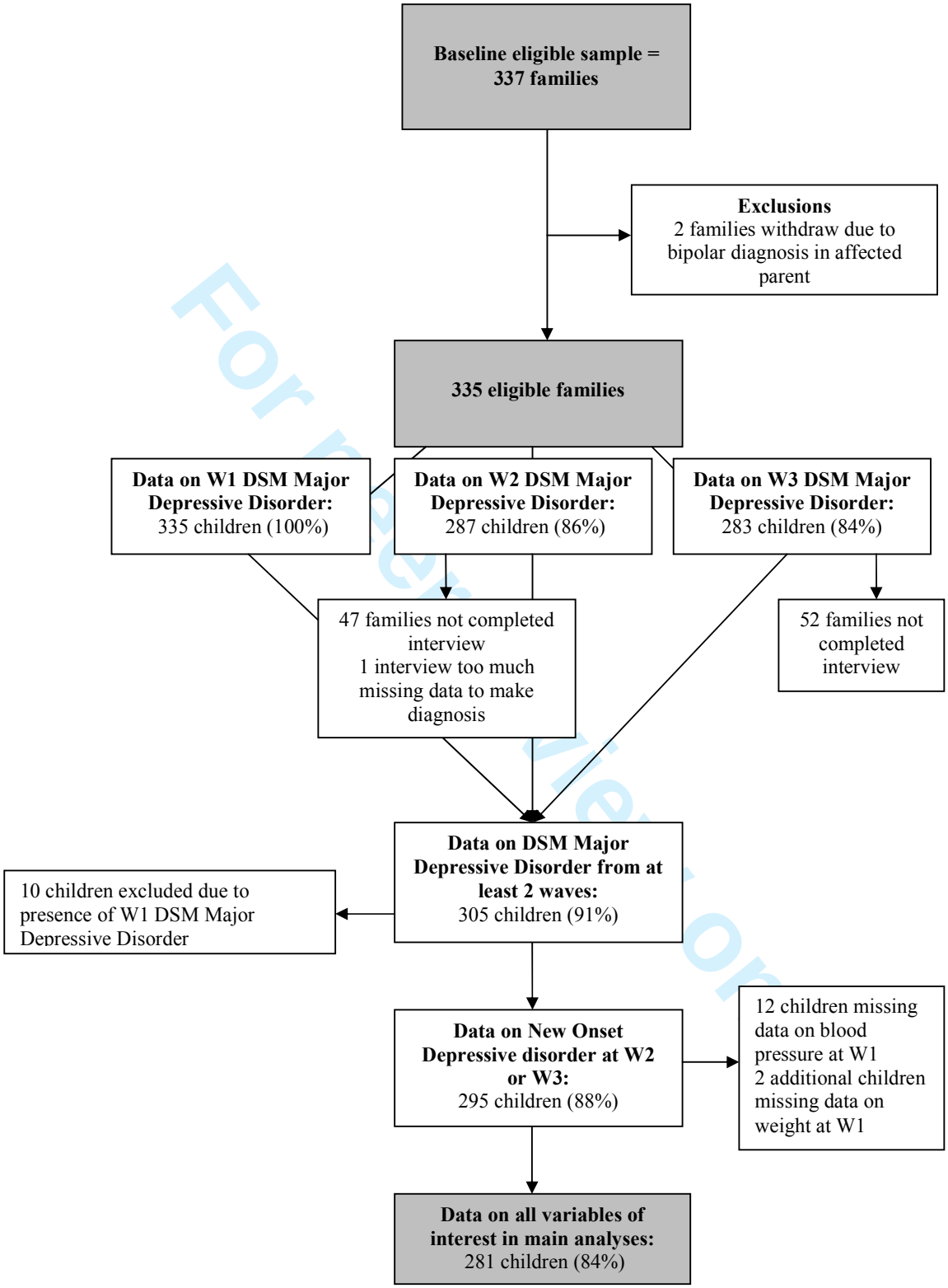
Method

Data were derived from a prospective longitudinal study of offspring of parents with recurrent depression–'The Early Prediction of Adolescent Depression (EPAD) study'. At baseline, the sample included 337 families (315 mothers and 22 fathers) that were recruited from general practices across South Wales, by writing to eligible families, and from a database of adults with previously identified unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test the main hypotheses of the original project whilst allowing detailed assessments at each time point. Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to and currently living with the affected parent. Additional exclusion criteria included children with moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the study because the depressed parent had been diagnosed as suffering from bipolar disorder since the wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed using age-appropriate standard research diagnostic interviews independently by two trained research psychologists on three occasions over the course of the study which began in April 2007 and finished in April 2011. The average time between the baseline and second assessment was 16.2 months and between the second and third assessment was 12.5 months. Further details on the sample characteristics and methodology have been described previously.[9]

For the main analyses, 30 families were excluded because they had not completed at least two waves of data. A further 10 children were excluded from main analyses because they already met criteria for DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not been completed at baseline either because there had been a fault in the equipment or the child had refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data were collected from parents and children via semi-structured research diagnostic interviews and blood

pressure and weight were assessed by the interviewer. Additional data on physical health problems, maternal education and social class were collected from parents and children from self-completed questionnaires that were mailed to the families two weeks before their interview. Ethical approval for the study was obtained from the Multi-centre Research Ethics Committee for Wales.

85 *Figure 1*



Flow chart of retention at each assessment in the EPAD sample

Data were also utilised from a birth cohort study 'The Avon Longitudinal Study of Parents and Children (ALSPAC)' to allow replication of findings from the first high-risk sample. The cohort was set up to examine genetic and environmental determinants of health and development.[10] The initial cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date of delivery between 1st April 1991 and 31st December 1992 (www.alspac.bris.ac.uk). All pregnant women resident in three health districts in the old administrative county of Avon who had an estimated delivery between the above dates were eligible to participate. In addition, pregnant women that had migrated into the catchment area before the point of delivery were eligible. Recruitment was carried out by attempting to make contact with eligible women through ALSPAC staff visiting community locations and through using antenatal and maternity health services and media information to encourage contact and promote the study.[10] The parents completed regular postal questionnaires concerning their child's health and development since birth. The children have completed questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range: 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children whose mothers had experienced recurrent depression (at least two episodes); 612 children were included in these analyses (347 females and 265 males). Ethical approval for the study was obtained from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

Measures

EPAD study:

Assessment of depression in the offspring of parents with recurrent depression

The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic interview that has high reliability and that is used to assess children's psychiatric symptoms [11]. Parents are asked about their children's psychopathology and children are independently interviewed using the interview schedules (parent and child versions). The presence of any given symptom has to be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

selected recordings at each time point (10 parent report and 10 child report) and through weekly supervision by an academic clinician with extensive experience in using the interview. Average agreement between raters for DSM-IV psychiatric disorder was excellent (κ =0.92), as was average agreement for depression symptoms (κ =0.93). CAPA was used at each assessment and assesses the presence of a major depressive disorder in the child over the preceding three months. The parent and child versions were completed independently, with interviews conducted in separate rooms where possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of DSM-IV major depressive disorder symptoms was also computed from the CAPA.

New onset major depressive disorder - The presence of a new onset DSM-IV diagnosis of major depressive disorder at either the second or third assessment was defined by excluding children that had a baseline diagnosis of DSM-IV major depressive disorder.

Blood pressure –An Omron 705IT sphygmomanometer was used to measure blood pressure at each assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were measured using standardised guidelines set out by the American Heart association.[12] At least two readings were taken at least one minute apart using the right arm. When the difference between two readings was 5mmHg or less an average was taken.

Weight and other potential confounders – Weight was considered to be a confounder of the relationship between blood pressure and depression due to its potential association with both.[13, 14] Interviewers measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also examined whether the results were affected by the presence of physical health problems (parent reported), any medication use (child or parent reported) and using body mass index (BMI) instead of weight.

Demographics – The mother and father questionnaires completed at baseline were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels, degree or postgraduate qualification). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

ALSPAC:

Maternal history of recurrent depression – Mothers completed regular questionnaires from pregnancy to when the child was aged 12 years including the questions 'Have you had depression in the last year/ last two years/ since your child was born/ever'. The mother was also asked 'Have you ever had severe depression' on three occasions over this time period. Research diagnostic interview generated psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data set thus had to be defined where mother had reported having depression on at least two separate occasions, and if at least one of these occasions was reported as being severe. These criteria were used to create a subsample that was as similar as possible to the primary high-risk sample.

Child depressive disorder – Parent reports on their child's symptoms were obtained using a structured diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA, has been used widely for large scale population studies. The parent-rated DAWBA was completed when the target age of the children was 13 years. Children were directly interviewed using the DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV diagnosis of depression and generates diagnoses (see www.DAWBA.com for more information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part of the ALSPAC data collection process. [16]

Blood pressure – Systolic and diastolic blood pressure were measured at the clinic assessments when the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

Weight and other potential confounders – Interviewers measured the weight and height of the children in light clothing and without shoes at the clinic assessments when the target age of the children was 12 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then calculated (kg/m²). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal medical records.

Demographics – The mother and father questionnaires completed during pregnancy were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels or degree). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

Statistical methods

Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the high-risk sample and then in the replication cohort using the subsample of children with mothers that have experienced recurrent depression in the past. Next, regression analyses were performed to examine the association between blood pressure and depression in the high-risk sample and then in the subsample from the replication cohort. Logistic regression analyses were used when the dependent variable was dichotomous and ordinary least squares linear regression analysis was used when the dependent variable was continuous. Continuous outcome data that were not normally distributed were transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship between systolic blood pressure and future depressive disorder was examined by investigating the percentage of children with future depressive disorder by blood pressure quintiles, again in both samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. Lastly, the association between systolic blood pressure and future depressive disorder was investigated in the general population by using the entire ALSPAC sample and the presence of a multiplicative interaction between maternal depression and systolic blood pressure on future depressive disorder was examined. Listwise deletion was used to deal with missing data in all analyses and data were analysed using SPSS (v20).

Results

Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent depression), the ALSPAC replication subsample of children with mothers that have experienced recurrent depression and the whole ALSPAC sample

Table 1 shows that the three samples are comparable on a range of demographics (child age, gender, maternal education and parental social class).

Table 1

	EPAD (n=281)	**ALSPAC** (subsample of offspring of recurrently depressed mothers; n=612)	**ALSPAC** (whole sample; n=4830)
Child age: mean (sd)	12.4 (2.0)	12.8 (0.2)	12.8 (0.2)
Child gender (% female)	58.4	56.7	52.1
Maternal education (% higher education)	51.9	44.3	47.2
Parental social class (% non-manual)	74.0	84.1	87.7

Demographics at baseline in the EPAD sample, ALSPAC subsample of offspring of recurrently depressed mothers and the whole ALSPAC sample

Descriptives from EPAD high-risk sample

Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at baseline. Systolic blood pressure at baseline was significantly correlated with age (r=.23, p<.001), but diastolic blood pressure was not (r=.02, p=.728). Systolic blood pressure was thus standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable.[17] Mean blood pressures for each age group in this sample were generally higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated with weight (r=.25, p<.001), but diastolic blood pressure was not (r=.07, p=.236). Given this finding all analyses with systolic blood pressure are reported controlling for weight.

Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder (8.54%).

Descriptives from ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic (r=.45, p<.001) and diastolic blood pressure (r=.18, p<.001), therefore all results are reported controlling for weight.

Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at age 15 (2.94%).

Initial analyses in EPAD high-risk sample

Logistic regression analyses were performed to investigate the association between blood pressure and new onset depressive disorder in the EPAD sample of children. 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. Diastolic blood pressure at baseline did not significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01; p=.120).

Results remained the same when the outcome was expanded to include the new onset of more broadly defined mood-related diagnoses (primary diagnosis: major depressive disorder n=22, dysthymia n=1, cyclothymia n=1, bipolar disorder n=3, adjustment disorder with depressed mood n=4 and depressive disorder not otherwise specified n=5). Results also remained similar when separately adjusting for medication use and physical health problems in the child and when adjusting for BMI instead of weight. The association was not significantly moderated by gender (p=.769).

Given few adolescents developed new onset depressive disorder, the analysis was repeated using total depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood

pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome, and again controlling for weight, showed significant association (β = -.13; p=.040).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This was non-significant (β = -.05; p =.412). Given the low number of individuals with depressive disorder at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again the results were non-significant (β = -.07; p = .286).

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Logistic regression analyses were undertaken in the replication sample. Lower systolic blood pressure at age 12 significantly predicted depressive disorder at age 15 (OR = .48, 95% CI .27 to .85; p=.012), however, diastolic blood pressure did not (OR = .98, 95% CI .93 to 1.05; p=.597). Results remained similar when adjusting for BMI instead of weight and when additionally adjusting for maternal systolic blood pressure in pregnancy. The association was not significantly moderated by gender (p=.102).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant (β = -.04; p = .378).

Relationship between blood pressure and depressive disorder in high-risk EPAD sample

To further investigate the relationship between systolic blood pressure and depressive disorder in the EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 2

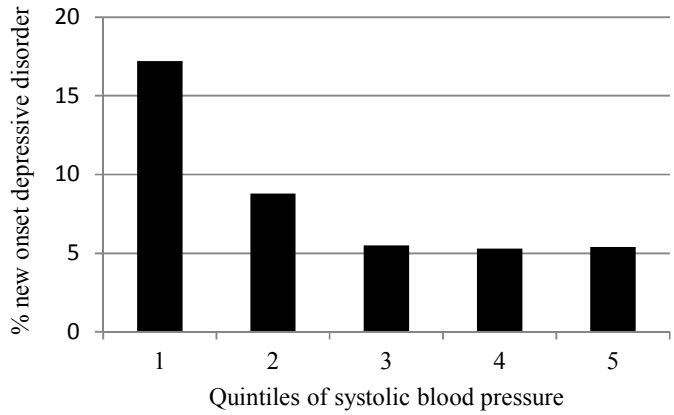


Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of systolic blood pressure at baseline in the EPAD sample

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

To further investigate the relationship between systolic blood pressure and depression in the replication sample, blood pressure was split into quintiles to examine the percentage of children with depression at age 15 by blood pressure categories and the linearity of the relationship.

As can be seen in Figure 3, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 3

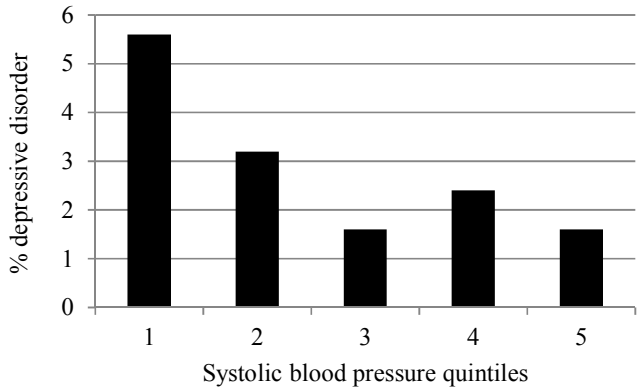


Figure to show percentage of children with depressive disorder at age 15 years by quintiles of systolic blood pressure at age 12 years in the ALSPAC sample

Analyses so far have highlighted a significant association between lower systolic blood pressure and future depression in two different samples of offspring of parents with recurrent depression. Next, ROC analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. A cut off point of below 0.025 standard deviations above the mean using standardised systolic blood pressure [17] showed a sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the association between low blood pressure and future depressive disorder using each of the cut offs identified in each sample (Table 2).

Table 2

	OR (95% CI)[1]	
	Optimal cut off in EPAD sample (< .025)	Optimal cut off in ALSPAC sample (< -.485)
EPAD sample	3.13 (1.30, 7.53)	3.43 (1.45, 8.13)
ALSPAC sample	3.00 (.93, 9.71)	3.62 (1.23, 10.65)

[1]Adjusted for child weight at W1

Association between low blood pressure and future depressive disorder in the EPAD and ALSPAC samples using the optimal cut off for low blood pressure identified in each sample using ROC curve analysis

From these analyses it seems a cut off for low systolic blood pressure for children aged 12 years lies between 108 and 113mmHg.

Lastly, supplementary analyses were performed to examine the association between blood pressure and future depression in the general population using the entire ALSPAC sample.

Supplementary analyses using entire ALSPAC sample:

1) **Testing the relationship between depressive disorder and blood pressure in the general population (not limiting analysis to those adolescents with a parental history of recurrent depression)**

Descriptives

Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.44$, $p<.001$) and diastolic blood pressure ($r=.19$, $p<.001$), therefore all results are reported controlling for weight.

Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last month at age 15 (1.55%).

Preliminary analyses

Logistic regression analyses were performed to investigate the association between blood pressure and depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .76 to 1.27; p=.875). Diastolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04; p=.604).

2) **Examining whether a history of recurrent maternal depression moderated the relationship between systolic blood pressure and depression**

Logistic regression analyses were then performed to test if recurrent maternal depression moderated the relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic blood pressure and maternal recurrent depression were centred to convert them to their deviation form to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95% CI .27 to .89; p=.019).

Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal depression was present, children with low blood pressure showed the highest percentage of depressive disorder. However, when recurrent maternal depression was not present, children with high blood pressure showed the highest percentage of depressive disorder.

Figure 4

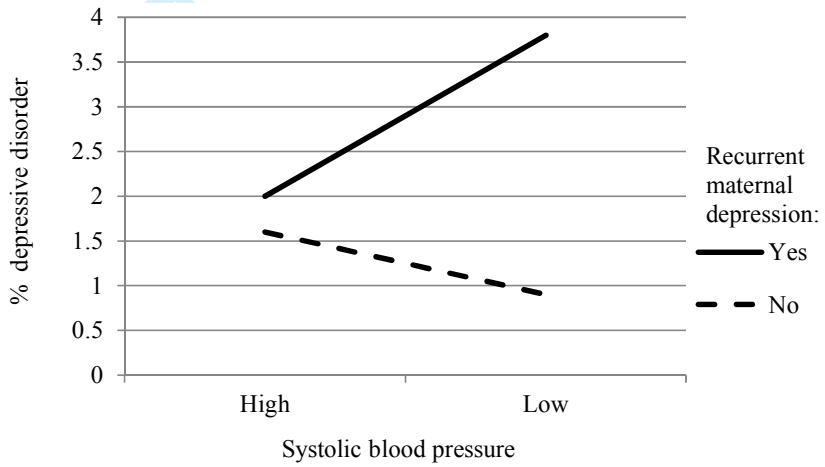


Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low' systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample

Discussion

In this study we found that lower systolic blood pressure significantly predicted future new onset depressive disorder amongst a sample of children and adolescents at high risk of developing depression because of a parental history of recurrent depression. This finding was replicated in a large community based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression (replication sample). When investigating this relationship in more detail, it seemed that those with the lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut off value for systolic blood pressure in 12 year old children was identified as being within the range of 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort (ALSPAC), the association between blood pressure and major depressive disorder was no longer significant. There was no evidence for an association in the opposite direction (depression predicting future blood pressure levels) either in the study sample or in the replication cohort nor was there an association between diastolic blood pressure and future depression in either dataset.

In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive disorder was slightly higher than population norms, it was those whose blood pressure was lower who were at most risk of developing depressive disorder. This was not true in adolescents from the general population. There have been no previously published longitudinal studies examining the relationship between blood pressure and depression in children from the general population or children at high-risk of depression. In adults, findings have been mixed but links between low blood pressure and depression have been noted. These have not only been noted cross-sectionally in adults,[19, 20] but a study on elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] In adolescents who did not have a parent with recurrent depressive disorder, higher blood pressure showed some association with a higher risk of future depressive disorder. Given the limited scientific literature on this topic the mechanisms by which low blood pressure might precede depression for adolescent offspring of individuals with recurrent depressive disorder are unclear and we can at present only speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or environmental) that contribute to both lower blood pressure and depression that are especially enriched in those offspring most at risk of developing depressive disorder in the near future. Another possibility is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major

depressive disorder. There is strikingly limited research on biological links between early mental health problems and physical health as well as on autonomic system function in young people who are familially vulnerable to depression [21]. Our findings highlight the need for further research on links between mental and physical health in young people.

Strengths and Limitations

This is the first study we are aware of to report on the longitudinal relationship between blood pressure and depressive disorder in adolescents, an important period for the onset of depression. In the main sample, children and adolescents were followed up at three points over a four year period with a high retention rate of over 80%. A similar pattern of results was found in a large community based cohort study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples, diagnoses were systematically ascertained using interview and blood pressure readings were measured according to standardised protocol. In addition, potential confounders of the relationship were taken account of. There were also possible limitations of the study. Blood pressures were measured using an electronic device which uses an oscillometric technique rather than the auscultatory technique that most population norms are based on and it has been noted that these readings are not equivalent. However there is a lack of consensus as to whether using different methods leads to any systematic bias and inaccuracies seem more related to not using a standardised technique rather than the instrument.[22] In addition, the cut off values identified in the high risk and replication samples differed slightly. This may have been because of differences in measurement techniques in the two studies. These results need to be replicated in other samples in order to establish more precise cut off for low systolic blood pressure. Despite being a high-risk sample, the number of children with depressive disorder was small and many of the sample had not been though the age of maximum risk for developing a depressive disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of children with depressive disorder was also low in the replication sample, partly because only a self-report measure of depressive disorder was available at age 15, and partly because of selective attrition over time. Previous studies have reported that although attrition has affected prevalence rates of depression in the mother and internalising disorders in the children, the associations between risks and outcomes remained intact, although conservative estimates of the likely true effects.[23, 24] Lastly, the subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe

group as maternal self-report of depression was used as opposed to defining episodes of depression using DSM-IV criteria as was done in the main dataset.

In summary, in our study of adolescents at high risk of depression we found that low blood pressure was associated with major depressive disorder. This finding was replicated in an independent cohort. Future research is needed using different populations to confirm this relationship as it is a novel finding and to investigate the mechanisms by which the relationship between low blood pressure and depressive disorder in children at risk for depression may arise.

Acknowledgments

Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable Trust and the National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship.

We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for their help with recruiting them and the whole EPAD team. We thank the other investigators involved in the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar, Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules Thorn Charitable Trust.

Conflict of interest

None of the authors have conflict of interest/financial disclosures.

Role of funding source

Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors (AKT). The funders had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the paper for publication.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **page 4 & 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **page 4 & 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **page 4 & 7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **pages 7, 8, 9 & 10**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **pages 7, 8, 9 & 10**
Bias	9	Describe any efforts to address potential sources of bias **page 3, pages 8 & 10 (addressing confounders), and pages 19**
Study size	10	Explain how the study size was arrived at **pages 4, 6 & 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **pages7, 8, 9 & 10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **pages 8, 10, 11 & 12**
		(*b*) Describe any methods used to examine subgroups and interactions **pages 10, 16 & 17**
		(*c*) Explain how missing data were addressed **page 10**
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **pages 10, 12, 13 & 15**
Results		

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **pages 4, 6 & 7**
		(b) Give reasons for non-participation at each stage **pages 4, 6 & 7**
		(c) Consider use of a flow diagram **page 6**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **page 11, 12 & 16**
		(b) Indicate number of participants with missing data for each variable of interest **pages 4, 6 & 7**
		(c) Summarise follow-up time (eg, average and total amount) **page 4**
Outcome data	15*	Report numbers of outcome events or summary measures over time **page 11, 12 & 16**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **pages 8, 10, 12, 13, 15 & 16**
		(*b*) Report category boundaries when continuous variables were categorized **page 13, 14 & 15**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **pages 11-17**
Discussion		
Key results	18	Summarise key results with reference to study objectives **page 18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **pages 19 & 20**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **page 18**
Generalisability	21	Discuss the generalisability (external validity) of the study results **pages 18 & 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **page 21**

*Give information separately for exposed and unexposed groups. **n/a**

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ open

Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003206.R2
Article Type:	Research
Date Submitted by the Author:	22-Aug-2013
Complete List of Authors:	Hammerton, Gemma; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences Harold, Gordon; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences Thapar, Anita; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences Thapar, Ajay; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Cardiovascular medicine, Paediatrics
Keywords:	MENTAL HEALTH, EPIDEMIOLOGY, Hypertension < CARDIOLOGY

Title: Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Abstract

Objective – To examine the relationship between blood pressure and depressive disorder in children and adolescents at high-risk for depression.

Design – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study of offspring of parents with recurrent depression and an on-going birth cohort for replication.

Setting – Community based studies.

Participants – High-risk sample includes 281 families where children were aged 9-17 years at baseline and 10-19 years at the final data point. Replication cohort includes 4830 families where children were aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring with mothers that had reported recurrent depression.

Main outcome measures –New onset DSM-IV defined depressive disorder in the offspring using established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the replication sample.

Results – Blood pressure was standardised for age and gender to create standard deviation scores and child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and future depression was also found in the replication cohort in the second subset of high-risk children whose mothers had experienced recurrent depression in the past.

Conclusion – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of parents with depression. Further studies are needed to investigate how this association arises.

Key words

Depression; Blood Pressure; ALSPAC; Adolescent; Cohort Studies

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Article focus:

- To examine the relationship between blood pressure and future depressive disorder in adolescents at high-risk for depression.

Key messages

- Low systolic blood pressure predicts future depressive disorder in adolescent offspring of parents with recurrent depression.

Strength and Limitations

- Replication of findings in two independent cohort studies, one a high risk sample and one a population based cohort.
- Mechanism by which low blood pressure is linked to depression risk needs further investigation.

Introduction

The two leading causes of death and disability in the developed world are depression and cardiovascular disease. The association between depression and cardiovascular disease is well established in adults,[1] although the mechanisms by which it arises are still not clear. It has been suggested that these links reflect early associations between depression and cardiovascular risk factors. High blood pressure is an important cardiovascular risk factor and it has also been linked to depression in adults in some studies.[2] Other studies, however, have found the converse. They suggest that depression is associated with low blood pressure and that it is only depression treated with certain antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the findings are inconsistent, with some studies finding depression as a predictor of either high blood pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure predicting depression.[6]

Although both depression and the early indicators of cardiovascular disease have been found to have onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger populations. In this study, the main aim was to investigate the relationship between blood pressure and subsequent first onset episode of depression in a prospective cohort of children and adolescents at high risk of depression. The secondary aim was to replicate findings in an independent cohort.

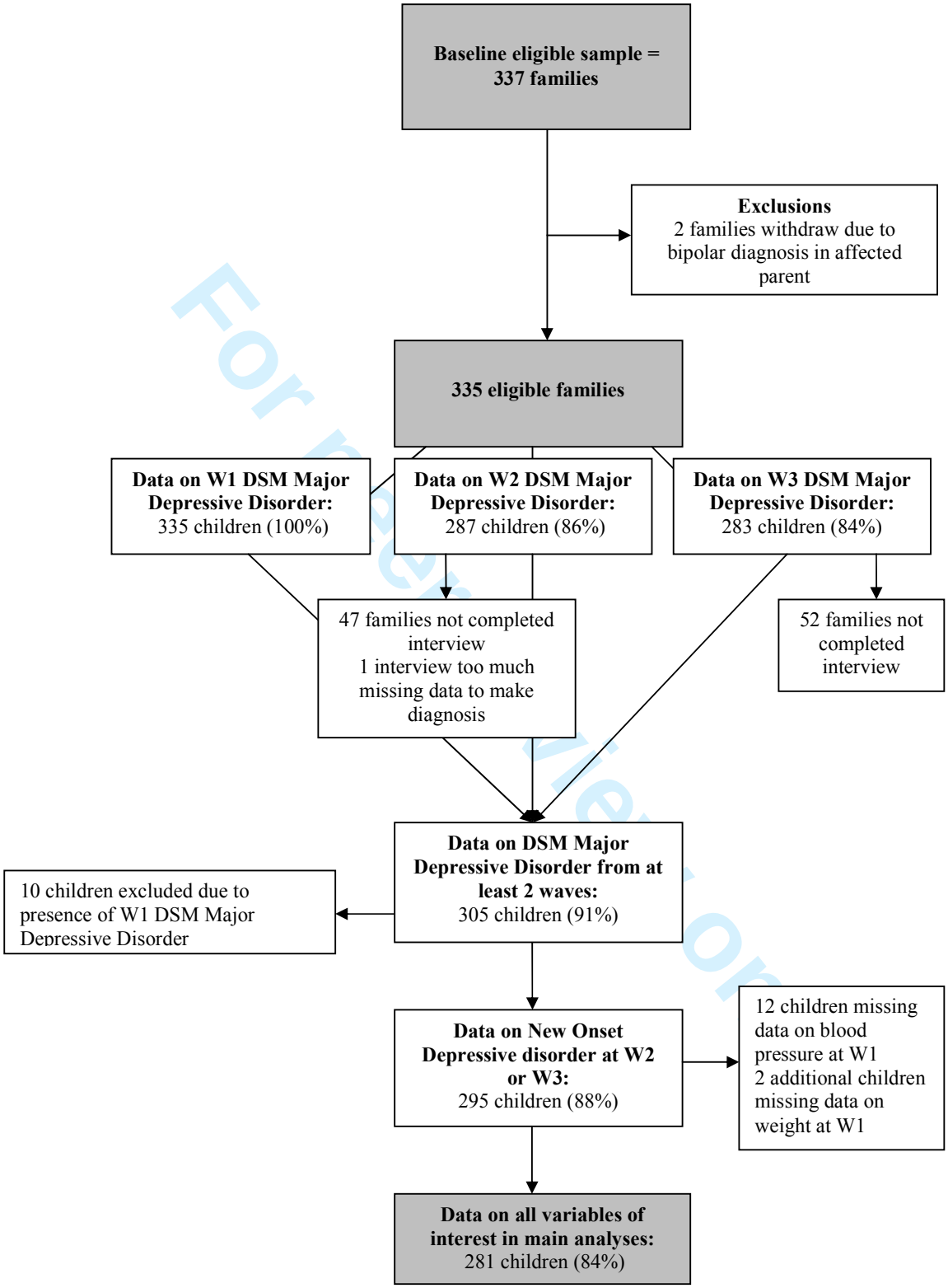
Method

Data were derived from a prospective longitudinal study of offspring of parents with recurrent depression–'The Early Prediction of Adolescent Depression (EPAD) study'. At baseline, the sample included 337 families (315 mothers and 22 fathers) that were recruited from general practices across South Wales, by writing to eligible families, and from a database of adults with previously identified unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test the main hypotheses of the original project whilst allowing detailed assessments at each time point. Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to and currently living with the affected parent. Additional exclusion criteria included children with moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the study because the depressed parent had been diagnosed as suffering from bipolar disorder since the wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed using age-appropriate standard research diagnostic interviews independently by two trained research psychologists on three occasions over the course of the study which began in April 2007 and finished in April 2011. The average time between the baseline and second assessment was 16.2 months and between the second and third assessment was 12.5 months. Further details on the sample characteristics and methodology have been described previously.[9]

For the main analyses, 30 families were excluded because they had not completed at least two waves of data. A further 10 children were excluded from main analyses because they already met criteria for DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not been completed at baseline either because there had been a fault in the equipment or the child had refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data were collected from parents and children via semi-structured research diagnostic interviews and blood

pressure and weight were assessed by the interviewer. Additional data on physical health problems, maternal education and social class were collected from parents and children from self-completed questionnaires that were mailed to the families two weeks before their interview. Ethical approval for the study was obtained from the Multi-centre Research Ethics Committee for Wales.

Figure 1



Flow chart of retention at each assessment in the EPAD sample

Data were also utilised from a birth cohort study 'The Avon Longitudinal Study of Parents and Children (ALSPAC)' to allow replication of findings from the first high-risk sample. The cohort was set up to examine genetic and environmental determinants of health and development.[10] The initial cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date of delivery between 1st April 1991 and 31st December 1992 (www.alspac.bris.ac.uk). All pregnant women resident in three health districts in the old administrative county of Avon who had an estimated delivery between the above dates were eligible to participate. In addition, pregnant women that had migrated into the catchment area before the point of delivery were eligible. Recruitment was carried out by attempting to make contact with eligible women through ALSPAC staff visiting community locations and through using antenatal and maternity health services and media information to encourage contact and promote the study.[10] The parents completed regular postal questionnaires concerning their child's health and development since birth. The children have completed questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range: 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children whose mothers had experienced recurrent depression (at least two episodes); 612 children were included in these analyses (347 females and 265 males). Ethical approval for the study was obtained from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

Measures

EPAD study:

Assessment of depression in the offspring of parents with recurrent depression

The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic interview that has high reliability and that is used to assess children's psychiatric symptoms [11]. Parents are asked about their children's psychopathology and children are independently interviewed using the interview schedules (parent and child versions). The presence of any given symptom has to be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

selected recordings at each time point (10 parent report and 10 child report) and through weekly supervision by an academic clinician with extensive experience in using the interview. Average agreement between raters for DSM-IV psychiatric disorder was excellent (κ =0.92), as was average agreement for depression symptoms (κ =0.93). CAPA was used at each assessment and assesses the presence of a major depressive disorder in the child over the preceding three months. The parent and child versions were completed independently, with interviews conducted in separate rooms where possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of DSM-IV major depressive disorder symptoms was also computed from the CAPA.

New onset major depressive disorder - The presence of a new onset DSM-IV diagnosis of major depressive disorder at either the second or third assessment was defined by excluding children that had a baseline diagnosis of DSM-IV major depressive disorder.

Blood pressure –An Omron 705IT sphygmomanometer was used to measure blood pressure at each assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were measured using standardised guidelines set out by the American Heart association.[12] At least two readings were taken at least one minute apart using the right arm. When the difference between two readings was 5mmHg or less an average was taken.

Weight and other potential confounders – Weight was considered to be a confounder of the relationship between blood pressure and depression due to its potential association with both.[13, 14] Interviewers measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also examined whether the results were affected by the presence of physical health problems (parent reported), any medication use (child or parent reported) and using body mass index (BMI) instead of weight.

Demographics – The mother and father questionnaires completed at baseline were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels, degree or postgraduate qualification). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

ALSPAC:

Maternal history of recurrent depression – Mothers completed regular questionnaires from pregnancy to when the child was aged 12 years including the questions 'Have you had depression in the last year/ last two years/ since your child was born/ever'. The mother was also asked 'Have you ever had severe depression' on three occasions over this time period. Research diagnostic interview generated psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data set thus had to be defined where mother had reported having depression on at least two separate occasions, and if at least one of these occasions was reported as being severe. These criteria were used to create a subsample that was as similar as possible to the primary high-risk sample.

Child depressive disorder – Parent reports on their child's symptoms were obtained using a structured diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA, has been used widely for large scale population studies. The parent-rated DAWBA was completed when the target age of the children was 13 years. Children were directly interviewed using the DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV diagnosis of depression and generates diagnoses (see www.DAWBA.com for more information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part of the ALSPAC data collection process. [16]

Blood pressure – Systolic and diastolic blood pressure were measured at the clinic assessments when the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

Weight and other potential confounders – Interviewers measured the weight and height of the children in light clothing and without shoes at the clinic assessments when the target age of the children was 12 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then calculated (kg/m²). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal medical records.

Demographics – The mother and father questionnaires completed during pregnancy were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels or degree). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

Statistical methods

Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the high-risk sample and then in the replication cohort using the subsample of children with mothers that have experienced recurrent depression in the past. Next, regression analyses were performed to examine the association between blood pressure and depression in the high-risk sample and then in the subsample from the replication cohort. Logistic regression analyses were used when the dependent variable was dichotomous and ordinary least squares linear regression analysis was used when the dependent variable was continuous. Continuous outcome data that were not normally distributed were transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship between systolic blood pressure and future depressive disorder was examined by investigating the percentage of children with future depressive disorder by blood pressure quintiles, again in both samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. Lastly, the association between systolic blood pressure and future depressive disorder was investigated in the general population by using the entire ALSPAC sample and the presence of a multiplicative interaction between maternal depression and systolic blood pressure on future depressive disorder was examined. Listwise deletion was used to deal with missing data in all analyses and data were analysed using SPSS (v20).

Results

Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent depression), the ALSPAC replication subsample of children with mothers that have experienced recurrent depression and the whole ALSPAC sample

Table 1 shows that the three samples are comparable on a range of demographics (child age, gender, maternal education and parental social class).

Table 1

	EPAD (n=281)	**ALSPAC** (subsample of offspring of recurrently depressed mothers; n=612)	**ALSPAC** (whole sample; n=4830)
Child age: mean (sd)	12.4 (2.0)	12.8 (0.2)	12.8 (0.2)
Child gender (% female)	58.4	56.7	52.1
Maternal education (% higher education)	51.9	44.3	47.2
Parental social class (% non-manual)	74.0	84.1	87.7

Demographics at baseline in the EPAD sample, ALSPAC subsample of offspring of recurrently depressed mothers and the whole ALSPAC sample

Descriptives from EPAD high-risk sample

Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at baseline. Systolic blood pressure at baseline was significantly correlated with age ($r=.23$, $p<.001$), but diastolic blood pressure was not ($r=.02$, $p=.728$). Systolic blood pressure was thus standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable.[17] Mean blood pressures for each age group in this sample were generally higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated with weight ($r=.25$, $p<.001$), but diastolic blood pressure was not ($r=.07$, $p=.236$). Given this finding all analyses with systolic blood pressure are reported controlling for weight.

Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder (8.54%).

Descriptives from ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.45$, $p<.001$) and diastolic blood pressure ($r=.18$, $p<.001$), therefore all results are reported controlling for weight.

Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at age 15 (2.94%).

Initial analyses in EPAD high-risk sample

Logistic regression analyses were performed to investigate the association between blood pressure and new onset depressive disorder in the EPAD sample of children. It was found that as systolic blood pressure increased, risk for new onset depressive disorder decreased, when adjusting for child's weight at baseline (OR = .65, 95% CI .44 to .96; p=.029), i.e. lower systolic blood pressure at baseline significantly predicted new onset depressive disorder. Diastolic blood pressure at baseline did not significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01; p=.120).

Results remained the same when the outcome was expanded to include the new onset of more broadly defined mood-related diagnoses (primary diagnosis: major depressive disorder n=22, dysthymia n=1, cyclothymia n=1, bipolar disorder n=3, adjustment disorder with depressed mood n=4 and depressive disorder not otherwise specified n=5). Results also remained similar when separately adjusting for medication use and physical health problems in the child and when adjusting for BMI instead of weight. The association was not significantly moderated by gender (p=.769).

Given few adolescents developed new onset depressive disorder, the analysis was repeated using total depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood

pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome, and again controlling for weight, showed significant association (β = -.13; p=.040).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This was non-significant (β = -.05; p =.412). Given the low number of individuals with depressive disorder at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again the results were non-significant (β = -.07; p = .286).

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Logistic regression analyses were undertaken in the replication sample. Again, it was found that as systolic blood pressure increased, risk for future depressive disorder decreased, when adjusting for child's weight at baseline (OR = .48, 95% CI .27 to .85; p=.012), i.e. lower systolic blood pressure at age 12 significantly predicted depressive disorder at age 15. Diastolic blood pressure at age 12 years did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .93 to 1.05; p=.597). Results remained similar when adjusting for BMI instead of weight and when additionally adjusting for maternal systolic blood pressure in pregnancy. The association was not significantly moderated by gender (p=.102).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant (β = -.04; p = .378).

Relationship between blood pressure and depressive disorder in high-risk EPAD sample

To further investigate the relationship between systolic blood pressure and depressive disorder in the EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with

the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 2

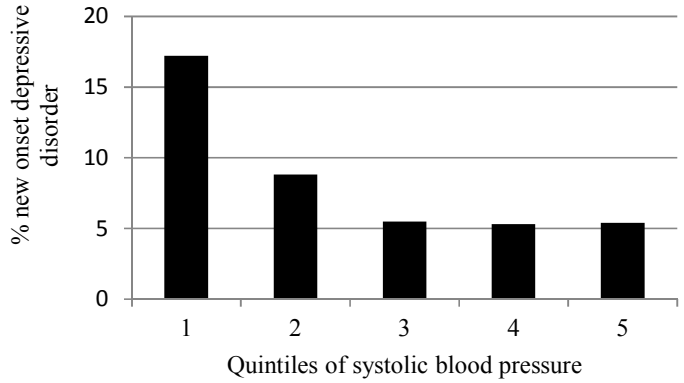


Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of systolic blood pressure at baseline in the EPAD sample

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

To further investigate the relationship between systolic blood pressure and depression in the replication sample, blood pressure was split into quintiles to examine the percentage of children with depression at age 15 by blood pressure categories and the linearity of the relationship.

As can be seen in Figure 3, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 3

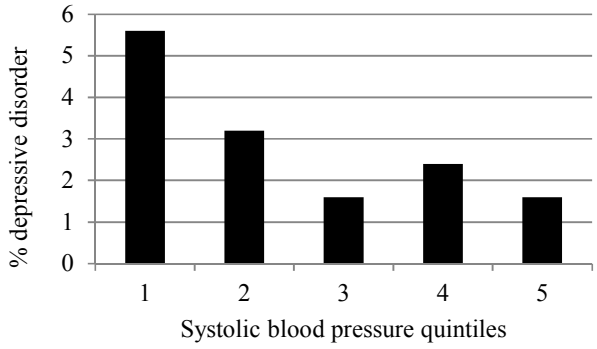


Figure to show percentage of children with depressive disorder at age 15 years by quintiles of systolic blood pressure at age 12 years in the ALSPAC sample

Analyses so far have highlighted a significant association between lower systolic blood pressure and future depression in two different samples of offspring of parents with recurrent depression. Next, ROC analysis was performed to establish a cut off for blood pressure in both samples that maximised both sensitivity and specificity for detection of future depressive disorder. A cut off point of below 0.025 standard deviations above the mean using standardised systolic blood pressure [17] showed a sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the association between low blood pressure and future depressive disorder using each of the cut offs identified in each sample (Table 2).

Table 2

	OR (95% CI)[1]	
	Optimal cut off in EPAD sample (< .025)	Optimal cut off in ALSPAC sample (< -.485)
EPAD sample	3.13 (1.30, 7.53)	3.43 (1.45, 8.13)
ALSPAC sample	3.00 (.93, 9.71)	3.62 (1.23, 10.65)

[1]Adjusted for child weight at W1

Association between low blood pressure and future depressive disorder in the EPAD and ALSPAC samples using the optimal cut off for low blood pressure identified in each sample using ROC curve analysis

From these analyses it seems a cut off for low systolic blood pressure for children aged 12 years lies between 108 and 113mmHg.

Lastly, supplementary analyses were performed to examine the association between blood pressure and future depression in the general population using the entire ALSPAC sample.

Supplementary analyses using entire ALSPAC sample:

1) **Testing the relationship between depressive disorder and blood pressure in the general population (not limiting analysis to those adolescents with a parental history of recurrent depression)**

Descriptives

Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.44$, $p<.001$) and diastolic blood pressure ($r=.19$, $p<.001$), therefore all results are reported controlling for weight.

Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last month at age 15 (1.55%).

Preliminary analyses

Logistic regression analyses were performed to investigate the association between blood pressure and depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .76 to 1.27; p=.875). Diastolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04; p=.604).

2) **Examining whether a history of recurrent maternal depression moderated the relationship between systolic blood pressure and depression**

Logistic regression analyses were then performed to test if recurrent maternal depression moderated the relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic blood pressure and maternal recurrent depression were centred to convert them to their deviation form to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95% CI .27 to .89; p=.019).

Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal depression was present, children with low blood pressure showed the highest percentage of depressive disorder. However, when recurrent maternal depression was not present, children with high blood pressure showed the highest percentage of depressive disorder.

Figure 4

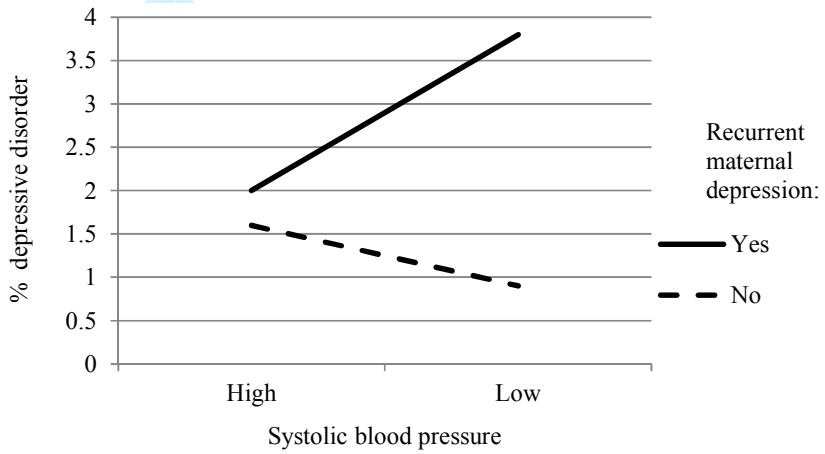


Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low' systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample

Discussion

In this study we found that lower systolic blood pressure significantly predicted future new onset depressive disorder amongst a sample of children and adolescents at high risk of developing depression because of a parental history of recurrent depression. This finding was replicated in a large community based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression (replication sample). When investigating this relationship in more detail, it seemed that those with the lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut off value for systolic blood pressure in 12 year old children was identified as being within the range of 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort (ALSPAC), the association between blood pressure and major depressive disorder was no longer significant. There was no evidence for an association in the opposite direction (depression predicting future blood pressure levels) either in the study sample or in the replication cohort nor was there an association between diastolic blood pressure and future depression in either dataset.

In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive disorder was slightly higher than population norms, it was those whose blood pressure was lower who were at most risk of developing depressive disorder. This was not true in adolescents from the general population. In adolescents from the general population who did not have a parent with recurrent depressive disorder, higher blood pressure showed some association with a higher risk of future depressive disorder. There have been no previously published longitudinal studies examining the relationship between blood pressure and depression in children from the general population or children at high-risk of depression. In adults a "vascular depression" hypothesis has been proposed to explain links between elevated blood pressure and depression [19] but some adult studies have found cross-sectional links between low blood pressure and depression.[20, 21] In addition, a study on elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] The aim in our study was however to look at links between blood pressure and depression prior to the usual age of onset of hypertensive disease to examine developmental changes. Given the limited scientific literature on this topic, the mechanisms by which low blood pressure might precede depression for adolescent offspring of individuals with recurrent depressive disorder are unclear and we can at present only speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or environmental) that contribute to both lower blood pressure and depression that are especially enriched

in those offspring most at risk of developing depressive disorder in the near future. Another possibility is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major depressive disorder. There is strikingly limited research on biological links between early mental health problems and physical health as well as on autonomic system function in young people who are familially vulnerable to depression [22]. Our findings highlight the need for further research on links between mental and physical health in young people.

Strengths and Limitations

This is the first study we are aware of to report on the longitudinal relationship between blood pressure and depressive disorder in adolescents, an important period for the onset of depression. In the main sample, children and adolescents were followed up at three points over a four year period with a high retention rate of over 80%. A similar pattern of results was found in a large community based cohort study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples, diagnoses were systematically ascertained using interview and blood pressure readings were measured according to standardised protocol. In addition, potential confounders of the relationship were taken account of. There were also possible limitations of the study. Blood pressures were measured using an electronic device which uses an oscillometric technique rather than the auscultatory technique that most population norms are based on and it has been noted that these readings are not equivalent. However there is a lack of consensus as to whether using different methods leads to any systematic bias and inaccuracies seem more related to not using a standardised technique rather than the instrument.[23] In addition, the cut off values identified in the high risk and replication samples differed slightly. This may have been because of differences in measurement techniques in the two studies. These results need to be replicated in other samples in order to establish more precise cut off for low systolic blood pressure. There was also relatively a high false positive rate for the cut offs identified in both the high risk and the replication sample (34% and 39% respectively). However the aim of this analysis was not to develop a screening tool for depression but to use ROC curve analysis as a method to maximise both sensitivity and specificity in determining the optimal cut off value for low blood pressure. Moreover some of the individuals labelled as “false positives” will have sub-threshold depression which has been found to be associated with impairment, and to predict escalation to future disorder;[24, 25]. Despite

being a high-risk sample, the number of children with depressive disorder was small and many of the sample had not been though the age of maximum risk for developing a depressive disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of children with depressive disorder was also low in the replication sample, partly because only a self-report measure of depressive disorder was available at age 15, and partly because of selective attrition over time. Previous studies have reported that although attrition has affected prevalence rates of depression in the mother and internalising disorders in the children, the associations between risks and outcomes remained intact, although conservative estimates of the likely true effects.[26, 27] Lastly, the subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe group as maternal self-report of depression was used as opposed to defining episodes of depression using DSM-IV criteria as was done in the main dataset.

In summary, in our study of adolescents at high risk of depression we found that low blood pressure was associated with major depressive disorder. This finding was replicated in an independent cohort. Future research is needed using different populations to confirm this relationship as it is a novel finding and to investigate the mechanisms by which the relationship between low blood pressure and depressive disorder in children at risk for depression may arise.

Acknowledgments

Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable Trust and the National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship.

We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for their help with recruiting them and the whole EPAD team. We thank the other investigators involved in the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar, Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules Thorn Charitable Trust.

Conflict of interest

None of the authors have conflict of interest/financial disclosures.

Role of funding source

Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors (AKT). The funders had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the paper for publication.

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Title: Depression and blood pressure in high-risk children and adolescents: an investigation using two longitudinal cohorts.

Abstract

Objective – To examine the relationship between blood pressure and depressive disorder in children and adolescents at high-risk for depression.

Design – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study of offspring of parents with recurrent depression and an on-going birth cohort for replication.

Setting – Community based studies.

Participants – High-risk sample includes 281 families where children were aged 9-17 years at baseline and 10-19 years at the final data point. Replication cohort includes 4830 families where children were aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring with mothers that had reported recurrent depression.

Main outcome measures –New onset DSM-IV defined depressive disorder in the offspring using established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the replication sample.

Results – Blood pressure was standardised for age and gender to create standard deviation scores and child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and future depression was also found in the replication cohort in the second subset of high-risk children whose mothers had experienced recurrent depression in the past.

Conclusion – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of parents with depression. Further studies are needed to investigate how this association arises.

Key words

Depression; Blood Pressure; ALSPAC; Adolescent; Cohort Studies

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Article focus:

- To examine the relationship between blood pressure and future depressive disorder in adolescents at high-risk for depression.

Key messages

- Low systolic blood pressure predicts future depressive disorder in adolescent offspring of parents with recurrent depression.

Strength and Limitations

- Replication of findings in two independent cohort studies, one a high risk sample and one a population based cohort.
- Mechanism by which low blood pressure is linked to depression risk needs further investigation.

Introduction

The two leading causes of death and disability in the developed world are depression and cardiovascular disease. The association between depression and cardiovascular disease is well established in adults,[1] although the mechanisms by which it arises are still not clear. It has been suggested that these links reflect early associations between depression and cardiovascular risk factors. High blood pressure is an important cardiovascular risk factor and it has also been linked to depression in adults in some studies.[2] Other studies, however, have found the converse. They suggest that depression is associated with low blood pressure and that it is only depression treated with certain antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the findings are inconsistent, with some studies finding depression as a predictor of either high blood pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure predicting depression.[6]

Although both depression and the early indicators of cardiovascular disease have been found to have onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger populations. In this study, the main aim was to investigate the relationship between blood pressure and subsequent first onset episode of depression in a prospective cohort of children and adolescents at high risk of depression. The secondary aim was to replicate findings in an independent cohort.

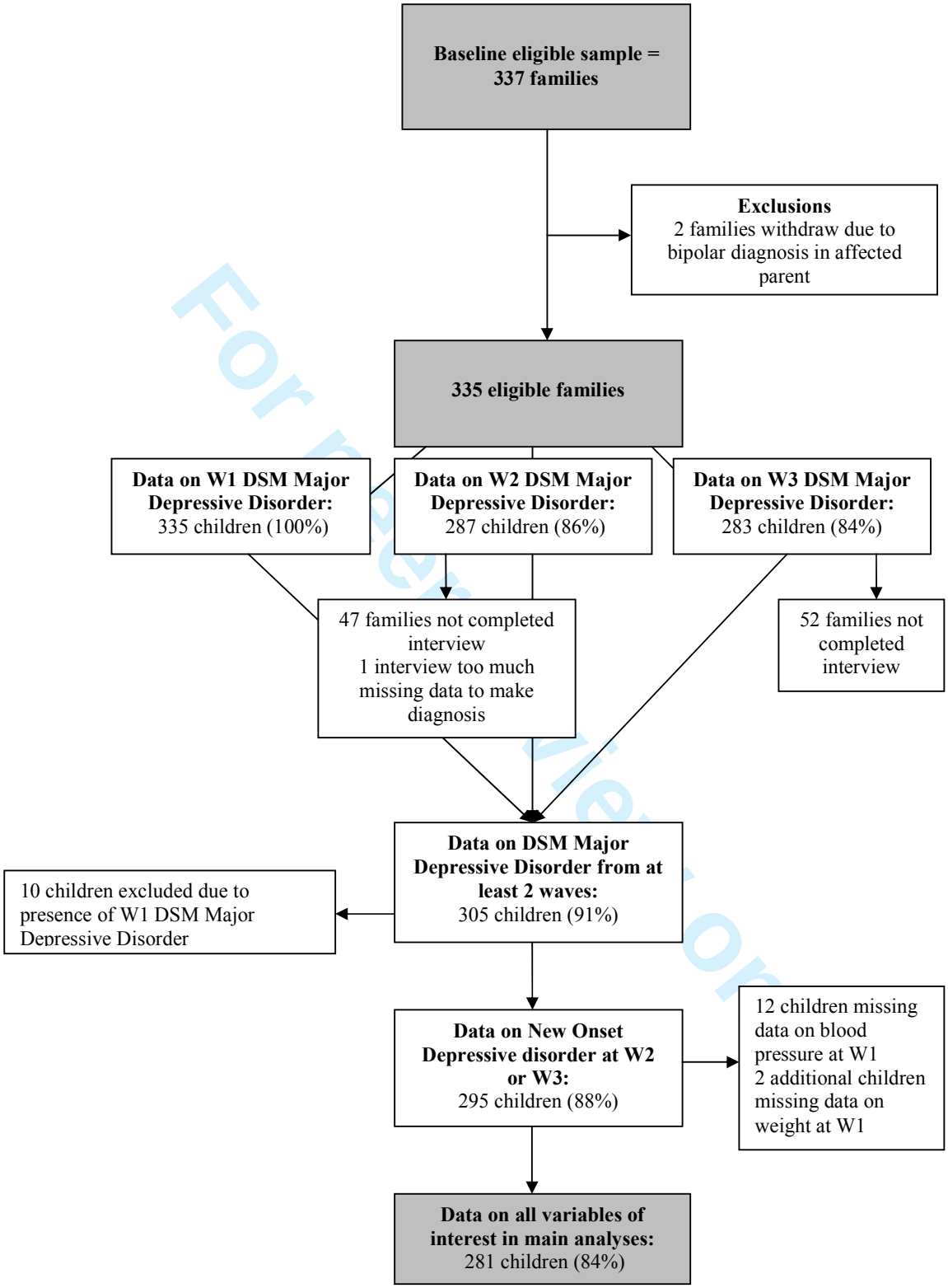
Method

Data were derived from a prospective longitudinal study of offspring of parents with recurrent depression–'The Early Prediction of Adolescent Depression (EPAD) study'. At baseline, the sample included 337 families (315 mothers and 22 fathers) that were recruited from general practices across South Wales, by writing to eligible families, and from a database of adults with previously identified unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test the main hypotheses of the original project whilst allowing detailed assessments at each time point. Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to and currently living with the affected parent. Additional exclusion criteria included children with moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the study because the depressed parent had been diagnosed as suffering from bipolar disorder since the wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed using age-appropriate standard research diagnostic interviews independently by two trained research psychologists on three occasions over the course of the study which began in April 2007 and finished in April 2011. The average time between the baseline and second assessment was 16.2 months and between the second and third assessment was 12.5 months. Further details on the sample characteristics and methodology have been described previously.[9]

For the main analyses, 30 families were excluded because they had not completed at least two waves of data. A further 10 children were excluded from main analyses because they already met criteria for DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not been completed at baseline either because there had been a fault in the equipment or the child had refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data were collected from parents and children via semi-structured research diagnostic interviews and blood

pressure and weight were assessed by the interviewer. Additional data on physical health problems, maternal education and social class were collected from parents and children from self-completed questionnaires that were mailed to the families two weeks before their interview. Ethical approval for the study was obtained from the Multi-centre Research Ethics Committee for Wales.

85 *Figure 1*



Flow chart of retention at each assessment in the EPAD sample

Data were also utilised from a birth cohort study 'The Avon Longitudinal Study of Parents and Children (ALSPAC)' to allow replication of findings from the first high-risk sample. The cohort was set up to examine genetic and environmental determinants of health and development.[10] The initial cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date of delivery between 1st April 1991 and 31st December 1992 (www.alspac.bris.ac.uk). All pregnant women resident in three health districts in the old administrative county of Avon who had an estimated delivery between the above dates were eligible to participate. In addition, pregnant women that had migrated into the catchment area before the point of delivery were eligible. Recruitment was carried out by attempting to make contact with eligible women through ALSPAC staff visiting community locations and through using antenatal and maternity health services and media information to encourage contact and promote the study.[10] The parents completed regular postal questionnaires concerning their child's health and development since birth. The children have completed questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range: 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children whose mothers had experienced recurrent depression (at least two episodes); 612 children were included in these analyses (347 females and 265 males). Ethical approval for the study was obtained from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

Measures

EPAD study:

Assessment of depression in the offspring of parents with recurrent depression

The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic interview that has high reliability and that is used to assess children's psychiatric symptoms [11]. Parents are asked about their children's psychopathology and children are independently interviewed using the interview schedules (parent and child versions). The presence of any given symptom has to be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

selected recordings at each time point (10 parent report and 10 child report) and through weekly supervision by an academic clinician with extensive experience in using the interview. Average agreement between raters for DSM-IV psychiatric disorder was excellent (κ =0.92), as was average agreement for depression symptoms (κ =0.93). CAPA was used at each assessment and assesses the presence of a major depressive disorder in the child over the preceding three months. The parent and child versions were completed independently, with interviews conducted in separate rooms where possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of DSM-IV major depressive disorder symptoms was also computed from the CAPA.

New onset major depressive disorder - The presence of a new onset DSM-IV diagnosis of major depressive disorder at either the second or third assessment was defined by excluding children that had a baseline diagnosis of DSM-IV major depressive disorder.

Blood pressure –An Omron 705IT sphygmomanometer was used to measure blood pressure at each assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were measured using standardised guidelines set out by the American Heart association.[12] At least two readings were taken at least one minute apart using the right arm. When the difference between two readings was 5mmHg or less an average was taken.

Weight and other potential confounders – Weight was considered to be a confounder of the relationship between blood pressure and depression due to its potential association with both.[13, 14] Interviewers measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also examined whether the results were affected by the presence of physical health problems (parent reported), any medication use (child or parent reported) and using body mass index (BMI) instead of weight.

Demographics – The mother and father questionnaires completed at baseline were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels, degree or postgraduate qualification). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

ALSPAC:

Maternal history of recurrent depression – Mothers completed regular questionnaires from pregnancy to when the child was aged 12 years including the questions 'Have you had depression in the last year/ last two years/ since your child was born/ever'. The mother was also asked 'Have you ever had severe depression' on three occasions over this time period. Research diagnostic interview generated psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data set thus had to be defined where mother had reported having depression on at least two separate occasions, and if at least one of these occasions was reported as being severe. These criteria were used to create a subsample that was as similar as possible to the primary high-risk sample.

Child depressive disorder – Parent reports on their child's symptoms were obtained using a structured diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA, has been used widely for large scale population studies. The parent-rated DAWBA was completed when the target age of the children was 13 years. Children were directly interviewed using the DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV diagnosis of depression and generates diagnoses (see www.DAWBA.com for more information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part of the ALSPAC data collection process. [16]

Blood pressure – Systolic and diastolic blood pressure were measured at the clinic assessments when the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

Weight and other potential confounders – Interviewers measured the weight and height of the children in light clothing and without shoes at the clinic assessments when the target age of the children was 12 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then calculated (kg/m²). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal medical records.

Demographics – The mother and father questionnaires completed during pregnancy were used to assess maternal education and highest parental social class. Maternal education was categorised according to whether the mother had completed higher education (A-Levels or degree). Parental social class was categorised according to whether either parent reported having a non-manual occupation.

Statistical methods

Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the high-risk sample and then in the replication cohort using the subsample of children with mothers that have experienced recurrent depression in the past. Next, regression analyses were performed to examine the association between blood pressure and depression in the high-risk sample and then in the subsample from the replication cohort. Logistic regression analyses were used when the dependent variable was dichotomous and ordinary least squares linear regression analysis was used when the dependent variable was continuous. Continuous outcome data that were not normally distributed were transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship between systolic blood pressure and future depressive disorder was examined by investigating the percentage of children with future depressive disorder by blood pressure quintiles, again in both samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for blood pressure in both samples that showed adequate sensitivity and specificity for detecting future depressive disorder. Lastly, the association between systolic blood pressure and future depressive disorder was investigated in the general population by using the entire ALSPAC sample and the presence of a multiplicative interaction between maternal depression and systolic blood pressure on future depressive disorder was examined. Listwise deletion was used to deal with missing data in all analyses and data were analysed using SPSS (v20).

Results

Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent depression), the ALSPAC replication subsample of children with mothers that have experienced recurrent depression and the whole ALSPAC sample

Table 1 shows that the three samples are comparable on a range of demographics (child age, gender, maternal education and parental social class).

Table 1

	EPAD (n=281)	**ALSPAC** (subsample of offspring of recurrently depressed mothers; n=612)	**ALSPAC** (whole sample; n=4830)
Child age: mean (sd)	12.4 (2.0)	12.8 (0.2)	12.8 (0.2)
Child gender (% female)	58.4	56.7	52.1
Maternal education (% higher education)	51.9	44.3	47.2
Parental social class (% non-manual)	74.0	84.1	87.7

Demographics at baseline in the EPAD sample, ALSPAC subsample of offspring of recurrently depressed mothers and the whole ALSPAC sample

Descriptives from EPAD high-risk sample

Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at baseline. Systolic blood pressure at baseline was significantly correlated with age ($r=.23$, $p<.001$), but diastolic blood pressure was not ($r=.02$, $p=.728$). Systolic blood pressure was thus standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable.[17] Mean blood pressures for each age group in this sample were generally higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated with weight ($r=.25$, $p<.001$), but diastolic blood pressure was not ($r=.07$, $p=.236$). Given this finding all analyses with systolic blood pressure are reported controlling for weight.

Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder (8.54%).

Descriptives from ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.45$, $p<.001$) and diastolic blood pressure ($r=.18$, $p<.001$), therefore all results are reported controlling for weight.

Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at age 15 (2.94%).

Initial analyses in EPAD high-risk sample

Logistic regression analyses were performed to investigate the association between blood pressure and new onset depressive disorder in the EPAD sample of children. It was found that as systolic blood pressure increased, risk for new onset depressive disorder decreased, when adjusting for child's weight at baseline (OR = .65, 95% CI .44 to .96; p=.029), i.e. lower systolic blood pressure at baseline significantly predicted new onset depressive disorder. Diastolic blood pressure at baseline did not significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01; p=.120).

Results remained the same when the outcome was expanded to include the new onset of more broadly defined mood-related diagnoses (primary diagnosis: major depressive disorder n=22, dysthymia n=1, cyclothymia n=1, bipolar disorder n=3, adjustment disorder with depressed mood n=4 and depressive disorder not otherwise specified n=5). Results also remained similar when separately adjusting for medication use and physical health problems in the child and when adjusting for BMI instead of weight. The association was not significantly moderated by gender (p=.769).

Given few adolescents developed new onset depressive disorder, the analysis was repeated using total depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood

pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome, and again controlling for weight, showed significant association (β = -.13; p=.040).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This was non-significant (β = -.05; p =.412). Given the low number of individuals with depressive disorder at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again the results were non-significant (β = -.07; p = .286).

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

Logistic regression analyses were undertaken in the replication sample. Again, it was found that as systolic blood pressure increased, risk for future depressive disorder decreased, when adjusting for child's weight at baseline (OR = .48, 95% CI .27 to .85; p=.012), i.e. lower systolic blood pressure at age 12 significantly predicted depressive disorder at age 15. Diastolic blood pressure at age 12 years did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .93 to 1.05; p=.597). Results remained similar when adjusting for BMI instead of weight and when additionally adjusting for maternal systolic blood pressure in pregnancy. The association was not significantly moderated by gender (p=.102).

To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant (β = -.04; p = .378).

Relationship between blood pressure and depressive disorder in high-risk EPAD sample

To further investigate the relationship between systolic blood pressure and depressive disorder in the EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with

the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 2

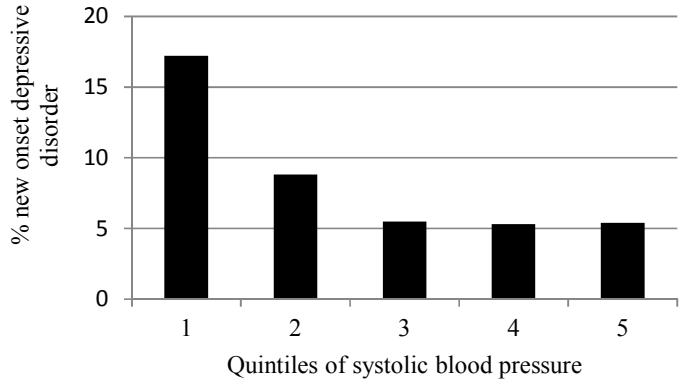


Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of systolic blood pressure at baseline in the EPAD sample

Replication in ALSPAC dataset – using the subsample of children with mothers that have experienced recurrent depression in the past

To further investigate the relationship between systolic blood pressure and depression in the replication sample, blood pressure was split into quintiles to examine the percentage of children with depression at age 15 by blood pressure categories and the linearity of the relationship.

As can be seen in Figure 3, there is a lower risk of depressive disorder with higher levels of blood pressure, with the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder cases.

Figure 3

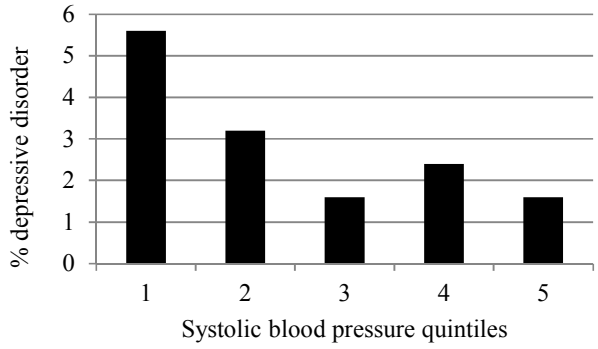


Figure to show percentage of children with depressive disorder at age 15 years by quintiles of systolic blood pressure at age 12 years in the ALSPAC sample

Analyses so far have highlighted a significant association between lower systolic blood pressure and future depression in two different samples of offspring of parents with recurrent depression. Next, ROC analysis was performed to establish a cut off for blood pressure in both samples that maximised both sensitivity and specificity for detection of future depressive disorder. A cut off point of below 0.025 standard deviations above the mean using standardised systolic blood pressure [17] showed a sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the association between low blood pressure and future depressive disorder using each of the cut offs identified in each sample (Table 2).

Table 2

	OR (95% CI)[1]	
	Optimal cut off in EPAD sample (< .025)	Optimal cut off in ALSPAC sample (< -.485)
EPAD sample	3.13 (1.30, 7.53)	3.43 (1.45, 8.13)
ALSPAC sample	3.00 (.93, 9.71)	3.62 (1.23, 10.65)

[1]Adjusted for child weight at W1

Association between low blood pressure and future depressive disorder in the EPAD and ALSPAC samples using the optimal cut off for low blood pressure identified in each sample using ROC curve analysis

From these analyses it seems a cut off for low systolic blood pressure for children aged 12 years lies between 108 and 113mmHg.

Lastly, supplementary analyses were performed to examine the association between blood pressure and future depression in the general population using the entire ALSPAC sample.

Supplementary analyses using entire ALSPAC sample:

1) **Testing the relationship between depressive disorder and blood pressure in the general population (not limiting analysis to those adolescents with a parental history of recurrent depression)**

Descriptives

Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood pressure was standardised for age and gender to create standard deviation scores and all analyses for systolic blood pressure were run with the standardised variable. The association between blood pressure and weight at age 12 was significant for both systolic ($r=.44$, $p<.001$) and diastolic blood pressure ($r=.19$, $p<.001$), therefore all results are reported controlling for weight.

Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last month at age 15 (1.55%).

Preliminary analyses

Logistic regression analyses were performed to investigate the association between blood pressure and depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .76 to 1.27; p=.875). Diastolic blood pressure at age 12 did not significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04; p=.604).

2) **Examining whether a history of recurrent maternal depression moderated the relationship between systolic blood pressure and depression**

Logistic regression analyses were then performed to test if recurrent maternal depression moderated the relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic blood pressure and maternal recurrent depression were centred to convert them to their deviation form to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95% CI .27 to .89; p=.019).

Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal depression was present, children with low blood pressure showed the highest percentage of depressive disorder. However, when recurrent maternal depression was not present, children with high blood pressure showed the highest percentage of depressive disorder.

Figure 4

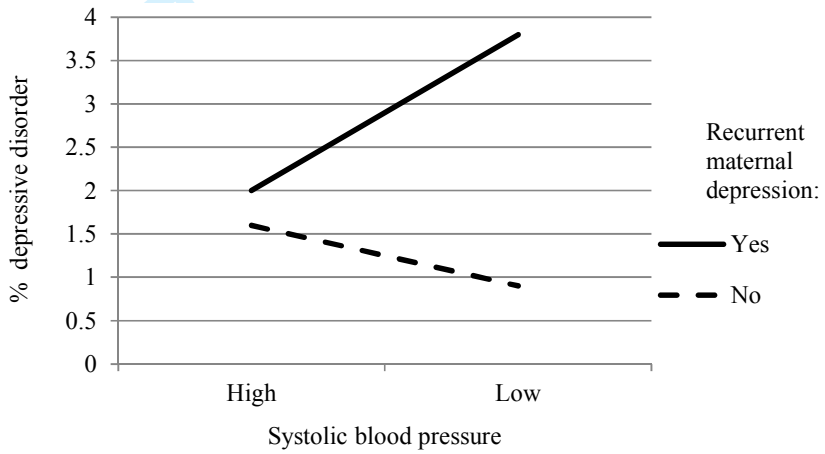


Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low' systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample

Discussion

In this study we found that lower systolic blood pressure significantly predicted future new onset depressive disorder amongst a sample of children and adolescents at high risk of developing depression because of a parental history of recurrent depression. This finding was replicated in a large community based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression (replication sample). When investigating this relationship in more detail, it seemed that those with the lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut off value for systolic blood pressure in 12 year old children was identified as being within the range of 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort (ALSPAC), the association between blood pressure and major depressive disorder was no longer significant. There was no evidence for an association in the opposite direction (depression predicting future blood pressure levels) either in the study sample or in the replication cohort nor was there an association between diastolic blood pressure and future depression in either dataset.

In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive disorder was slightly higher than population norms, it was those whose blood pressure was lower who were at most risk of developing depressive disorder. This was not true in adolescents from the general population. In adolescents from the general population who did not have a parent with recurrent depressive disorder, higher blood pressure showed some association with a higher risk of future depressive disorder. There have been no previously published longitudinal studies examining the relationship between blood pressure and depression in children from the general population or children at high-risk of depression. In adults a "vascular depression" hypothesis has been proposed to explain links between elevated blood pressure and depression [19] but some adult studies have found cross-sectional links between low blood pressure and depression.[20, 21] In addition, a study on elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] The aim in our study was however to look at links between blood pressure and depression prior to the usual age of onset of hypertensive disease to examine developmental changes. Given the limited scientific literature on this topic, the mechanisms by which low blood pressure might precede depression for adolescent offspring of individuals with recurrent depressive disorder are unclear and we can at present only speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or environmental) that contribute to both lower blood pressure and depression that are especially enriched

in those offspring most at risk of developing depressive disorder in the near future. Another possibility is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major depressive disorder. There is strikingly limited research on biological links between early mental health problems and physical health as well as on autonomic system function in young people who are familially vulnerable to depression [22]. Our findings highlight the need for further research on links between mental and physical health in young people.

Strengths and Limitations

This is the first study we are aware of to report on the longitudinal relationship between blood pressure and depressive disorder in adolescents, an important period for the onset of depression. In the main sample, children and adolescents were followed up at three points over a four year period with a high retention rate of over 80%. A similar pattern of results was found in a large community based cohort study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples, diagnoses were systematically ascertained using interview and blood pressure readings were measured according to standardised protocol. In addition, potential confounders of the relationship were taken account of. There were also possible limitations of the study. Blood pressures were measured using an electronic device which uses an oscillometric technique rather than the auscultatory technique that most population norms are based on and it has been noted that these readings are not equivalent. However there is a lack of consensus as to whether using different methods leads to any systematic bias and inaccuracies seem more related to not using a standardised technique rather than the instrument.[23] In addition, the cut off values identified in the high risk and replication samples differed slightly. This may have been because of differences in measurement techniques in the two studies. These results need to be replicated in other samples in order to establish more precise cut off for low systolic blood pressure. There was also relatively a high false positive rate for the cut offs identified in both the high risk and the replication sample (34% and 39% respectively). However the aim of this analysis was not to develop a screening tool for depression but to use ROC curve analysis as a method to maximise both sensitivity and specificity in determining the optimal cut off value for low blood pressure. Moreover some of the individuals labelled as “false positives” will have sub-threshold depression which has been found to be associated with impairment, and to predict escalation to future disorder;[24, 25]. Despite

being a high-risk sample, the number of children with depressive disorder was small and many of the sample had not been though the age of maximum risk for developing a depressive disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of children with depressive disorder was also low in the replication sample, partly because only a self-report measure of depressive disorder was available at age 15, and partly because of selective attrition over time. Previous studies have reported that although attrition has affected prevalence rates of depression in the mother and internalising disorders in the children, the associations between risks and outcomes remained intact, although conservative estimates of the likely true effects.[26, 27] Lastly, the subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe group as maternal self-report of depression was used as opposed to defining episodes of depression using DSM-IV criteria as was done in the main dataset.

In summary, in our study of adolescents at high risk of depression we found that low blood pressure was associated with major depressive disorder. This finding was replicated in an independent cohort. Future research is needed using different populations to confirm this relationship as it is a novel finding and to investigate the mechanisms by which the relationship between low blood pressure and depressive disorder in children at risk for depression may arise.

Acknowledgments

Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable Trust and the National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship.

We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for their help with recruiting them and the whole EPAD team. We thank the other investigators involved in the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar, Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules Thorn Charitable Trust.

Conflict of interest

None of the authors have conflict of interest/financial disclosures.

Role of funding source

Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors (AKT). The funders had no further role in the study design, the collection, analysis and interpretation of data, the writing of the report, or in the decision to submit the paper for publication.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **page 3**
Methods		
Study design	4	Present key elements of study design early in the paper **page 4 & 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **page 4 & 7**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **page 4 & 7**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **pages 7, 8, 9 & 10**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **pages 7, 8, 9 & 10**
Bias	9	Describe any efforts to address potential sources of bias **page 3, pages 8 & 10 (addressing confounders), and pages 19**
Study size	10	Explain how the study size was arrived at **pages 4, 6 & 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **pages7, 8, 9 & 10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **pages 8, 10, 11 & 12**
		(*b*) Describe any methods used to examine subgroups and interactions **pages 10, 16 & 17**
		(*c*) Explain how missing data were addressed **page 10**
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **pages 10, 12, 13 & 15**
Results		

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **pages 4, 6 & 7**
		(b) Give reasons for non-participation at each stage **pages 4, 6 & 7**
		(c) Consider use of a flow diagram **page 6**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **page 11, 12 & 16**
		(b) Indicate number of participants with missing data for each variable of interest **pages 4, 6 & 7**
		(c) Summarise follow-up time (eg, average and total amount) **page 4**
Outcome data	15*	Report numbers of outcome events or summary measures over time **page 11, 12 & 16**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **pages 8, 10, 12, 13, 15 & 16**
		(*b*) Report category boundaries when continuous variables were categorized **page 13, 14 & 15**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **pages 11-17**
Discussion		
Key results	18	Summarise key results with reference to study objectives **page 18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **pages 19 & 20**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **page 18**
Generalisability	21	Discuss the generalisability (external validity) of the study results **pages 18 & 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **page 21**

*Give information separately for exposed and unexposed groups. **n/a**

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.