



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

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| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID:                  | bmjopen-2013-003206  |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 10-May-2013  |
| Complete List of Authors:       | Hammerton, Gemma; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Harold, Gordon; University of Leicester, Biological Sciences and Psychology; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Thapar, Anita; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Thapar, Ajay; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences |
| <b>Primary Subject Heading</b>: | Epidemiology   |
| Secondary Subject Heading:      | Mental health, Cardiovascular medicine   |
| Keywords:                       | MENTAL HEALTH, EPIDEMIOLOGY, Hypertension < CARDIOLOGY   |
|                                 |  |

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3 **Title:** Depression and blood pressure in high-risk children and adolescents: an investigation using two  
4 longitudinal cohorts.  
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8 **Abstract**

9 *Objective* – To examine the relationship between blood pressure and depressive disorder in children  
10 and adolescents at high-risk for depression.  
11

12 *Design* – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study  
13 of offspring of parents with recurrent depression and an on-going birth cohort for replication.  
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15 *Setting* – Community based studies.  
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17 *Participants* – High-risk sample includes 281 families where children were aged 9-17 years at baseline  
18 and 10-19 years at the final data point. Replication cohort includes 4830 families where children were  
19 aged 11-14 years at baseline and 14-17 years at follow up and a subsample of 612 families with  
20 mothers that had reported recurrent depression.  
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22 *Main outcome measures* – High-risk sample: new onset DSM-IV defined depressive disorder using the  
23 Child and Adolescent Psychiatric Assessment (CAPA). Replication sample: DSM-IV defined  
24 depressive disorder using the Development and Wellbeing Assessment (DAWBA).  
25

26 *Results* – Blood pressure was standardised for age and gender to create standard deviation scores and  
27 child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood  
28 pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI  
29 .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict  
30 systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and  
31 future depression was also found in the replication cohort in those children whose mothers had  
32 experienced recurrent depression in the past.  
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34 *Conclusion* – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of  
35 parents with depression. Further studies are needed to investigate how this association arises.  
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44 **Key words**

45 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.

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## 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.

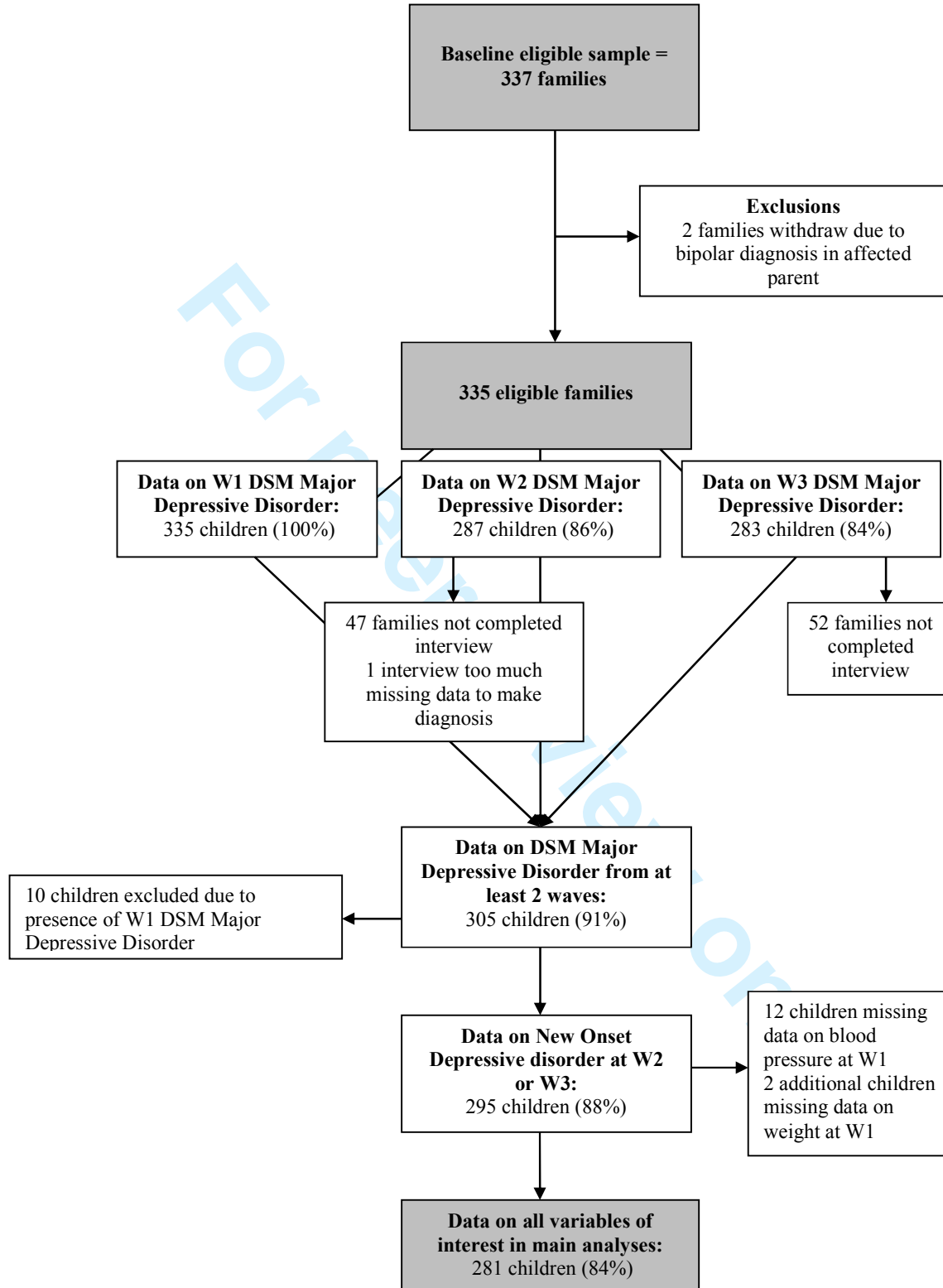
## Method

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

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

## 32 Measures

33 EPAD study:

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

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3 *New onset major depressive disorder* - The presence of a new onset major depressive disorder at either  
4 the second or third assessment was defined by excluding children that had a baseline diagnosis of  
5 DSM-IV major depressive disorder.  
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10 *Blood pressure* –An Omron 705IT sphygmomanometer was used to measure blood pressure at each  
11 assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard  
12 cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was  
13 used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were  
14 measured using standardised guidelines set out by the American Heart association.[12] At least two  
15 readings were taken at least one minute apart using the right arm. When the difference between two  
16 readings was 5mmHg or less an average was taken.  
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23 *Weight and other potential confounders* – Weight was considered to be a confounder of the relationship  
24 between blood pressure and depression due to its potential association with both.[13, 14] Interviewers  
25 measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also  
26 examined whether the results were affected by the presence of physical health problems (parent  
27 reported), any medication use (child or parent reported) and using body mass index (BMI) instead of  
28 weight.  
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36 ALSPAC:

37 *Maternal history of recurrent depression* – Mothers completed regular questionnaires from pregnancy  
38 to when the child was aged 12 years including the questions ‘Have you had depression in the last year/  
39 last two years/ since your child was born/ever’. The mother was also asked ‘Have you ever had severe  
40 depression’ on three occasions over this time period. Families were included in the subsample of  
41 recurrently depressed mothers if the mother had reported having depression on at least two separate  
42 occasions, and if at least one of these occasions was reported as being severe. These criteria were used  
43 to create a subsample that was as similar as possible to the primary high-risk sample.  
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51 *Child depressive disorder* – Parent versions of the Development and Wellbeing Assessment  
52 (DAWBA),[15] were used at the assessment when the target age of the children was 13 years and child  
53 versions of the DAWBA were used at the assessment when the target age of the children was 15 years  
54 to assess the presence of a depressive disorder over the preceding month. DSM-IV diagnoses of  
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3 depression were generated at each time point using a well-defined computerised algorithm that predicts  
4 the likelihood of a clinical rater assigning each child a DSM-IV diagnosis of depression (see  
5 [www.DAWBA.com](http://www.DAWBA.com) for more information). Each individual is assigned one of six probability bands,  
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7 and the top two levels were used as a computer generated DAWBA diagnosis.[16]  
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11 *Blood pressure* – Systolic and diastolic blood pressure were measured at the clinic assessments when  
12 the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each  
13 assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.  
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17 *Weight and BMI* – Interviewers measured the weight and height of the children in light clothing and  
18 without shoes at the clinic assessments when the target ages of the children was 12 years. Weight was  
19 measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height was measured to  
20 the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then calculated (kg/m<sup>2</sup>).  
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## 26 **Statistical methods**

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28 Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the  
29 high-risk sample and then in the replication cohort using the subsample of children with mothers that  
30 have experienced recurrent depression in the past. Next, regression analyses were performed to  
31 examine the association between blood pressure and depression in the high-risk sample and then in the  
32 subsample from the replication cohort. Logistic regression analyses were used when the dependent  
33 variable was dichotomous and ordinary least squares linear regression analysis was used when the  
34 dependent variable was continuous. Continuous outcome data that were not normally distributed were  
35 transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship  
36 between systolic blood pressure and future depressive disorder was examined by investigating the  
37 percentage of children with future depressive disorder by blood pressure quintiles, again in both  
38 samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for  
39 blood pressure in both samples that showed adequate sensitivity and specificity for detecting future  
40 depressive disorder. Lastly, the association between systolic blood pressure and future depressive  
41 disorder was investigated in the general population by using the entire ALSPAC sample and the  
42 presence of a multiplicative interaction between maternal depression and systolic blood pressure on  
43 future depressive disorder was examined. Listwise deletion was used to deal with missing data in all  
44 analyses and data were analysed using SPSS (v20).**Results**  
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3 For demographic comparability of samples see supplementary material (online publication only).  
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#### 6 **Descriptives from EPAD high-risk sample**

7 Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and  
8 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant  
9 differences between males and females for systolic or diastolic blood pressure at baseline. Systolic  
10 blood pressure at baseline was significantly correlated with age ( $r=.23$ ,  $p<.001$ ), but diastolic blood  
11 pressure was not ( $r=.02$ ,  $p=.728$ ). Systolic blood pressure was thus standardised for age and gender to  
12 create standard deviation scores and all analyses for systolic blood pressure were run with the  
13 standardised variable. Standardised scores were calculated using the 2007 blood pressure centiles for  
14 Great Britain.[17] Mean blood pressures for each age group in this sample were generally higher than  
15 population norms.[17, 18] Systolic blood pressure at baseline was significantly associated with weight  
16 ( $r=.25$ ,  $p<.001$ ), but diastolic blood pressure was not ( $r=.07$ ,  $p=.236$ ). Given this finding all analyses  
17 with systolic blood pressure are reported controlling for weight.  
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29 Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder  
30 (8.54%).  
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#### 33 **Descriptives from ALSPAC dataset – using the subsample of children with mothers that have** 34 **experienced recurrent depression in the past**

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37 Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61  
38 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences  
39 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
40 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
41 systolic blood pressure were run with the standardised variable. The association between blood  
42 pressure and weight at age 12 was significant for both systolic ( $r=.45$ ,  $p<.001$ ) and diastolic blood  
43 pressure ( $r=.18$ ,  $p<.001$ ), therefore all results are reported controlling for weight.  
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51 Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder at age 15 (2.94%).  
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#### 54 **Initial analyses in EPAD high-risk sample**

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56 Logistic regression analyses were performed to investigate the association between blood pressure and  
57 new onset depressive disorder in the EPAD sample. Lower systolic blood pressure at baseline  
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3 significantly predicted new onset depressive disorder (OR = .65, 95% CI .44 to .96; p=.029) when  
4 adjusting for child's weight at baseline. Diastolic blood pressure at baseline did not significantly  
5 predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01; p=.120).  
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9 Results remained the same when the outcome was expanded to include the new onset of any mood  
10 disorder including major depressive disorder, dysthymia, cyclothymia, bipolar disorder and adjustment  
11 disorder with depressed mood. Results also remained similar when separately adjusting for medication  
12 use and physical health problems in the child and when adjusting for BMI instead of weight. The  
13 association was not significantly moderated by gender (p=.769).  
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19 Given few adolescents developed new onset depressive disorder, the analysis was repeated using total  
20 depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood  
21 pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome,  
22 and again controlling for weight, showed significant association ( $\beta = -.13$ ; p=.040).  
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28 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis  
29 was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood  
30 pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This  
31 was non-significant ( $\beta = -.05$ ; p=.412). Given the low number of individuals with depressive disorder  
32 at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again  
33 the results were non-significant ( $\beta = -.07$ ; p = .286).  
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#### 40 **Replication in ALSPAC dataset – using the subsample of children with mothers that have** 41 **experienced recurrent depression in the past** 42

43 Logistic regression analyses were undertaken in the replication sample. Lower systolic blood pressure  
44 at age 12 significantly predicted depressive disorder at age 15 (OR = .48, 95% CI .27 to .85; p=.012),  
45 however, diastolic blood pressure did not (OR = .98, 95% CI .93 to 1.05; p=.597). Results remained  
46 similar when adjusting for BMI instead of weight. The association was not significantly moderated by  
47 gender (p=.102).  
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53 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses  
54 was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood  
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pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant ( $\beta = .04$ ;  $p = .378$ ).

#### **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

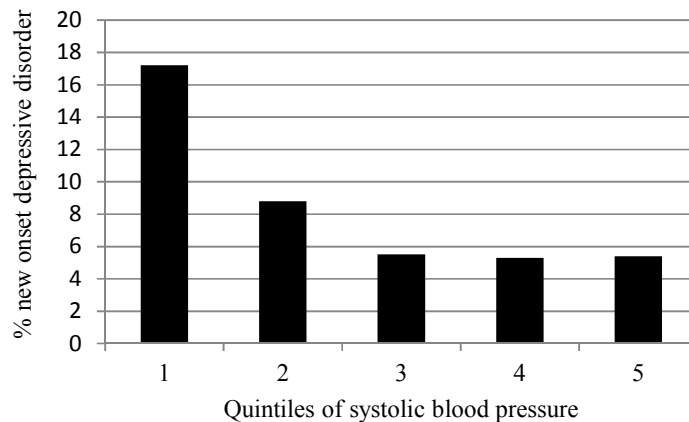


Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of systolic blood pressure at baseline in the EPAD sample

#### **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

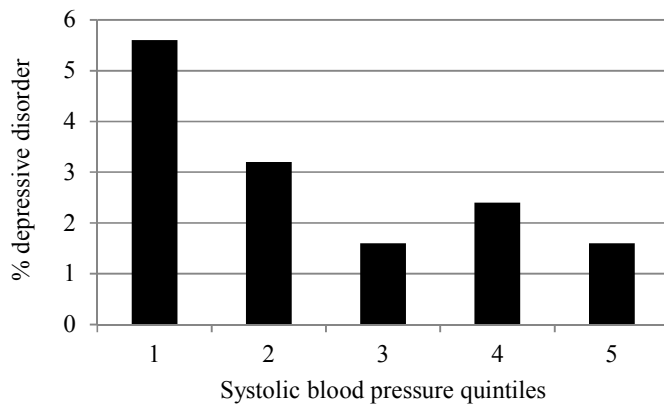


Figure to show percentage of children with depressive disorder at age 15 years by quintiles of systolic blood pressure at age 12 years in the ALSPAC sample

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<sup>17</sup> 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<sup>17</sup> 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

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|  | OR (95% CI) <sup>1</sup> |
|--|--------------------------|

|               | Optimal cut off in EPAD<br>sample (< .025) | Optimal cut off in<br>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)                            |

<sup>1</sup>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*

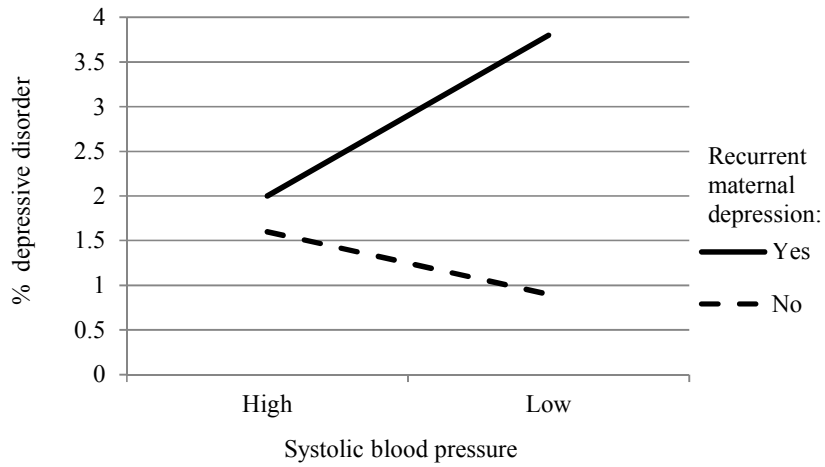


Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low' systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample

Peer review only

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## 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

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3 biological mechanism,[21] may explain the link between low blood pressure and mood disorder. Why  
4 this finding is limited to children of parents with a history of recurrent depression is unclear. Some  
5 animal studies have shown that early life stress (such as maternal deprivation in rats during postnatal  
6 days) has long-term effects on brain function and biology with implications for the development of  
7 depression or vulnerability to stress later in life.[22] Therefore the results from the current study could  
8 be explained by blood pressure being an initial manifestation of response to adversity and depression a  
9 later manifestation. However no empirical evidence for such an association has been found.  
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### 16 17 **Strengths and Limitations**

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20 This is the first study we are aware of to report on the longitudinal relationship between blood pressure  
21 and depressive disorder in adolescents, an important period for the onset of depression. In the main  
22 sample, children and adolescents were followed up at three points over a four year period with a high  
23 retention rate of over 80%. A similar pattern of results was found in a large community based cohort  
24 study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples,  
25 diagnoses were systematically ascertained using interview and blood pressure readings were measured  
26 according to standardised protocol. In addition, potential confounders of the relationship were taken  
27 account of. There were also possible limitations of the study. Blood pressures were measured using an  
28 electronic device which uses an oscillometric technique rather than the auscultatory technique that most  
29 population norms are based on and it has been noted that these readings are not equivalent. However  
30 there is a lack of consensus as to whether using different methods leads to any systematic bias and  
31 inaccuracies seem more related to not using a standardised technique rather than the instrument.[23] In  
32 addition, the cut off values identified in the high risk and replication samples differed slightly. This  
33 may have been because of differences in measurement techniques in the two studies. These results need  
34 to be replicated in other samples in order to establish more precise cut off for low systolic blood  
35 pressure. Despite being a high-risk sample, the number of children with depressive disorder was small  
36 and many of the sample had not been though the age of maximum risk for developing a depressive  
37 disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of  
38 children with depressive disorder was also low in the replication sample, partly because only a self-  
39 report measure of depressive disorder was available at age 15, and partly because of selective attrition  
40 over time. Previous studies have reported that although attrition has affected prevalence rates of  
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3 depression in the mother and internalising disorders in the children, the associations between risks and  
4 outcomes remained intact, although conservative estimates of the likely true effects.[24, 25] Lastly, the  
5 subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe  
6 group as maternal self-report of depression was used as opposed to defining episodes of depression  
7 using DSM-IV criteria as was done in the main dataset.  
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13 In summary, in our study of adolescents at high risk of depression we found that low blood pressure  
14 was associated with major depressive disorder. This finding was replicated in an independent cohort.  
15 Future research is needed using different populations to confirm this relationship as it is a novel finding  
16 and to investigate the mechanisms by which the relationship between low blood pressure and  
17 depressive disorder in children at risk for depression may arise.  
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### 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

|   | <b>EPAD</b><br>(n=281) | <b>ALSPAC</b><br>(subsample of depressed<br>mothers; n=612) | <b>ALSPAC</b><br>(whole sample;<br>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   |
|------------------------------|---------|--|
| <b>Title and abstract</b>    | 1       | (a) Indicate the study's design with a commonly used term in the title or the abstract<br><b>page 1</b><br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found<br><b>page 1</b>  |
| <b>Introduction</b>          |         |  |
| Background/rationale         | 2       | Explain the scientific background and rationale for the investigation being reported<br><b>page 3</b>  |
| Objectives                   | 3       | State specific objectives, including any prespecified hypotheses<br><b>page 3</b>  |
| <b>Methods</b>               |         |  |
| Study design                 | 4       | Present key elements of study design early in the paper<br><b>page 4 &amp; 6</b>   |
| Setting                      | 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection<br><b>page 4 &amp; 6</b>   |
| Participants                 | 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br><b>page 4 &amp; 6</b><br>(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<br><b>pages 6, 7 &amp; 9</b>  |
| Data sources/<br>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<br><b>pages 6, 7 &amp; 8</b>  |
| Bias                         | 9       | Describe any efforts to address potential sources of bias<br><b>page 3, pages 7, 9, 10 (addressing confounders), and pages 17</b>  |
| Study size                   | 10      | Explain how the study size was arrived at<br><b>pages 4, 5 &amp; 6</b>   |
| Quantitative variables       | 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why<br><b>pages 6, 7 &amp; 8</b>  |
| Statistical methods          | 12      | (a) Describe all statistical methods, including those used to control for confounding<br><b>pages 7, 8, 9 &amp; 10</b><br>(b) Describe any methods used to examine subgroups and interactions<br><b>pages 8 &amp; 14</b><br>(c) Explain how missing data were addressed<br><b>page 8</b><br>(d) If applicable, explain how loss to follow-up was addressed<br>(e) Describe any sensitivity analyses<br><b>pages 8, 10 &amp; 11</b> |
| <b>Results</b>               |         |  |

|    |                          |     |  |
|----|--------------------------|-----|--|
| 1  | 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<br><b>pages 4, 5 &amp; 6</b>             |
| 2  |                          |     | (b) Give reasons for non-participation at each stage<br><b>pages 4, 5 &amp; 6</b>  |
| 3  |                          |     | (c) Consider use of a flow diagram<br><b>page 5</b>  |
| 4  | Descriptive data         | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br><b>page 9, 13 &amp; web only material</b>  |
| 5  |                          |     | (b) Indicate number of participants with missing data for each variable of interest<br><b>pages 4, 5 &amp; 6</b>   |
| 6  |                          |     | (c) Summarise follow-up time (eg, average and total amount)<br><b>page 4</b>   |
| 7  | Outcome data             | 15* | Report numbers of outcome events or summary measures over time<br><b>page 9</b>  |
| 8  | 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<br><b>pages 6, 9 &amp; 10</b> |
| 9  |                          |     | (b) Report category boundaries when continuous variables were categorized<br><b>page 11 &amp; 12</b>   |
| 10 |                          |     | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period   |
| 11 | Other analyses           | 17  | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses<br><b>pages 10-15</b>   |
| 12 | <b>Discussion</b>        |     |  |
| 13 | Key results              | 18  | Summarise key results with reference to study objectives<br><b>page 16</b>   |
| 14 | 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<br><b>pages 17 &amp; 18</b>   |
| 15 | Interpretation           | 20  | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence<br><b>page 16</b>   |
| 16 | Generalisability         | 21  | Discuss the generalisability (external validity) of the study results<br><b>pages 16 &amp; 17</b>  |
| 17 | <b>Other information</b> |     |  |
| 18 | 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<br><b>page 19</b>  |

\*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>.



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

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| 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<br>Harold, Gordon; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Thapar, Anita; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Thapar, Ajay; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences |
| <b>Primary Subject Heading</b>: | Epidemiology  |
| Secondary Subject Heading:      | Mental health, Cardiovascular medicine  |
| Keywords:                       | MENTAL HEALTH, EPIDEMIOLOGY, Hypertension < CARDIOLOGY  |
|                                 |   |

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Manuscripts

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3 1 **Title:** Depression and blood pressure in high-risk children and adolescents: an investigation using two  
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5 2 longitudinal cohorts.

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8 3 **Abstract**

9 4 *Objective* – To examine the relationship between blood pressure and depressive disorder in children  
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11 and adolescents at high-risk for depression.

12 6 *Design* – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study  
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14 of offspring of parents with recurrent depression and an on-going birth cohort for replication.

15 8 *Setting* – Community based studies.

16 9 *Participants* – High-risk sample includes 281 families where children were aged 9-17 years at baseline  
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18 and 10-19 years at the final data point. Replication cohort includes 4830 families where children were  
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20 aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring  
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22 with mothers that had reported recurrent depression.

23 13 *Main outcome measures* –New onset DSM-IV defined depressive disorder in the offspring using  
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25 established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment  
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27 (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the  
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29 replication sample.

30 17 *Results* – Blood pressure was standardised for age and gender to create standard deviation scores and  
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32 child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood  
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34 pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI  
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36 .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict  
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38 systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and  
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40 future depression was also found in the replication cohort in the second subset of high-risk children  
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42 whose mothers had experienced recurrent depression in the past.

43 24 *Conclusion* – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of  
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45 parents with depression. Further studies are needed to investigate how this association arises.

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50 26 **Key words**

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52 27 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.

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3 29 **Introduction**  
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5 30 The two leading causes of death and disability in the developed world are depression and  
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7 31 cardiovascular disease. The association between depression and cardiovascular disease is well  
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9 32 established in adults,[1] although the mechanisms by which it arises are still not clear. It has been  
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11 33 suggested that these links reflect early associations between depression and cardiovascular risk factors.  
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13 34 High blood pressure is an important cardiovascular risk factor and it has also been linked to depression  
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15 35 in adults in some studies.[2] Other studies, however, have found the converse. They suggest that  
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17 36 depression is associated with low blood pressure and that it is only depression treated with certain  
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19 37 antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by  
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21 38 which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it  
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23 39 is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the  
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25 40 findings are inconsistent, with some studies finding depression as a predictor of either high blood  
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27 41 pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure  
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29 42 predicting depression.[6]

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33 44 Although both depression and the early indicators of cardiovascular disease have been found to have  
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35 45 onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger  
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37 46 populations. In this study, the main aim was to investigate the relationship between blood pressure and  
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39 47 subsequent first onset episode of depression in a prospective cohort of children and adolescents at high  
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41 48 risk of depression. The secondary aim was to replicate findings in an independent cohort.  
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3 50 **Method**  
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5 51 Data were derived from a prospective longitudinal study of offspring of parents with recurrent  
6 52 depression—‘The Early Prediction of Adolescent Depression (EPAD) study’. At baseline, the sample  
7 53 included 337 families (315 mothers and 22 fathers) that were recruited from general practices across  
8 54 South Wales, by writing to eligible families, and from a database of adults with previously identified  
9 55 unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test  
10 56 the main hypotheses of the original project whilst allowing detailed assessments at each time point.  
11 57 Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive  
12 58 disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview  
13 59 that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment  
14 60 in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an  
15 61 experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected  
16 62 for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to  
17 63 and currently living with the affected parent. Additional exclusion criteria included children with  
18 64 moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or  
19 65 psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the  
20 66 study because the depressed parent had been diagnosed as suffering from bipolar disorder since the  
21 67 wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed  
22 68 using age-appropriate standard research diagnostic interviews independently by two trained research  
23 69 psychologists on three occasions over the course of the study which began in April 2007 and finished  
24 70 in April 2011. The average time between the baseline and second assessment was 16.2 months and  
25 71 between the second and third assessment was 12.5 months. Further details on the sample characteristics  
26 72 and methodology have been described previously.[9]

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46 73 For the main analyses, 30 families were excluded because they had not completed at least two waves of  
47 74 data. A further 10 children were excluded from main analyses because they already met criteria for  
48 75 DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede  
49 76 onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not  
50 77 been completed at baseline either because there had been a fault in the equipment or the child had  
51 78 refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data  
52 79 were collected from parents and children via semi-structured research diagnostic interviews and blood  
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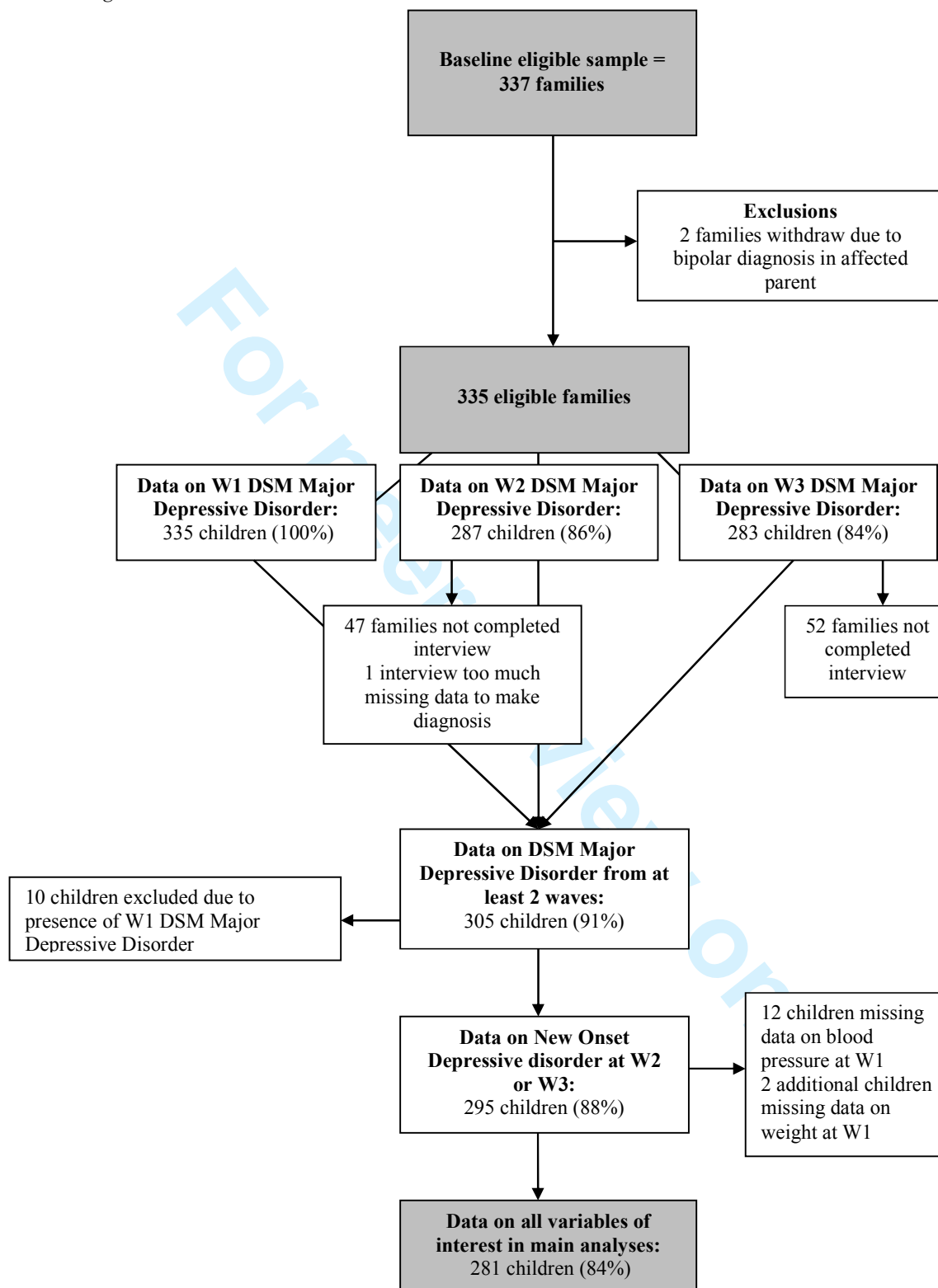
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80 pressure and weight were assessed by the interviewer. Additional data on physical health problems,  
81 maternal education and social class were collected from parents and children from self-completed  
82 questionnaires that were mailed to the families two weeks before their interview. Ethical approval for  
83 the study was obtained from the Multi-centre Research Ethics Committee for Wales.  
84

For peer review only



85 *Figure 1*



*Flow chart of retention at each assessment in the EPAD sample*

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3 86 Data were also utilised from a birth cohort study ‘The Avon Longitudinal Study of Parents and  
4 87 Children (ALSPAC)’ to allow replication of findings from the first high-risk sample. The cohort was  
5 88 set up to examine genetic and environmental determinants of health and development.[10] The initial  
6 89 cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date  
7 90 of delivery between 1<sup>st</sup> April 1991 and 31<sup>st</sup> December 1992 ([www.alspac.bris.ac.uk](http://www.alspac.bris.ac.uk)). All pregnant  
8 91 women resident in three health districts in the old administrative county of Avon who had an estimated  
9 92 delivery between the above dates were eligible to participate. In addition, pregnant women that had  
10 93 migrated into the catchment area before the point of delivery were eligible. Recruitment was carried  
11 94 out by attempting to make contact with eligible women through ALSPAC staff visiting community  
12 95 locations and through using antenatal and maternity health services and media information to  
13 96 encourage contact and promote the study.[10] The parents completed regular postal questionnaires  
14 97 concerning their child’s health and development since birth. The children have completed  
15 98 questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole  
16 99 sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and  
17 100 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range:  
18 101 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children  
19 102 whose mothers had experienced recurrent depression (at least two episodes); 612 children were  
20 103 included in these analyses (347 females and 265 males). Ethical approval for the study was obtained  
21 104 from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

## 105 **Measures**

106 EPAD study:

107 *Assessment of depression in the offspring of parents with recurrent depression*

108 The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic  
109 interview that has high reliability and that is used to assess children's psychiatric symptoms [11].

110 Parents are asked about their children's psychopathology and children are independently interviewed  
111 using the interview schedules (parent and child versions). The presence of any given symptom has to  
112 be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined  
113 symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews  
114 were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

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3 115 selected recordings at each time point (10 parent report and 10 child report) and through weekly  
4  
5 116 supervision by an academic clinician with extensive experience in using the interview. Average  
6  
7 117 agreement between raters for DSM-IV psychiatric disorder was excellent ( $\kappa=0.92$ ), as was average  
8  
9 118 agreement for depression symptoms ( $\kappa=0.93$ ). CAPA was used at each assessment and assesses the  
10  
11 119 presence of a major depressive disorder in the child over the preceding three months. The parent and  
12  
13 120 child versions were completed independently, with interviews conducted in separate rooms where  
14  
15 121 possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using  
16  
17 122 DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either  
18  
19 123 parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms  
20  
21 124 was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed  
22  
23 125 weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of  
24  
25 126 DSM-IV major depressive disorder symptoms was also computed from the CAPA.

26  
27 127 *New onset major depressive disorder* - The presence of a new onset DSM-IV diagnosis of major  
28  
29 128 depressive disorder at either the second or third assessment was defined by excluding children that had  
30  
31 129 a baseline diagnosis of DSM-IV major depressive disorder.

32  
33 130 *Blood pressure* –An Omron 705IT sphygmomanometer was used to measure blood pressure at each  
34  
35 131 assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard  
36  
37 132 cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was  
38  
39 133 used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were  
40  
41 134 measured using standardised guidelines set out by the American Heart association.[12] At least two  
42  
43 135 readings were taken at least one minute apart using the right arm. When the difference between two  
44  
45 136 readings was 5mmHg or less an average was taken.

46  
47 137 *Weight and other potential confounders* – Weight was considered to be a confounder of the relationship  
48  
49 138 between blood pressure and depression due to its potential association with both.[13, 14] Interviewers  
50  
51 139 measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also  
52  
53 140 examined whether the results were affected by the presence of physical health problems (parent  
54  
55 141 reported), any medication use (child or parent reported) and using body mass index (BMI) instead of  
56  
57 142 weight.  
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3 143 *Demographics* – The mother and father questionnaires completed at baseline were used to assess  
4 144 maternal education and highest parental social class. Maternal education was categorised according to  
5 145 whether the mother had completed higher education (A-Levels, degree or postgraduate qualification).  
6  
7 146 Parental social class was categorised according to whether either parent reported having a non-manual  
8  
9 147 occupation.

10  
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13 148 ALSPAC:

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15 149 *Maternal history of recurrent depression* – Mothers completed regular questionnaires from pregnancy  
16 150 to when the child was aged 12 years including the questions ‘Have you had depression in the last year/  
17 151 last two years/ since your child was born/ever’. The mother was also asked ‘Have you ever had severe  
18 152 depression’ on three occasions over this time period. Research diagnostic interview generated  
19 153 psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data  
20 154 set thus had to be defined where mother had reported having depression on at least two separate  
21 155 occasions, and if at least one of these occasions was reported as being severe. These criteria were used  
22 156 to create a subsample that was as similar as possible to the primary high-risk sample.

23  
24 157 *Child depressive disorder* – Parent reports on their child's symptoms were obtained using a structured  
25 158 diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA,  
26 159 has been used widely for large scale population studies. The parent-rated DAWBA was completed  
27 160 when the target age of the children was 13 years. Children were directly interviewed using the  
28 161 DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the  
29 162 preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-  
30 163 defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a  
31 164 DSM-IV diagnosis of depression and generates diagnoses (see [www.DAWBA.com](http://www.DAWBA.com) for more  
32 165 information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part  
33 166 of the ALSPAC data collection process. [16]

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50 167 *Blood pressure* – Systolic and diastolic blood pressure were measured at the clinic assessments when  
51 168 the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each  
52 169 assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

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3 170 *Weight and other potential confounders* – Interviewers measured the weight and height of the children  
4  
5 171 in light clothing and without shoes at the clinic assessments when the target age of the children was 12  
6  
7 172 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height  
8  
9 173 was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then  
10  
11 174 calculated (kg/m<sup>2</sup>). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal  
12  
13 175 medical records.

14  
15 176 *Demographics* – The mother and father questionnaires completed during pregnancy were used to assess  
16  
17 177 maternal education and highest parental social class. Maternal education was categorised according to  
18  
19 178 whether the mother had completed higher education (A-Levels or degree). Parental social class was  
20  
21 179 categorised according to whether either parent reported having a non-manual occupation.

### 22 23 180 **Statistical methods**

24  
25 181 Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the  
26  
27 182 high-risk sample and then in the replication cohort using the subsample of children with mothers that  
28  
29 183 have experienced recurrent depression in the past. Next, regression analyses were performed to  
30  
31 184 examine the association between blood pressure and depression in the high-risk sample and then in the  
32  
33 185 subsample from the replication cohort. Logistic regression analyses were used when the dependent  
34  
35 186 variable was dichotomous and ordinary least squares linear regression analysis was used when the  
36  
37 187 dependent variable was continuous. Continuous outcome data that were not normally distributed were  
38  
39 188 transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship  
40  
41 189 between systolic blood pressure and future depressive disorder was examined by investigating the  
42  
43 190 percentage of children with future depressive disorder by blood pressure quintiles, again in both  
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45 191 samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for  
46  
47 192 blood pressure in both samples that showed adequate sensitivity and specificity for detecting future  
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49 193 depressive disorder. Lastly, the association between systolic blood pressure and future depressive  
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51 194 disorder was investigated in the general population by using the entire ALSPAC sample and the  
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53 195 presence of a multiplicative interaction between maternal depression and systolic blood pressure on  
54  
55 196 future depressive disorder was examined. Listwise deletion was used to deal with missing data in all  
56  
57 197 analyses and data were analysed using SPSS (v20). **Results**

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

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

203 *Table 1*

|   | <b>EPAD</b><br>(n=281) | <b>ALSPAC</b><br>(subsample of offspring<br>of recurrently<br>depressed mothers;<br>n=612) | <b>ALSPAC</b><br>(whole sample;<br>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                                       |

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

206 **Descriptives from EPAD high-risk sample**

207 Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and  
 208 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant  
 209 differences between males and females for systolic or diastolic blood pressure at baseline. Systolic  
 210 blood pressure at baseline was significantly correlated with age ( $r=.23$ ,  $p<.001$ ), but diastolic blood  
 211 pressure was not ( $r=.02$ ,  $p=.728$ ). Systolic blood pressure was thus standardised for age and gender to  
 212 create standard deviation scores and all analyses for systolic blood pressure were run with the  
 213 standardised variable.[17] Mean blood pressures for each age group in this sample were generally  
 214 higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated  
 215 with weight ( $r=.25$ ,  $p<.001$ ), but diastolic blood pressure was not ( $r=.07$ ,  $p=.236$ ). Given this finding  
 216 all analyses with systolic blood pressure are reported controlling for weight.

217 Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder  
 218 (8.54%).

1  
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3 219 **Descriptives from ALSPAC dataset – using the subsample of children with mothers that have**  
4  
5 220 **experienced recurrent depression in the past**

6  
7 221 Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61  
8  
9 222 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences  
10  
11 223 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
12  
13 224 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
14  
15 225 systolic blood pressure were run with the standardised variable. The association between blood  
16  
17 226 pressure and weight at age 12 was significant for both systolic ( $r=.45$ ,  $p<.001$ ) and diastolic blood  
18  
19 227 pressure ( $r=.18$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

20  
21 228 Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at  
22  
23 229 age 15 (2.94%).

24  
25 230 **Initial analyses in EPAD high-risk sample**

26  
27 231 Logistic regression analyses were performed to investigate the association between blood pressure and  
28  
29 232 new onset depressive disorder in the EPAD sample of children. Lower systolic blood pressure at  
30  
31 233 baseline significantly predicted new onset depressive disorder (OR = .65, 95% CI .44 to .96;  $p=.029$ )  
32  
33 234 when adjusting for child's weight at baseline. Diastolic blood pressure at baseline did not significantly  
34  
35 235 predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01;  $p=.120$ ).

36  
37 236 Results remained the same when the outcome was expanded to include the new onset of more broadly  
38  
39 237 defined mood-related diagnoses (primary diagnosis: major depressive disorder  $n=22$ , dysthymia  $n=1$ ,  
40  
41 238 cyclothymia  $n=1$ , bipolar disorder  $n=3$ , adjustment disorder with depressed mood  $n=4$  and depressive  
42  
43 239 disorder not otherwise specified  $n=5$ ). Results also remained similar when separately adjusting for  
44  
45 240 medication use and physical health problems in the child and when adjusting for BMI instead of  
46  
47 241 weight. The association was not significantly moderated by gender ( $p=.769$ ).

48  
49 242 Given few adolescents developed new onset depressive disorder, the analysis was repeated using total  
50  
51 243 depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood  
52  
53 244 pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome,  
54  
55 245 and again controlling for weight, showed significant association ( $\beta = -.13$ ;  $p=.040$ ).

1  
2  
3 246 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis  
4  
5 247 was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood  
6  
7 248 pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This  
8  
9 249 was non-significant ( $\beta = -.05$ ;  $p = .412$ ). Given the low number of individuals with depressive disorder  
10  
11 250 at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again  
12  
13 251 the results were non-significant ( $\beta = -.07$ ;  $p = .286$ ).

14  
15 252 **Replication in ALSPAC dataset – using the subsample of children with mothers that have**  
16  
17 253 **experienced recurrent depression in the past**

18  
19 254 Logistic regression analyses were undertaken in the replication sample. Lower systolic blood pressure  
20  
21 255 at age 12 significantly predicted depressive disorder at age 15 (OR = .48, 95% CI .27 to .85;  $p = .012$ ),  
22  
23 256 however, diastolic blood pressure did not (OR = .98, 95% CI .93 to 1.05;  $p = .597$ ). Results remained  
24  
25 257 similar when adjusting for BMI instead of weight and when additionally adjusting for maternal systolic  
26  
27 258 blood pressure in pregnancy. The association was not significantly moderated by gender ( $p = .102$ ).

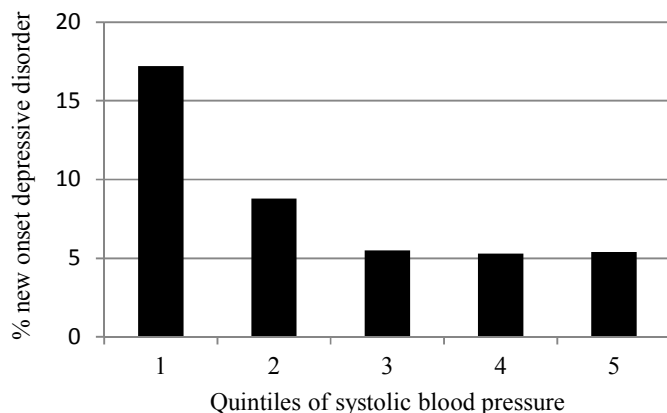
28  
29 259 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses  
30  
31 260 was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood  
32  
33 261 pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant ( $\beta = -$   
34  
35 262  $.04$ ;  $p = .378$ ).

36  
37 263 **Relationship between blood pressure and depressive disorder in high-risk EPAD sample**

38  
39 264 To further investigate the relationship between systolic blood pressure and depressive disorder in the  
40  
41 265 EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new  
42  
43 266 onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be  
44  
45 267 seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with  
46  
47 268 the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder  
48  
49 269 cases.



270 *Figure 2*



271

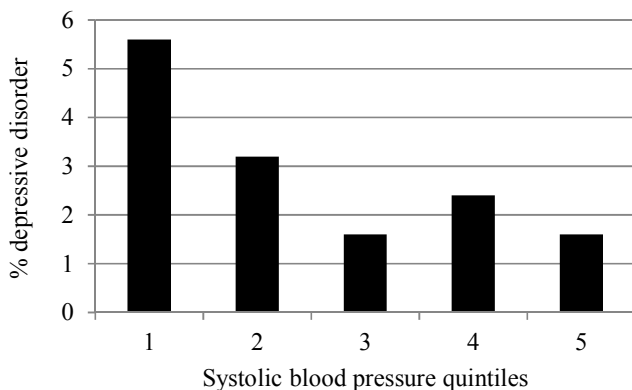
272 *Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of*  
 273 *systolic blood pressure at baseline in the EPAD sample*

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

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

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

282 *Figure 3*



283

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

286 Analyses so far have highlighted a significant association between lower systolic blood pressure and  
 287 future depression in two different samples of offspring of parents with recurrent depression. Next, ROC  
 288 analysis was performed to establish a cut off for blood pressure in both samples that showed adequate  
 289 sensitivity and specificity for detecting future depressive disorder. A cut off point of below 0.025  
 290 standard deviations above the mean using standardised systolic blood pressure [17] showed a  
 291 sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately  
 292 equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12  
 293 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised  
 294 systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC  
 295 replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a  
 296 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the  
 297 association between low blood pressure and future depressive disorder using each of the cut offs  
 298 identified in each sample (Table 2).

299 *Table 2*

|               | OR (95% CI) <sup>1</sup>                   |   |
|---------------|--|---|
|               | Optimal cut off in EPAD<br>sample (< .025) | Optimal cut off in<br>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)                            |

301 <sup>1</sup>Adjusted for child weight at W1

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

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

1  
2  
3 307 Lastly, supplementary analyses were performed to examine the association between blood pressure and  
4  
5 308 future depression in the general population using the entire ALSPAC sample.  
6

7  
8 **309 Supplementary analyses using entire ALSPAC sample:**

9  
10 **310 1) Testing the relationship between depressive disorder and blood pressure in the general**  
11 **311 population (not limiting analysis to those adolescents with a parental history of recurrent**  
12 **312 depression)**

13  
14  
15  
16 **313 Descriptives**

17  
18 314 Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53  
19  
20 315 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences  
21  
22 316 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
23  
24 317 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
25  
26 318 systolic blood pressure were run with the standardised variable. The association between blood  
27  
28 319 pressure and weight at age 12 was significant for both systolic ( $r=.44$ ,  $p<.001$ ) and diastolic blood  
29  
30 320 pressure ( $r=.19$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

31  
32 321 Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last  
33  
34 322 month at age 15 (1.55%).

35  
36 **323 Preliminary analyses**

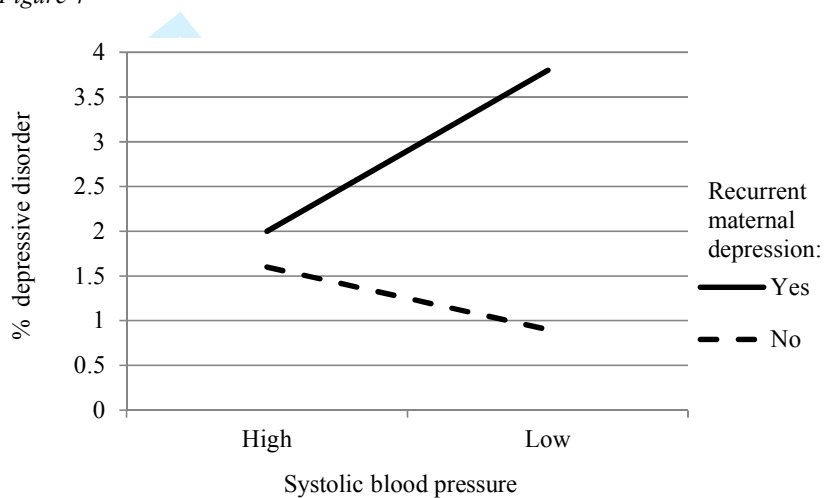
37  
38 324 Logistic regression analyses were performed to investigate the association between blood pressure and  
39  
40 325 depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder  
41  
42 326 at age 15 (OR = .98, 95% CI .76 to 1.27;  $p=.875$ ). Diastolic blood pressure at age 12 did not  
43  
44 327 significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04;  $p=.604$ ).

45  
46 **328 2) Examining whether a history of recurrent maternal depression moderated the**  
47  
48 **329 relationship between systolic blood pressure and depression**

49  
50 330 Logistic regression analyses were then performed to test if recurrent maternal depression moderated the  
51  
52 331 relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic  
53  
54 332 blood pressure and maternal recurrent depression were centred to convert them to their deviation form  
55  
56 333 to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95%  
57  
58 334 CI .27 to .89;  $p=.019$ ).

1  
2  
3 335 Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that  
4 336 the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal  
5 337 depression was present, children with low blood pressure showed the highest percentage of depressive  
6 338 disorder. However, when recurrent maternal depression was not present, children with high blood  
7 339 pressure showed the highest percentage of depressive disorder.

12  
13 340 *Figure 4*



28  
29 341

30 342 *Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low'*  
31 343 *systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample*

1  
2  
3 344 **Discussion**

4 345 In this study we found that lower systolic blood pressure significantly predicted future new onset  
5  
6 346 depressive disorder amongst a sample of children and adolescents at high risk of developing depression  
7  
8 347 because of a parental history of recurrent depression. This finding was replicated in a large community  
9  
10 348 based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression  
11  
12 349 (replication sample). When investigating this relationship in more detail, it seemed that those with the  
13  
14 350 lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut  
15  
16 351 off value for systolic blood pressure in 12 year old children was identified as being within the range of  
17  
18 352 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort  
19  
20 353 (ALSPAC), the association between blood pressure and major depressive disorder was no longer  
21  
22 354 significant. There was no evidence for an association in the opposite direction (depression predicting  
23  
24 355 future blood pressure levels) either in the study sample or in the replication cohort nor was there an  
25  
26 356 association between diastolic blood pressure and future depression in either dataset.

27  
28 357 In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive  
29  
30 358 disorder was slightly higher than population norms, it was those whose blood pressure was lower who  
31  
32 359 were at most risk of developing depressive disorder. This was not true in adolescents from the general  
33  
34 360 population. There have been no previously published longitudinal studies examining the relationship  
35  
36 361 between blood pressure and depression in children from the general population or children at high-risk  
37  
38 362 of depression. In adults, findings have been mixed but links between low blood pressure and depression  
39  
40 363 have been noted. These have not only been noted cross-sectionally in adults,[19, 20] but a study on  
41  
42 364 elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] In  
43  
44 365 adolescents who did not have a parent with recurrent depressive disorder, higher blood pressure  
45  
46 366 showed some association with a higher risk of future depressive disorder. Given the limited scientific  
47  
48 367 literature on this topic the mechanisms by which low blood pressure might precede depression for  
49  
50 368 adolescent offspring of individuals with recurrent depressive disorder are unclear and we can at present  
51  
52 369 only speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or  
53  
54 370 environmental) that contribute to both lower blood pressure and depression that are especially enriched  
55  
56 371 in those offspring most at risk of developing depressive disorder in the near future. Another possibility  
57  
58 372 is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents  
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60 373 an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major

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3 374 depressive disorder. There is strikingly limited research on biological links between early mental health  
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5 375 problems and physical health as well as on autonomic system function in young people who are  
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7 376 familially vulnerable to depression [21]. Our findings highlight the need for further research on links  
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9 377 between mental and physical health in young people.

10  
11 378 **Strengths and Limitations**  
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14 379 This is the first study we are aware of to report on the longitudinal relationship between blood pressure  
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16 380 and depressive disorder in adolescents, an important period for the onset of depression. In the main  
17  
18 381 sample, children and adolescents were followed up at three points over a four year period with a high  
19  
20 382 retention rate of over 80%. A similar pattern of results was found in a large community based cohort  
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22 383 study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples,  
23  
24 384 diagnoses were systematically ascertained using interview and blood pressure readings were measured  
25  
26 385 according to standardised protocol. In addition, potential confounders of the relationship were taken  
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28 386 account of. There were also possible limitations of the study. Blood pressures were measured using an  
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30 387 electronic device which uses an oscillometric technique rather than the auscultatory technique that most  
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32 388 population norms are based on and it has been noted that these readings are not equivalent. However  
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34 389 there is a lack of consensus as to whether using different methods leads to any systematic bias and  
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36 390 inaccuracies seem more related to not using a standardised technique rather than the instrument.[22] In  
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38 391 addition, the cut off values identified in the high risk and replication samples differed slightly. This  
39  
40 392 may have been because of differences in measurement techniques in the two studies. These results need  
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42 393 to be replicated in other samples in order to establish more precise cut off for low systolic blood  
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44 394 pressure. Despite being a high-risk sample, the number of children with depressive disorder was small  
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46 395 and many of the sample had not been though the age of maximum risk for developing a depressive  
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48 396 disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of  
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50 397 children with depressive disorder was also low in the replication sample, partly because only a self-  
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52 398 report measure of depressive disorder was available at age 15, and partly because of selective attrition  
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54 399 over time. Previous studies have reported that although attrition has affected prevalence rates of  
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56 400 depression in the mother and internalising disorders in the children, the associations between risks and  
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58 401 outcomes remained intact, although conservative estimates of the likely true effects.[23, 24] Lastly, the  
59  
60 402 subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe

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3 403 group as maternal self-report of depression was used as opposed to defining episodes of depression  
4  
5 404 using DSM-IV criteria as was done in the main dataset.  
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7  
8 405 In summary, in our study of adolescents at high risk of depression we found that low blood pressure  
9  
10 406 was associated with major depressive disorder. This finding was replicated in an independent cohort.  
11  
12 407 Future research is needed using different populations to confirm this relationship as it is a novel finding  
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14 408 and to investigate the mechanisms by which the relationship between low blood pressure and  
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16 409 depressive disorder in children at risk for depression may arise.  
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3 410 **Acknowledgments**  
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6 411 Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable  
7 412 Trust and the National Institute for Social Care and Health Research Academic Health Science  
8  
9 413 Collaboration (AHSC) fellowship.  
10

11  
12 414 We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for  
13 415 their help with recruiting them and the whole EPAD team. We thank the other investigators involved in  
14 416 the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael  
15 417 Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the  
16 418 families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the  
17 419 whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical  
18 420 workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research  
19 421 Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support  
20 422 for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar,  
21 423 Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research  
22 424 was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules  
23 425 Thorn Charitable Trust.  
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36 426 **Conflict of interest**  
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38 427 None of the authors have conflict of interest/financial disclosures.  
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42 428 **Role of funding source**  
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44 429 Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant  
45 430 and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research  
46 431 Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors  
47 432 (AKT). The funders had no further role in the study design, the collection, analysis and interpretation  
48 433 of data, the writing of the report, or in the decision to submit the paper for publication.  
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434 **Contributorship**

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

443

444 **Data sharing:** no additional data available.445 **References**

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3 1 **Title:** Depression and blood pressure in high-risk children and adolescents: an investigation using two  
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5 2 longitudinal cohorts.

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8 3 **Abstract**

9 4 *Objective* – To examine the relationship between blood pressure and depressive disorder in children  
10  
11 5 and adolescents at high-risk for depression.

12 6 *Design* – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study  
13  
14 7 of offspring of parents with recurrent depression and an on-going birth cohort for replication.

15 8 *Setting* – Community based studies.

16 9 *Participants* – High-risk sample includes 281 families where children were aged 9-17 years at baseline  
17  
18 10 and 10-19 years at the final data point. Replication cohort includes 4830 families where children were  
19  
20 11 aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring  
21  
22 12 with mothers that had reported recurrent depression.

23 13 *Main outcome measures* – New onset DSM-IV defined depressive disorder in the offspring using  
24  
25 14 established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment  
26  
27 15 (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the  
28  
29 16 replication sample.

30 17 *Results* – Blood pressure was standardised for age and gender to create standard deviation scores and  
31  
32 18 child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood  
33  
34 19 pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI  
35  
36 20 .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict  
37  
38 21 systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and  
39  
40 22 future depression was also found in the replication cohort in the second subset of high-risk children  
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42 23 whose mothers had experienced recurrent depression in the past.

43 24 *Conclusion* – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of  
44  
45 25 parents with depression. Further studies are needed to investigate how this association arises.

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51 26 **Key words**

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53 27 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.

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3 29 **Introduction**

4 30 The two leading causes of death and disability in the developed world are depression and  
5  
6 31 cardiovascular disease. The association between depression and cardiovascular disease is well  
7  
8 32 established in adults,[1] although the mechanisms by which it arises are still not clear. It has been  
9  
10 33 suggested that these links reflect early associations between depression and cardiovascular risk factors.  
11  
12 34 High blood pressure is an important cardiovascular risk factor and it has also been linked to depression  
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14 35 in adults in some studies.[2] Other studies, however, have found the converse. They suggest that  
15  
16 36 depression is associated with low blood pressure and that it is only depression treated with certain  
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18 37 antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by  
19  
20 38 which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it  
21  
22 39 is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the  
23  
24 40 findings are inconsistent, with some studies finding depression as a predictor of either high blood  
25  
26 41 pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure  
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28 42 predicting depression.[6]

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31 44 Although both depression and the early indicators of cardiovascular disease have been found to have  
32  
33 45 onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger  
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35 46 populations. In this study, the main aim was to investigate the relationship between blood pressure and  
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37 47 subsequent first onset episode of depression in a prospective cohort of children and adolescents at high  
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39 48 risk of depression. The secondary aim was to replicate findings in an independent cohort.  
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3 50 **Method**  
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5 51 Data were derived from a prospective longitudinal study of offspring of parents with recurrent  
6 52 depression—‘The Early Prediction of Adolescent Depression (EPAD) study’. At baseline, the sample  
7 53 included 337 families (315 mothers and 22 fathers) that were recruited from general practices across  
8 54 South Wales, by writing to eligible families, and from a database of adults with previously identified  
9 55 unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test  
10 56 the main hypotheses of the original project whilst allowing detailed assessments at each time point.

11 57 Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive  
12 58 disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview  
13 59 that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment  
14 60 in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an  
15 61 experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected  
16 62 for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to  
17 63 and currently living with the affected parent. Additional exclusion criteria included children with  
18 64 moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or  
19 65 psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the  
20 66 study because the depressed parent had been diagnosed as suffering from bipolar disorder since the  
21 67 wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed  
22 68 using age-appropriate standard research diagnostic interviews independently by two trained research  
23 69 psychologists on three occasions over the course of the study which began in April 2007 and finished  
24 70 in April 2011. The average time between the baseline and second assessment was 16.2 months and  
25 71 between the second and third assessment was 12.5 months. Further details on the sample characteristics  
26 72 and methodology have been described previously.[9]

27 73 For the main analyses, 30 families were excluded because they had not completed at least two waves of  
28 74 data. A further 10 children were excluded from main analyses because they already met criteria for  
29 75 DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede  
30 76 onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not  
31 77 been completed at baseline either because there had been a fault in the equipment or the child had  
32 78 refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data  
33 79 were collected from parents and children via semi-structured research diagnostic interviews and blood  
34

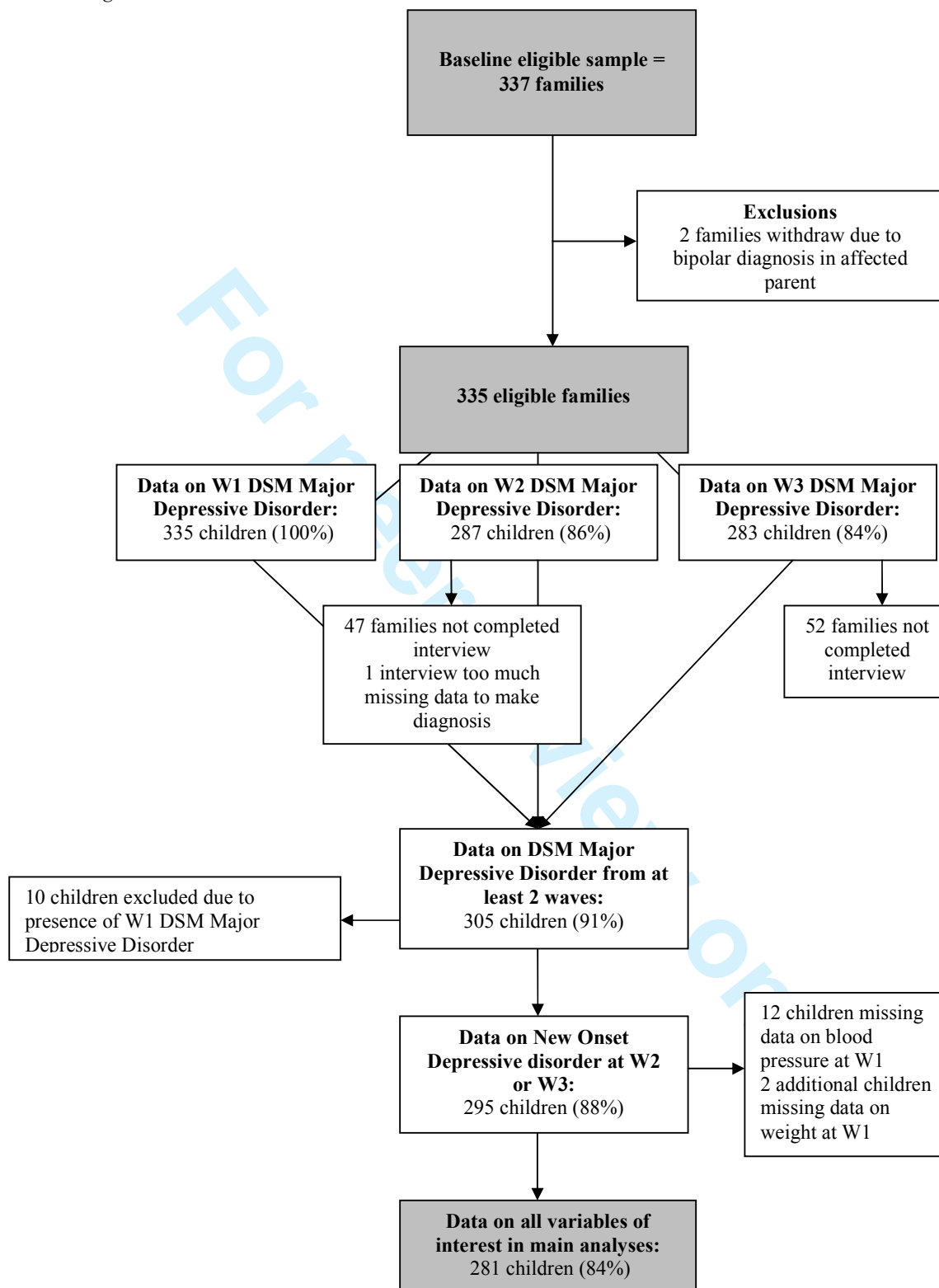
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80 pressure and weight were assessed by the interviewer. Additional data on physical health problems,  
81 maternal education and social class were collected from parents and children from self-completed  
82 questionnaires that were mailed to the families two weeks before their interview. Ethical approval for  
83 the study was obtained from the Multi-centre Research Ethics Committee for Wales.  
84

For peer review only



85 Figure 1



Flow chart of retention at each assessment in the EPAD sample

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3 86 Data were also utilised from a birth cohort study ‘The Avon Longitudinal Study of Parents and  
4 87 Children (ALSPAC)’ to allow replication of findings from the first high-risk sample. The cohort was  
5 88 set up to examine genetic and environmental determinants of health and development.[10] The initial  
6 89 cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date  
7 90 of delivery between 1<sup>st</sup> April 1991 and 31<sup>st</sup> December 1992 ([www.alspac.bris.ac.uk](http://www.alspac.bris.ac.uk)). All pregnant  
8 91 women resident in three health districts in the old administrative county of Avon who had an estimated  
9 92 delivery between the above dates were eligible to participate. In addition, pregnant women that had  
10 93 migrated into the catchment area before the point of delivery were eligible. Recruitment was carried  
11 94 out by attempting to make contact with eligible women through ALSPAC staff visiting community  
12 95 locations and through using antenatal and maternity health services and media information to  
13 96 encourage contact and promote the study.[10] The parents completed regular postal questionnaires  
14 97 concerning their child’s health and development since birth. The children have completed  
15 98 questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole  
16 99 sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and  
17 100 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range:  
18 101 14-17 years; mean age = 15.4 years). **Main replication analyses focused on the sub-sample of children  
19 102 whose mothers had experienced recurrent depression (at least two episodes)**; 612 children were  
20 103 included in these analyses (347 females and 265 males). Ethical approval for the study was obtained  
21 104 from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

## 105 **Measures**

106 EPAD study:

107 *Assessment of depression in the offspring of parents with recurrent depression*

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

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3 115 selected recordings at each time point (10 parent report and 10 child report) and through weekly  
4 116 supervision by an academic clinician with extensive experience in using the interview. Average  
5 117 agreement between raters for DSM-IV psychiatric disorder was excellent ( $\kappa=0.92$ ), as was average  
6 118 agreement for depression symptoms ( $\kappa=0.93$ ). CAPA was used at each assessment and assesses the  
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8 119 presence of a major depressive disorder in the child over the preceding three months. The parent and  
9  
10 120 child versions were completed independently, with interviews conducted in separate rooms where  
11  
12 121 possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using  
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14 122 DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either  
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16 123 parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms  
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18 124 was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed  
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20 125 weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of  
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22 126 DSM-IV major depressive disorder symptoms was also computed from the CAPA.

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26 127 *New onset major depressive disorder* - The presence of a new onset DSM-IV diagnosis of major  
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28 128 depressive disorder at either the second or third assessment was defined by excluding children that had  
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30 129 a baseline diagnosis of DSM-IV major depressive disorder.

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32 130 *Blood pressure* –An Omron 705IT sphygmomanometer was used to measure blood pressure at each  
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34 131 assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard  
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36 132 cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was  
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38 133 used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were  
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40 134 measured using standardised guidelines set out by the American Heart association.[12] At least two  
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42 135 readings were taken at least one minute apart using the right arm. When the difference between two  
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44 136 readings was 5mmHg or less an average was taken.

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46 137 *Weight and other potential confounders* – Weight was considered to be a confounder of the relationship  
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48 138 between blood pressure and depression due to its potential association with both.[13, 14] Interviewers  
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50 139 measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also  
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52 140 examined whether the results were affected by the presence of physical health problems (parent  
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54 141 reported), any medication use (child or parent reported) and using body mass index (BMI) instead of  
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56 142 weight.

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3 143 *Demographics* – The mother and father questionnaires completed at baseline were used to assess  
4 144 maternal education and highest parental social class. Maternal education was categorised according to  
5 145 whether the mother had completed higher education (A-Levels, degree or postgraduate qualification).  
6 146 Parental social class was categorised according to whether either parent reported having a non-manual  
7 147 occupation.  
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13 148 ALSPAC:  
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15 149 *Maternal history of recurrent depression* – Mothers completed regular questionnaires from pregnancy  
16 150 to when the child was aged 12 years including the questions ‘Have you had depression in the last year/  
17 151 last two years/ since your child was born/ever’. The mother was also asked ‘Have you ever had severe  
18 152 depression’ on three occasions over this time period. Research diagnostic interview generated  
19 153 psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data  
20 154 set thus had to be defined where mother had reported having depression on at least two separate  
21 155 occasions, and if at least one of these occasions was reported as being severe. These criteria were used  
22 156 to create a subsample that was as similar as possible to the primary high-risk sample.  
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31 157 *Child depressive disorder* – Parent reports on their child’s symptoms were obtained using a structured  
32 158 diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA,  
33 159 has been used widely for large scale population studies. The parent-rated DAWBA was completed  
34 160 when the target age of the children was 13 years. Children were directly interviewed using the  
35 161 DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the  
36 162 preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-  
37 163 defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a  
38 164 DSM-IV diagnosis of depression and generates diagnoses (see [www.DAWBA.com](http://www.DAWBA.com) for more  
39 165 information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part  
40 166 of the ALSPAC data collection process. [16]  
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50 167 *Blood pressure* – Systolic and diastolic blood pressure were measured at the clinic assessments when  
51 168 the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each  
52 169 assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.  
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3 170 *Weight and other potential confounders* – Interviewers measured the weight and height of the children  
4  
5 171 in light clothing and without shoes at the clinic assessments when the target age of the children was 12  
6  
7 172 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height  
8  
9 173 was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then  
10  
11 174 calculated (kg/m<sup>2</sup>). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal  
12  
13 175 medical records.

14  
15 176 *Demographics* – The mother and father questionnaires completed during pregnancy were used to assess  
16  
17 177 maternal education and highest parental social class. Maternal education was categorised according to  
18  
19 178 whether the mother had completed higher education (A-Levels or degree). Parental social class was  
20  
21 179 categorised according to whether either parent reported having a non-manual occupation.

## 22 23 24 180 **Statistical methods**

25 181 Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the  
26  
27 182 high-risk sample and then in the replication cohort using the subsample of children with mothers that  
28  
29 183 have experienced recurrent depression in the past. Next, regression analyses were performed to  
30  
31 184 examine the association between blood pressure and depression in the high-risk sample and then in the  
32  
33 185 subsample from the replication cohort. Logistic regression analyses were used when the dependent  
34  
35 186 variable was dichotomous and ordinary least squares linear regression analysis was used when the  
36  
37 187 dependent variable was continuous. Continuous outcome data that were not normally distributed were  
38  
39 188 transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship  
40  
41 189 between systolic blood pressure and future depressive disorder was examined by investigating the  
42  
43 190 percentage of children with future depressive disorder by blood pressure quintiles, again in both  
44  
45 191 samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for  
46  
47 192 blood pressure in both samples that showed adequate sensitivity and specificity for detecting future  
48  
49 193 depressive disorder. Lastly, the association between systolic blood pressure and future depressive  
50  
51 194 disorder was investigated in the general population by using the entire ALSPAC sample and the  
52  
53 195 presence of a multiplicative interaction between maternal depression and systolic blood pressure on  
54  
55 196 future depressive disorder was examined. Listwise deletion was used to deal with missing data in all  
56  
57 197 analyses and data were analysed using SPSS (v20).

198 **Results**199 **Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent**  
200 **depression), the ALSPAC replication subsample of children with mothers that have experienced**  
201 **recurrent depression and the whole ALSPAC sample**

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

204 *Table 1*

|   | <b>EPAD</b><br>(n=281) | <b>ALSPAC</b><br>(subsample of offspring<br>of recurrently<br>depressed mothers;<br>n=612) | <b>ALSPAC</b><br>(whole sample;<br>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                                       |

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

207 **Descriptives from EPAD high-risk sample**

208 Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and  
209 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant  
210 differences between males and females for systolic or diastolic blood pressure at baseline. Systolic  
211 blood pressure at baseline was significantly correlated with age ( $r=.23$ ,  $p<.001$ ), but diastolic blood  
212 pressure was not ( $r=.02$ ,  $p=.728$ ). Systolic blood pressure was thus standardised for age and gender to  
213 create standard deviation scores and all analyses for systolic blood pressure were run with the  
214 standardised variable.[17] Mean blood pressures for each age group in this sample were generally  
215 higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated  
216 with weight ( $r=.25$ ,  $p<.001$ ), but diastolic blood pressure was not ( $r=.07$ ,  $p=.236$ ). Given this finding  
217 all analyses with systolic blood pressure are reported controlling for weight.

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3 218 Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder  
4  
5 219 (8.54%).

6  
7  
8 220 **Descriptives from ALSPAC dataset – using the subsample of children with mothers that have**  
9  
10 221 **experienced recurrent depression in the past**

11 222 Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61  
12  
13 223 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences  
14  
15 224 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
16  
17 225 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
18  
19 226 systolic blood pressure were run with the standardised variable. The association between blood  
20  
21 227 pressure and weight at age 12 was significant for both systolic ( $r=.45$ ,  $p<.001$ ) and diastolic blood  
22  
23 228 pressure ( $r=.18$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

24  
25 229 Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at  
26  
27 230 age 15 (2.94%).

28  
29  
30 231 **Initial analyses in EPAD high-risk sample**

31 232 Logistic regression analyses were performed to investigate the association between blood pressure and  
32  
33 233 new onset depressive disorder in the EPAD sample of children. Lower systolic blood pressure at  
34  
35 234 baseline significantly predicted new onset depressive disorder (OR = .65, 95% CI .44 to .96;  $p=.029$ )  
36  
37 235 when adjusting for child's weight at baseline. Diastolic blood pressure at baseline did not significantly  
38  
39 236 predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01;  $p=.120$ ).

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41  
42 237 Results remained the same when the outcome was expanded to include the new onset of more broadly  
43  
44 238 defined mood-related diagnoses (primary diagnosis: major depressive disorder  $n=22$ , dysthymia  $n=1$ ,  
45  
46 239 cyclothymia  $n=1$ , bipolar disorder  $n=3$ , adjustment disorder with depressed mood  $n=4$  and depressive  
47  
48 240 disorder not otherwise specified  $n=5$ ). Results also remained similar when separately adjusting for  
49  
50 241 medication use and physical health problems in the child and when adjusting for BMI instead of  
51  
52 242 weight. The association was not significantly moderated by gender ( $p=.769$ ).

53  
54 243 Given few adolescents developed new onset depressive disorder, the analysis was repeated using total  
55  
56 244 depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood

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3 245 pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome,  
4 246 and again controlling for weight, showed significant association ( $\beta = -.13$ ;  $p=.040$ ).

7 247 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis  
8  
9 248 was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood  
10  
11 249 pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This  
12  
13 250 was non-significant ( $\beta = -.05$ ;  $p=.412$ ). Given the low number of individuals with depressive disorder  
14  
15 251 at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again  
16  
17 252 the results were non-significant ( $\beta = -.07$ ;  $p = .286$ ).

19  
20 253 **Replication in ALSPAC dataset – using the subsample of children with mothers that have**  
21  
22 254 **experienced recurrent depression in the past**

23 255 Logistic regression analyses were undertaken in the replication sample. Lower systolic blood pressure  
24  
25 256 at age 12 significantly predicted depressive disorder at age 15 (OR = .48, 95% CI .27 to .85;  $p=.012$ ),  
26  
27 257 however, diastolic blood pressure did not (OR = .98, 95% CI .93 to 1.05;  $p=.597$ ). Results remained  
28  
29 258 similar when adjusting for BMI instead of weight and when additionally adjusting for maternal systolic  
30  
31 259 blood pressure in pregnancy. The association was not significantly moderated by gender ( $p=.102$ ).

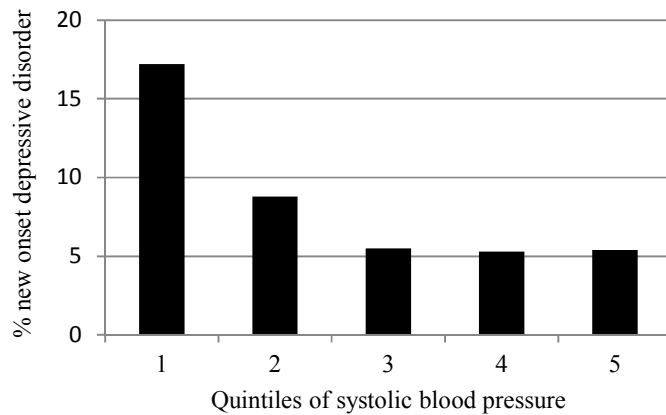
32  
33 260 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses  
34  
35 261 was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood  
36  
37 262 pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant ( $\beta = -$   
38  
39 263 .04;  $p = .378$ ).

40  
41  
42 264 **Relationship between blood pressure and depressive disorder in high-risk EPAD sample**

43 265 To further investigate the relationship between systolic blood pressure and depressive disorder in the  
44  
45 266 EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new  
46  
47 267 onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be  
48  
49 268 seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with  
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51 269 the lowest quintile of systolic blood pressure having the highest percentage of depressive disorder  
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53 270 cases.



271 *Figure 2*



272

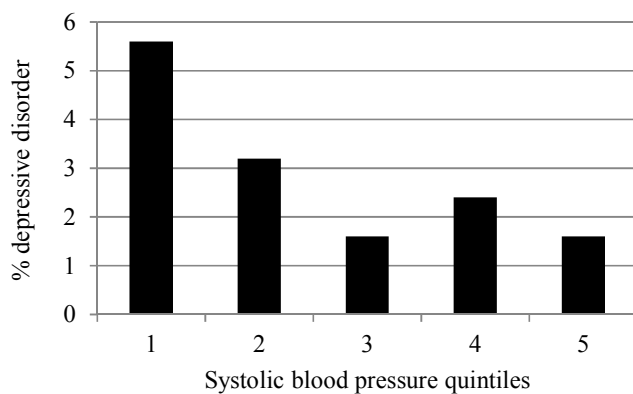
273 *Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of*  
 274 *systolic blood pressure at baseline in the EPAD sample*

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

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

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

283 *Figure 3*



284

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

287 Analyses so far have highlighted a significant association between lower systolic blood pressure and  
 288 future depression in two different samples of offspring of parents with recurrent depression. Next, ROC  
 289 analysis was performed to establish a cut off for blood pressure in both samples that showed adequate  
 290 sensitivity and specificity for detecting future depressive disorder. A cut off point of below 0.025  
 291 standard deviations above the mean using standardised systolic blood pressure [17] showed a  
 292 sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately  
 293 equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12  
 294 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised  
 295 systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC  
 296 replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a  
 297 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the  
 298 association between low blood pressure and future depressive disorder using each of the cut offs  
 299 identified in each sample (Table 2).

300 *Table 2*

|               | OR (95% CI) <sup>1</sup>                   |   |
|---------------|--|---|
|               | Optimal cut off in EPAD<br>sample (< .025) | Optimal cut off in<br>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)                            |

302 <sup>1</sup>Adjusted for child weight at W1

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

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

1  
2  
3 308 Lastly, supplementary analyses were performed to examine the association between blood pressure and  
4  
5 309 future depression in the general population using the entire ALSPAC sample.  
6  
7

8 **Supplementary analyses using entire ALSPAC sample:**

9  
10 **1) Testing the relationship between depressive disorder and blood pressure in the general**  
11 **population (not limiting analysis to those adolescents with a parental history of recurrent**  
12 **depression)**  
13

14  
15  
16 **Descriptives**

17  
18 315 Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53  
19  
20 316 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences  
21  
22 317 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
23  
24 318 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
25  
26 319 systolic blood pressure were run with the standardised variable. The association between blood  
27  
28 320 pressure and weight at age 12 was significant for both systolic ( $r=.44$ ,  $p<.001$ ) and diastolic blood  
29  
30 321 pressure ( $r=.19$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

31  
32 322 Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last  
33  
34 323 month at age 15 (1.55%).

35  
36 **Preliminary analyses**

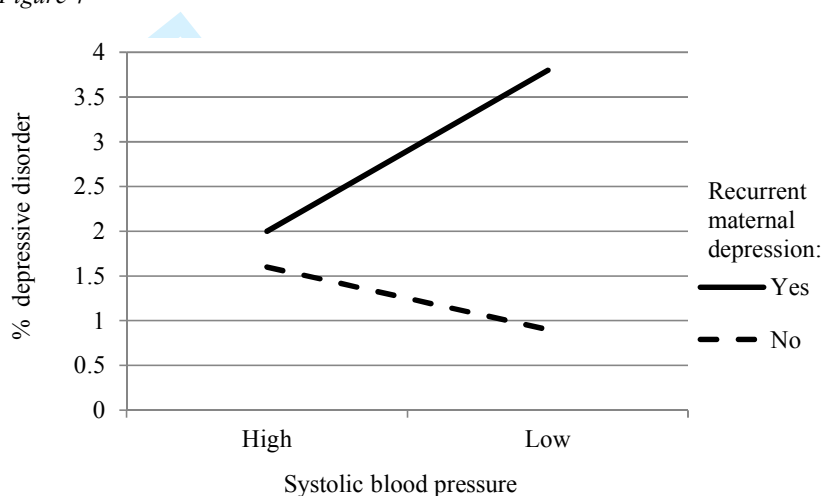
37  
38 325 Logistic regression analyses were performed to investigate the association between blood pressure and  
39  
40 326 depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder  
41  
42 327 at age 15 (OR = .98, 95% CI .76 to 1.27;  $p=.875$ ). Diastolic blood pressure at age 12 did not  
43  
44 328 significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04;  $p=.604$ ).

45  
46 **2) Examining whether a history of recurrent maternal depression moderated the**  
47 **relationship between systolic blood pressure and depression**  
48

49  
50 331 Logistic regression analyses were then performed to test if recurrent maternal depression moderated the  
51  
52 332 relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic  
53  
54 333 blood pressure and maternal recurrent depression were centred to convert them to their deviation form  
55  
56 334 to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95%  
57  
58 335 CI .27 to .89;  $p=.019$ ).

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2  
3 336 Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that  
4 337 the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal  
5 338 depression was present, children with low blood pressure showed the highest percentage of depressive  
6 339 disorder. However, when recurrent maternal depression was not present, children with high blood  
7 340 pressure showed the highest percentage of depressive disorder.

11  
12  
13 341 *Figure 4*



342  
343 *Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low'*  
344 *systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample*

1  
2  
3 345 **Discussion**

4 346 In this study we found that lower systolic blood pressure significantly predicted future new onset  
5  
6 347 depressive disorder amongst a sample of children and adolescents at high risk of developing depression  
7  
8 348 because of a parental history of recurrent depression. This finding was replicated in a large community  
9  
10 349 based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression  
11  
12 350 (replication sample). When investigating this relationship in more detail, it seemed that those with the  
13  
14 351 lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut  
15  
16 352 off value for systolic blood pressure in 12 year old children was identified as being within the range of  
17  
18 353 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort  
19  
20 354 (ALSPAC), the association between blood pressure and major depressive disorder was no longer  
21  
22 355 significant. There was no evidence for an association in the opposite direction (depression predicting  
23  
24 356 future blood pressure levels) either in the study sample or in the replication cohort nor was there an  
25  
26 357 association between diastolic blood pressure and future depression in either dataset.

27  
28 358 In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive  
29  
30 359 disorder was slightly higher than population norms, it was those whose blood pressure was lower who  
31  
32 360 were at most risk of developing depressive disorder. This was not true in adolescents from the general  
33  
34 361 population. There have been no previously published longitudinal studies examining the relationship  
35  
36 362 between blood pressure and depression in children from the general population or children at high-risk  
37  
38 363 of depression. In adults, findings have been mixed but links between low blood pressure and depression  
39  
40 364 have been noted. These have not only been noted cross-sectionally in adults,[19, 20] but a study on  
41  
42 365 elderly patients reported a fall in systolic blood pressure predicted the onset of depression.[6] In  
43  
44 366 adolescents who did not have a parent with recurrent depressive disorder, higher blood pressure  
45  
46 367 showed some association with a higher risk of future depressive disorder. Given the limited scientific  
47  
48 368 literature on this topic the mechanisms by which low blood pressure might precede depression for  
49  
50 369 adolescent offspring of individuals with recurrent depressive disorder are unclear and we can at present  
51  
52 370 only speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or  
53  
54 371 environmental) that contribute to both lower blood pressure and depression that are especially enriched  
55  
56 372 in those offspring most at risk of developing depressive disorder in the near future. Another possibility  
57  
58 373 is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents  
59  
60 374 an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major

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2  
3 375 depressive disorder. There is strikingly limited research on biological links between early mental health  
4 376 problems and physical health as well as on autonomic system function in young people who are  
5  
6 377 familially vulnerable to depression [21]. Our findings highlight the need for further research on links  
7  
8 378 between mental and physical health in young people.  
9

### 10 11 379 **Strengths and Limitations**

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13  
14 380 This is the first study we are aware of to report on the longitudinal relationship between blood pressure  
15  
16 381 and depressive disorder in adolescents, an important period for the onset of depression. In the main  
17  
18 382 sample, children and adolescents were followed up at three points over a four year period with a high  
19  
20 383 retention rate of over 80%. A similar pattern of results was found in a large community based cohort  
21  
22 384 study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples,  
23  
24 385 diagnoses were systematically ascertained using interview and blood pressure readings were measured  
25  
26 386 according to standardised protocol. In addition, potential confounders of the relationship were taken  
27  
28 387 account of. There were also possible limitations of the study. Blood pressures were measured using an  
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30 388 electronic device which uses an oscillometric technique rather than the auscultatory technique that most  
31  
32 389 population norms are based on and it has been noted that these readings are not equivalent. However  
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34 390 there is a lack of consensus as to whether using different methods leads to any systematic bias and  
35  
36 391 inaccuracies seem more related to not using a standardised technique rather than the instrument.[22] In  
37  
38 392 addition, the cut off values identified in the high risk and replication samples differed slightly. This  
39  
40 393 may have been because of differences in measurement techniques in the two studies. These results need  
41  
42 394 to be replicated in other samples in order to establish more precise cut off for low systolic blood  
43  
44 395 pressure. Despite being a high-risk sample, the number of children with depressive disorder was small  
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46 396 and many of the sample had not been though the age of maximum risk for developing a depressive  
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48 397 disorder so this could lead to an underestimate of the effects of risk factors. In addition, the number of  
49  
50 398 children with depressive disorder was also low in the replication sample, partly because only a self-  
51  
52 399 report measure of depressive disorder was available at age 15, and partly because of selective attrition  
53  
54 400 over time. Previous studies have reported that although attrition has affected prevalence rates of  
55  
56 401 depression in the mother and internalising disorders in the children, the associations between risks and  
57  
58 402 outcomes remained intact, although conservative estimates of the likely true effects.[23, 24] Lastly, the  
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60 403 subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe

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3 404 group as maternal self-report of depression was used as opposed to defining episodes of depression  
4  
5 405 using DSM-IV criteria as was done in the main dataset.  
6

7  
8 406 In summary, in our study of adolescents at high risk of depression we found that low blood pressure  
9  
10 407 was associated with major depressive disorder. This finding was replicated in an independent cohort.  
11  
12 408 Future research is needed using different populations to confirm this relationship as it is a novel finding  
13  
14 409 and to investigate the mechanisms by which the relationship between low blood pressure and  
15  
16 410 depressive disorder in children at risk for depression may arise.  
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3 411 **Acknowledgments**  
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5

6 412 Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable  
7 413 Trust and the National Institute for Social Care and Health Research Academic Health Science  
8  
9 414 Collaboration (AHSC) fellowship.  
10

11  
12 415 We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for  
13 416 their help with recruiting them and the whole EPAD team. We thank the other investigators involved in  
14  
15 417 the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael  
16  
17 418 Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the  
18  
19 419 families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the  
20  
21 420 whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical  
22  
23 421 workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research  
24  
25 422 Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support  
26  
27 423 for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar,  
28  
29 424 Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research  
30  
31 425 was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules  
32  
33 426 Thorn Charitable Trust.  
34

35  
36 427 **Conflict of interest**  
37

38  
39 428 None of the authors have conflict of interest/financial disclosures.  
40

41  
42 429 **Role of funding source**  
43

44  
45 430 Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant  
46  
47 431 and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research  
48  
49 432 Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors  
50  
51 433 (AKT). The funders had no further role in the study design, the collection, analysis and interpretation  
52  
53 434 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  |
|------------------------------|---------|---|
| <b>Title and abstract</b>    | 1       | (a) Indicate the study's design with a commonly used term in the title or the abstract<br><b>page 1</b><br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found<br><b>page 1</b>   |
| <b>Introduction</b>          |         |   |
| Background/rationale         | 2       | Explain the scientific background and rationale for the investigation being reported<br><b>page 3</b>   |
| Objectives                   | 3       | State specific objectives, including any prespecified hypotheses<br><b>page 3</b>   |
| <b>Methods</b>               |         |   |
| Study design                 | 4       | Present key elements of study design early in the paper<br><b>page 4 &amp; 7</b>  |
| Setting                      | 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection<br><b>page 4 &amp; 7</b>  |
| Participants                 | 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br><b>page 4 &amp; 7</b><br>(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<br><b>pages 7, 8, 9 &amp; 10</b>   |
| Data sources/<br>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<br><b>pages 7, 8, 9 &amp; 10</b>   |
| Bias                         | 9       | Describe any efforts to address potential sources of bias<br><b>page 3, pages 8 &amp; 10 (addressing confounders), and pages 19</b>   |
| Study size                   | 10      | Explain how the study size was arrived at<br><b>pages 4, 6 &amp; 7</b>  |
| Quantitative variables       | 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why<br><b>pages 7, 8, 9 &amp; 10</b>   |
| Statistical methods          | 12      | (a) Describe all statistical methods, including those used to control for confounding<br><b>pages 8, 10, 11 &amp; 12</b><br>(b) Describe any methods used to examine subgroups and interactions<br><b>pages 10, 16 &amp; 17</b><br>(c) Explain how missing data were addressed<br><b>page 10</b><br>(d) If applicable, explain how loss to follow-up was addressed<br>(e) Describe any sensitivity analyses<br><b>pages 10, 12, 13 &amp; 15</b> |
| <b>Results</b>               |         |   |

|    |  |     |  |
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| 1  | 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            |
| 2  |  |     | <b>pages 4, 6 &amp; 7</b>  |
| 3  |  |     | (b) Give reasons for non-participation at each stage   |
| 4  |  |     | <b>pages 4, 6 &amp; 7</b>  |
| 5  |  |     | (c) Consider use of a flow diagram   |
| 6  |  |     | <b>page 6</b>  |
| 7  |  |     | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders   |
| 8  |  |     | <b>page 11, 12 &amp; 16</b>  |
| 9  |  |     | (b) Indicate number of participants with missing data for each variable of interest  |
| 10 | <b>pages 4, 6 &amp; 7</b>  |     |  |
| 11 | (c) Summarise follow-up time (eg, average and total amount)  |     |  |
| 12 | <b>page 4</b>  |     |  |
| 13 | Descriptive data   | 14* | Report numbers of outcome events or summary measures over time   |
| 14 |  |     | <b>page 11, 12 &amp; 16</b>  |
| 15 |  |     | (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 |
| 16 | <b>pages 8, 10, 12, 13, 15 &amp; 16</b>  |     |  |
| 17 | (b) Report category boundaries when continuous variables were categorized  |     |  |
| 18 | <b>page 13, 14 &amp; 15</b>  |     |  |
| 19 | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |     |  |
| 20 | Outcome data   | 15* | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses   |
| 21 |  |     | <b>pages 11-17</b>   |
| 22 |  |     | <b>Discussion</b>  |
| 23 | Main results   | 16  | Summarise key results with reference to study objectives   |
| 24 |  |     | <b>page 18</b>   |
| 25 | 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   |
| 26 |  |     | <b>pages 19 &amp; 20</b>   |
| 27 |  |     | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence                                   |
| 28 | <b>page 18</b>   |     |  |
| 29 | Interpretation   | 20  | Discuss the generalisability (external validity) of the study results  |
| 30 |  |     | <b>pages 18 &amp; 19</b>   |
| 31 | Generalisability   | 21  | 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  |
| 32 |  |     | <b>page 21</b>   |
| 33 | <b>Other information</b>   |     |  |
| 34 | 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  |
| 35 |  |     | <b>page 21</b>   |

\*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>.



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

|                                 |   |
|---------------------------------|---|
| Journal:                        | <i>BMJ Open</i>   |
| 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<br>Harold, Gordon; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Thapar, Anita; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences<br>Thapar, Ajay; Cardiff University, Institute of Psychological Medicine and Clinical Neurosciences |
| <b>Primary Subject Heading</b>: | Epidemiology  |
| Secondary Subject Heading:      | Mental health, Cardiovascular medicine, Paediatrics   |
| Keywords:                       | MENTAL HEALTH, EPIDEMIOLOGY, Hypertension < CARDIOLOGY  |
|                                 |   |

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Manuscripts

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3 1 **Title:** Depression and blood pressure in high-risk children and adolescents: an investigation using two  
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5 2 longitudinal cohorts.

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8 3 **Abstract**

9 4 *Objective* – To examine the relationship between blood pressure and depressive disorder in children  
10  
11 5 and adolescents at high-risk for depression.

12 6 *Design* – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study  
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14 7 of offspring of parents with recurrent depression and an on-going birth cohort for replication.

15 8 *Setting* – Community based studies.

16 9 *Participants* – High-risk sample includes 281 families where children were aged 9-17 years at baseline  
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18 10 and 10-19 years at the final data point. Replication cohort includes 4830 families where children were  
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20 11 aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring  
21  
22 12 with mothers that had reported recurrent depression.

23 13 *Main outcome measures* –New onset DSM-IV defined depressive disorder in the offspring using  
24  
25 14 established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment  
26  
27 15 (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the  
28  
29 16 replication sample.

30 17 *Results* – Blood pressure was standardised for age and gender to create standard deviation scores and  
31  
32 18 child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood  
33  
34 19 pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI  
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36 20 .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict  
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38 21 systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and  
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40 22 future depression was also found in the replication cohort in the second subset of high-risk children  
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42 23 whose mothers had experienced recurrent depression in the past.

43 24 *Conclusion* – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of  
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45 25 parents with depression. Further studies are needed to investigate how this association arises.

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51 26 **Key words**

52  
53 27 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.

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3 **29 Introduction**

4 30 The two leading causes of death and disability in the developed world are depression and  
5 31 cardiovascular disease. The association between depression and cardiovascular disease is well  
6 32 established in adults,[1] although the mechanisms by which it arises are still not clear. It has been  
7 33 suggested that these links reflect early associations between depression and cardiovascular risk factors.  
8 34 High blood pressure is an important cardiovascular risk factor and it has also been linked to depression  
9 35 in adults in some studies.[2] Other studies, however, have found the converse. They suggest that  
10 36 depression is associated with low blood pressure and that it is only depression treated with certain  
11 37 antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by  
12 38 which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it  
13 39 is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the  
14 40 findings are inconsistent, with some studies finding depression as a predictor of either high blood  
15 41 pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure  
16 42 predicting depression.[6]

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31 44 Although both depression and the early indicators of cardiovascular disease have been found to have  
32 45 onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger  
33 46 populations. In this study, the main aim was to investigate the relationship between blood pressure and  
34 47 subsequent first onset episode of depression in a prospective cohort of children and adolescents at high  
35 48 risk of depression. The secondary aim was to replicate findings in an independent cohort.  
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3 50 **Method**  
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5 51 Data were derived from a prospective longitudinal study of offspring of parents with recurrent  
6 52 depression—‘The Early Prediction of Adolescent Depression (EPAD) study’. At baseline, the sample  
7 53 included 337 families (315 mothers and 22 fathers) that were recruited from general practices across  
8 54 South Wales, by writing to eligible families, and from a database of adults with previously identified  
9 55 unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test  
10 56 the main hypotheses of the original project whilst allowing detailed assessments at each time point.  
11 57 Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive  
12 58 disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview  
13 59 that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment  
14 60 in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an  
15 61 experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected  
16 62 for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to  
17 63 and currently living with the affected parent. Additional exclusion criteria included children with  
18 64 moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or  
19 65 psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the  
20 66 study because the depressed parent had been diagnosed as suffering from bipolar disorder since the  
21 67 wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed  
22 68 using age-appropriate standard research diagnostic interviews independently by two trained research  
23 69 psychologists on three occasions over the course of the study which began in April 2007 and finished  
24 70 in April 2011. The average time between the baseline and second assessment was 16.2 months and  
25 71 between the second and third assessment was 12.5 months. Further details on the sample characteristics  
26 72 and methodology have been described previously.[9]

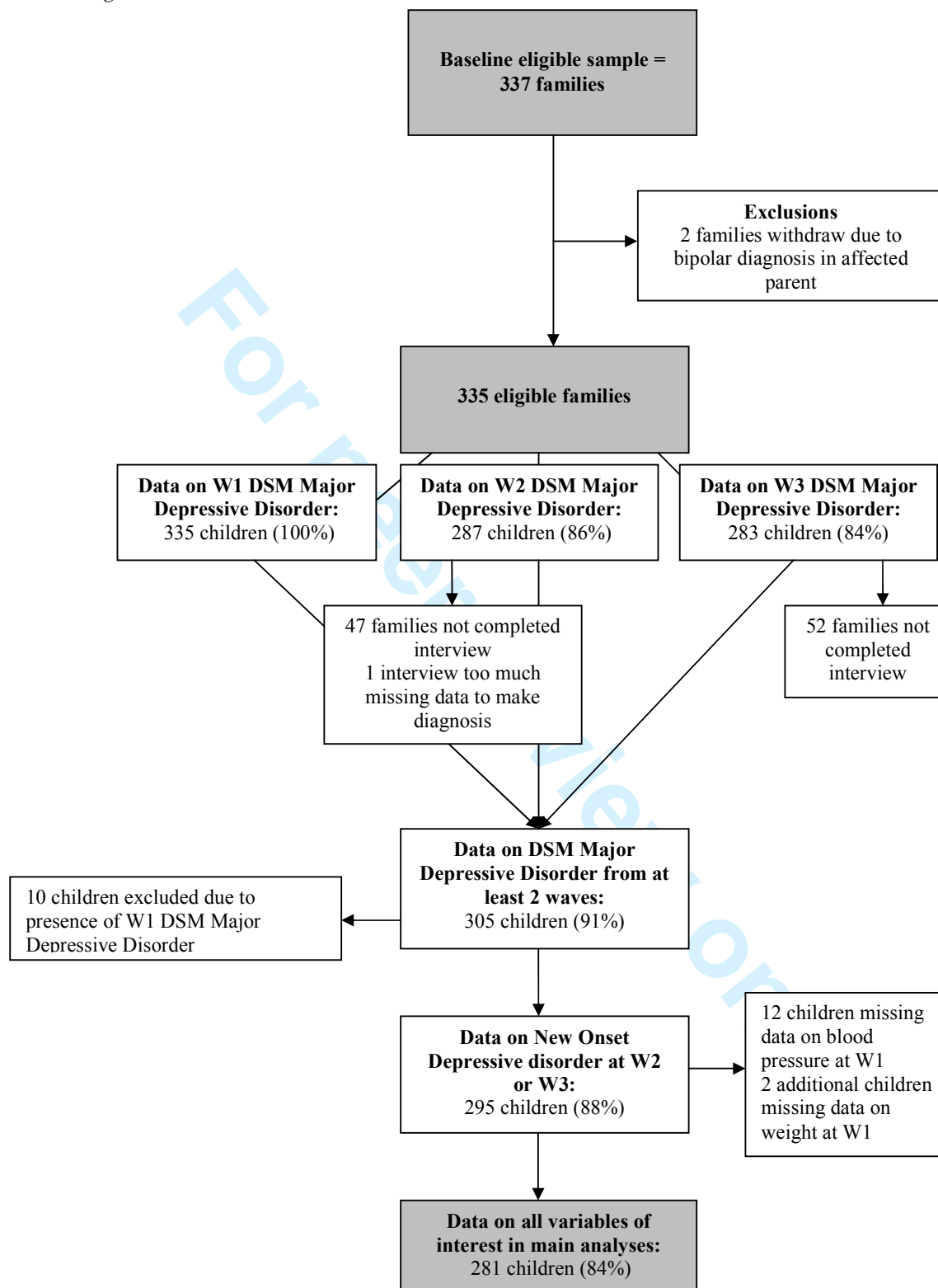
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46 73 For the main analyses, 30 families were excluded because they had not completed at least two waves of  
47 74 data. A further 10 children were excluded from main analyses because they already met criteria for  
48 75 DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede  
49 76 onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not  
50 77 been completed at baseline either because there had been a fault in the equipment or the child had  
51 78 refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data  
52 79 were collected from parents and children via semi-structured research diagnostic interviews and blood  
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80 pressure and weight were assessed by the interviewer. Additional data on physical health problems,  
81 maternal education and social class were collected from parents and children from self-completed  
82 questionnaires that were mailed to the families two weeks before their interview. Ethical approval for  
83 the study was obtained from the Multi-centre Research Ethics Committee for Wales.  
84

For peer review only

85 Figure 1



Flow chart of retention at each assessment in the EPAD sample

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3 86 Data were also utilised from a birth cohort study ‘The Avon Longitudinal Study of Parents and  
4 87 Children (ALSPAC)’ to allow replication of findings from the first high-risk sample. The cohort was  
5 88 set up to examine genetic and environmental determinants of health and development.[10] The initial  
6 89 cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date  
7 90 of delivery between 1<sup>st</sup> April 1991 and 31<sup>st</sup> December 1992 ([www.alspac.bris.ac.uk](http://www.alspac.bris.ac.uk)). All pregnant  
8 91 women resident in three health districts in the old administrative county of Avon who had an estimated  
9 92 delivery between the above dates were eligible to participate. In addition, pregnant women that had  
10 93 migrated into the catchment area before the point of delivery were eligible. Recruitment was carried  
11 94 out by attempting to make contact with eligible women through ALSPAC staff visiting community  
12 95 locations and through using antenatal and maternity health services and media information to  
13 96 encourage contact and promote the study.[10] The parents completed regular postal questionnaires  
14 97 concerning their child’s health and development since birth. The children have completed  
15 98 questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole  
16 99 sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and  
17 100 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range:  
18 101 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children  
19 102 whose mothers had experienced recurrent depression (at least two episodes); 612 children were  
20 103 included in these analyses (347 females and 265 males). Ethical approval for the study was obtained  
21 104 from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

## 105 **Measures**

106 EPAD study:

107 *Assessment of depression in the offspring of parents with recurrent depression*

108 The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic  
109 interview that has high reliability and that is used to assess children's psychiatric symptoms [11].

110 Parents are asked about their children's psychopathology and children are independently interviewed  
111 using the interview schedules (parent and child versions). The presence of any given symptom has to  
112 be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined  
113 symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews  
114 were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

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3 115 selected recordings at each time point (10 parent report and 10 child report) and through weekly  
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5 116 supervision by an academic clinician with extensive experience in using the interview. Average  
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7 117 agreement between raters for DSM-IV psychiatric disorder was excellent ( $\kappa=0.92$ ), as was average  
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9 118 agreement for depression symptoms ( $\kappa=0.93$ ). CAPA was used at each assessment and assesses the  
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11 119 presence of a major depressive disorder in the child over the preceding three months. The parent and  
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13 120 child versions were completed independently, with interviews conducted in separate rooms where  
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15 121 possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using  
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17 122 DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either  
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19 123 parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms  
20  
21 124 was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed  
22  
23 125 weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of  
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25 126 DSM-IV major depressive disorder symptoms was also computed from the CAPA.

26  
27 127 *New onset major depressive disorder* - The presence of a new onset DSM-IV diagnosis of major  
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29 128 depressive disorder at either the second or third assessment was defined by excluding children that had  
30  
31 129 a baseline diagnosis of DSM-IV major depressive disorder.

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33 130 *Blood pressure* –An Omron 705IT sphygmomanometer was used to measure blood pressure at each  
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35 131 assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard  
36  
37 132 cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was  
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39 133 used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were  
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41 134 measured using standardised guidelines set out by the American Heart association.[12] At least two  
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43 135 readings were taken at least one minute apart using the right arm. When the difference between two  
44  
45 136 readings was 5mmHg or less an average was taken.

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47 137 *Weight and other potential confounders* – Weight was considered to be a confounder of the relationship  
48  
49 138 between blood pressure and depression due to its potential association with both.[13, 14] Interviewers  
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51 139 measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also  
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53 140 examined whether the results were affected by the presence of physical health problems (parent  
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55 141 reported), any medication use (child or parent reported) and using body mass index (BMI) instead of  
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57 142 weight.

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3 143 *Demographics* – The mother and father questionnaires completed at baseline were used to assess  
4 144 maternal education and highest parental social class. Maternal education was categorised according to  
5 145 whether the mother had completed higher education (A-Levels, degree or postgraduate qualification).  
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7 146 Parental social class was categorised according to whether either parent reported having a non-manual  
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9 147 occupation.

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13 148 ALSPAC:

14 149 *Maternal history of recurrent depression* – Mothers completed regular questionnaires from pregnancy  
15 150 to when the child was aged 12 years including the questions ‘Have you had depression in the last year/  
16 151 last two years/ since your child was born/ever’. The mother was also asked ‘Have you ever had severe  
17 152 depression’ on three occasions over this time period. Research diagnostic interview generated  
18 153 psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data  
19 154 set thus had to be defined where mother had reported having depression on at least two separate  
20 155 occasions, and if at least one of these occasions was reported as being severe. These criteria were used  
21 156 to create a subsample that was as similar as possible to the primary high-risk sample.

22  
23  
24 157 *Child depressive disorder* – Parent reports on their child's symptoms were obtained using a structured  
25 158 diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA,  
26 159 has been used widely for large scale population studies. The parent-rated DAWBA was completed  
27 160 when the target age of the children was 13 years. Children were directly interviewed using the  
28 161 DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the  
29 162 preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-  
30 163 defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a  
31 164 DSM-IV diagnosis of depression and generates diagnoses (see [www.DAWBA.com](http://www.DAWBA.com) for more  
32 165 information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part  
33 166 of the ALSPAC data collection process. [16]

34  
35  
36 167 *Blood pressure* – Systolic and diastolic blood pressure were measured at the clinic assessments when  
37 168 the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each  
38 169 assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

1  
2  
3 170 *Weight and other potential confounders* – Interviewers measured the weight and height of the children  
4  
5 171 in light clothing and without shoes at the clinic assessments when the target age of the children was 12  
6  
7 172 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height  
8  
9 173 was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then  
10  
11 174 calculated (kg/m<sup>2</sup>). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal  
12  
13 175 medical records.

14  
15 176 *Demographics* – The mother and father questionnaires completed during pregnancy were used to assess  
16  
17 177 maternal education and highest parental social class. Maternal education was categorised according to  
18  
19 178 whether the mother had completed higher education (A-Levels or degree). Parental social class was  
20  
21 179 categorised according to whether either parent reported having a non-manual occupation.

### 22 23 180 **Statistical methods**

24  
25 181 Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the  
26  
27 182 high-risk sample and then in the replication cohort using the subsample of children with mothers that  
28  
29 183 have experienced recurrent depression in the past. Next, regression analyses were performed to  
30  
31 184 examine the association between blood pressure and depression in the high-risk sample and then in the  
32  
33 185 subsample from the replication cohort. Logistic regression analyses were used when the dependent  
34  
35 186 variable was dichotomous and ordinary least squares linear regression analysis was used when the  
36  
37 187 dependent variable was continuous. Continuous outcome data that were not normally distributed were  
38  
39 188 transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship  
40  
41 189 between systolic blood pressure and future depressive disorder was examined by investigating the  
42  
43 190 percentage of children with future depressive disorder by blood pressure quintiles, again in both  
44  
45 191 samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for  
46  
47 192 blood pressure in both samples that showed adequate sensitivity and specificity for detecting future  
48  
49 193 depressive disorder. Lastly, the association between systolic blood pressure and future depressive  
50  
51 194 disorder was investigated in the general population by using the entire ALSPAC sample and the  
52  
53 195 presence of a multiplicative interaction between maternal depression and systolic blood pressure on  
54  
55 196 future depressive disorder was examined. Listwise deletion was used to deal with missing data in all  
56  
57 197 analyses and data were analysed using SPSS (v20).

198 **Results**199 **Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent**  
200 **depression), the ALSPAC replication subsample of children with mothers that have experienced**  
201 **recurrent depression and the whole ALSPAC sample**

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

204 *Table 1*

|   | <b>EPAD</b><br>(n=281) | <b>ALSPAC</b><br>(subsample of offspring<br>of recurrently<br>depressed mothers;<br>n=612) | <b>ALSPAC</b><br>(whole sample;<br>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                                       |

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

207 **Descriptives from EPAD high-risk sample**

208 Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and  
209 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant  
210 differences between males and females for systolic or diastolic blood pressure at baseline. Systolic  
211 blood pressure at baseline was significantly correlated with age ( $r=.23$ ,  $p<.001$ ), but diastolic blood  
212 pressure was not ( $r=.02$ ,  $p=.728$ ). Systolic blood pressure was thus standardised for age and gender to  
213 create standard deviation scores and all analyses for systolic blood pressure were run with the  
214 standardised variable.[17] Mean blood pressures for each age group in this sample were generally  
215 higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated  
216 with weight ( $r=.25$ ,  $p<.001$ ), but diastolic blood pressure was not ( $r=.07$ ,  $p=.236$ ). Given this finding  
217 all analyses with systolic blood pressure are reported controlling for weight.



1  
2  
3 218 Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder  
4  
5 219 (8.54%).

6  
7  
8 220 **Descriptives from ALSPAC dataset – using the subsample of children with mothers that have**  
9  
10 221 **experienced recurrent depression in the past**

11 222 Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61  
12  
13 223 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences  
14  
15 224 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
16  
17 225 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
18  
19 226 systolic blood pressure were run with the standardised variable. The association between blood  
20  
21 227 pressure and weight at age 12 was significant for both systolic ( $r=.45$ ,  $p<.001$ ) and diastolic blood  
22  
23 228 pressure ( $r=.18$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

24  
25 229 Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at  
26  
27 230 age 15 (2.94%).

28  
29  
30 231 **Initial analyses in EPAD high-risk sample**

31 232 Logistic regression analyses were performed to investigate the association between blood pressure and  
32  
33 233 new onset depressive disorder in the EPAD sample of children. It was found that as systolic blood  
34  
35 234 pressure increased, risk for new onset depressive disorder decreased, when adjusting for child's weight  
36  
37 235 at baseline (OR = .65, 95% CI .44 to .96;  $p=.029$ ), i.e. lower systolic blood pressure at baseline  
38  
39 236 significantly predicted new onset depressive disorder. Diastolic blood pressure at baseline did not  
40  
41 237 significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01;  $p=.120$ ).

42  
43  
44 238 Results remained the same when the outcome was expanded to include the new onset of more broadly  
45  
46 239 defined mood-related diagnoses (primary diagnosis: major depressive disorder  $n=22$ , dysthymia  $n=1$ ,  
47  
48 240 cyclothymia  $n=1$ , bipolar disorder  $n=3$ , adjustment disorder with depressed mood  $n=4$  and depressive  
49  
50 241 disorder not otherwise specified  $n=5$ ). Results also remained similar when separately adjusting for  
51  
52 242 medication use and physical health problems in the child and when adjusting for BMI instead of  
53  
54 243 weight. The association was not significantly moderated by gender ( $p=.769$ ).

55  
56 244 Given few adolescents developed new onset depressive disorder, the analysis was repeated using total  
57  
58 245 depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood

1  
2  
3 246 pressure at baseline as a predictor and depression symptoms at the wave 3 assessment as the outcome,  
4  
5 247 and again controlling for weight, showed significant association ( $\beta = -.13$ ;  $p=.040$ ).

6  
7  
8 248 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analysis  
9  
10 249 was performed with a diagnosis of depressive disorder at baseline as a predictor and systolic blood  
11  
12 250 pressure at the wave 3 assessment as the outcome, again controlling for child's weight at baseline. This  
13  
14 251 was non-significant ( $\beta = -.05$ ;  $p = .412$ ). Given the low number of individuals with depressive disorder  
15  
16 252 at baseline the analysis was repeated using total depression symptoms at baseline as a predictor. Again  
17  
18 253 the results were non-significant ( $\beta = -.07$ ;  $p = .286$ ).

19  
20 254 **Replication in ALSPAC dataset – using the subsample of children with mothers that have**  
21  
22 255 **experienced recurrent depression in the past**

23  
24 256 Logistic regression analyses were undertaken in the replication sample. Again, it was found that as  
25  
26 257 systolic blood pressure increased, risk for future depressive disorder decreased, when adjusting for  
27  
28 258 child's weight at baseline (OR = .48, 95% CI .27 to .85;  $p=.012$ ), i.e. lower systolic blood pressure at  
29  
30 259 age 12 significantly predicted depressive disorder at age 15. Diastolic blood pressure at age 12 years  
31  
32 260 did not significantly predict depressive disorder at age 15 (OR = .98, 95% CI .93 to 1.05;  $p=.597$ ).  
33  
34 261 Results remained similar when adjusting for BMI instead of weight and when additionally adjusting for  
35  
36 262 maternal systolic blood pressure in pregnancy. The association was not significantly moderated by  
37  
38 263 gender ( $p=.102$ ).

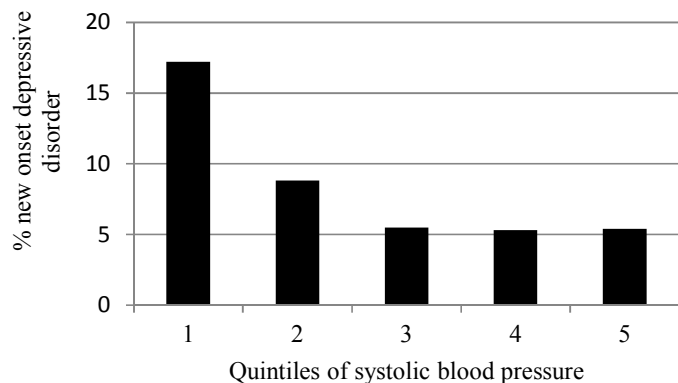
39  
40 264 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses  
41  
42 265 was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood  
43  
44 266 pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant ( $\beta = -$   
45  
46 267 .04;  $p = .378$ ).

47  
48 268 **Relationship between blood pressure and depressive disorder in high-risk EPAD sample**

49  
50 269 To further investigate the relationship between systolic blood pressure and depressive disorder in the  
51  
52 270 EPAD sample, blood pressure was split into quintiles to examine the percentage of children with new  
53  
54 271 onset depressive disorder by blood pressure categories and the linearity of the relationship. As can be  
55  
56 272 seen in Figure 2, there is a lower risk of depressive disorder with higher levels of blood pressure, with  
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58  
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60

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

275 *Figure 2*



276

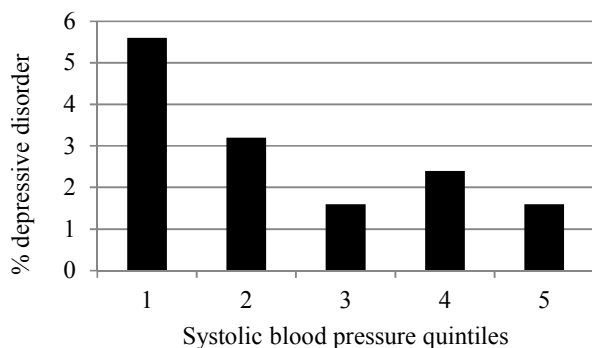
277 *Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of*  
 278 *systolic blood pressure at baseline in the EPAD sample*

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

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

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

287 *Figure 3*



288

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

291 Analyses so far have highlighted a significant association between lower systolic blood pressure and  
 292 future depression in two different samples of offspring of parents with recurrent depression. Next, ROC  
 293 analysis was performed to establish a cut off for blood pressure in both samples that maximised both  
 294 sensitivity and specificity for detection of future depressive disorder. A cut off point of below 0.025  
 295 standard deviations above the mean using standardised systolic blood pressure [17] showed a  
 296 sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately  
 297 equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12  
 298 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised  
 299 systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC  
 300 replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a  
 301 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the  
 302 association between low blood pressure and future depressive disorder using each of the cut offs  
 303 identified in each sample (Table 2).

304 *Table 2*

|               | OR (95% CI) <sup>1</sup>                   |   |
|---------------|--|---|
|               | Optimal cut off in EPAD<br>sample (< .025) | Optimal cut off in<br>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)                            |

306 <sup>1</sup>Adjusted for child weight at W1

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

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

1  
2  
3 312 Lastly, supplementary analyses were performed to examine the association between blood pressure and  
4  
5 313 future depression in the general population using the entire ALSPAC sample.  
6  
7

8 314 **Supplementary analyses using entire ALSPAC sample:**

9  
10 315 **1) Testing the relationship between depressive disorder and blood pressure in the general**  
11  
12 316 **population (not limiting analysis to those adolescents with a parental history of recurrent**  
13  
14 317 **depression)**

15  
16 318 **Descriptives**

17  
18 319 Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53  
19  
20 320 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences  
21  
22 321 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
23  
24 322 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
25  
26 323 systolic blood pressure were run with the standardised variable. The association between blood  
27  
28 324 pressure and weight at age 12 was significant for both systolic ( $r=.44$ ,  $p<.001$ ) and diastolic blood  
29  
30 325 pressure ( $r=.19$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

31  
32 326 Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last  
33  
34 327 month at age 15 (1.55%).

35  
36 328 **Preliminary analyses**

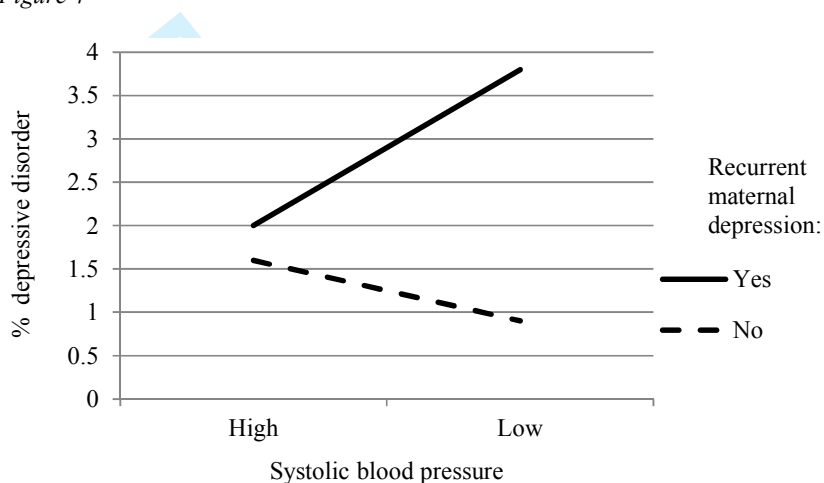
37  
38 329 Logistic regression analyses were performed to investigate the association between blood pressure and  
39  
40 330 depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder  
41  
42 331 at age 15 (OR = .98, 95% CI .76 to 1.27;  $p=.875$ ). Diastolic blood pressure at age 12 did not  
43  
44 332 significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04;  $p=.604$ ).

45  
46 333 **2) Examining whether a history of recurrent maternal depression moderated the**  
47  
48 334 **relationship between systolic blood pressure and depression**

49  
50 335 Logistic regression analyses were then performed to test if recurrent maternal depression moderated the  
51  
52 336 relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic  
53  
54 337 blood pressure and maternal recurrent depression were centred to convert them to their deviation form  
55  
56 338 to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95%  
57  
58 339 CI .27 to .89;  $p=.019$ ).

1  
2  
3 340 Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that  
4 341 the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal  
5 342 depression was present, children with low blood pressure showed the highest percentage of depressive  
6 343 disorder. However, when recurrent maternal depression was not present, children with high blood  
7 344 pressure showed the highest percentage of depressive disorder.

12  
13 345 *Figure 4*



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29 346  
30 347 *Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low'*  
31  
32 348 *systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample*

1  
2  
3 349 **Discussion**

4 350 In this study we found that lower systolic blood pressure significantly predicted future new onset  
5  
6 351 depressive disorder amongst a sample of children and adolescents at high risk of developing depression  
7  
8 352 because of a parental history of recurrent depression. This finding was replicated in a large community  
9  
10 353 based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression  
11  
12 354 (replication sample). When investigating this relationship in more detail, it seemed that those with the  
13  
14 355 lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut  
15  
16 356 off value for systolic blood pressure in 12 year old children was identified as being within the range of  
17  
18 357 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort  
19  
20 358 (ALSPAC), the association between blood pressure and major depressive disorder was no longer  
21  
22 359 significant. There was no evidence for an association in the opposite direction (depression predicting  
23  
24 360 future blood pressure levels) either in the study sample or in the replication cohort nor was there an  
25  
26 361 association between diastolic blood pressure and future depression in either dataset.

27  
28 362 In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive  
29  
30 363 disorder was slightly higher than population norms, it was those whose blood pressure was lower who  
31  
32 364 were at most risk of developing depressive disorder. This was not true in adolescents from the general  
33  
34 365 population. In adolescents from the general population who did not have a parent with recurrent  
35  
36 366 depressive disorder, higher blood pressure showed some association with a higher risk of future  
37  
38 367 depressive disorder. There have been no previously published longitudinal studies examining the  
39  
40 368 relationship between blood pressure and depression in children from the general population or children  
41  
42 369 at high-risk of depression. In adults a “vascular depression” hypothesis has been proposed to explain  
43  
44 370 links between elevated blood pressure and depression [19] but some adult studies have found cross-  
45  
46 371 sectional links between low blood pressure and depression.[20, 21] In addition, a study on elderly  
47  
48 372 patients reported a fall in systolic blood pressure predicted the onset of depression.[6] The aim in our  
49  
50 373 study was however to look at links between blood pressure and depression prior to the usual age of  
51  
52 374 onset of hypertensive disease to examine developmental changes. Given the limited scientific literature  
53  
54 375 on this topic, the mechanisms by which low blood pressure might precede depression for adolescent  
55  
56 376 offspring of individuals with recurrent depressive disorder are unclear and we can at present only  
57  
58 377 speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or  
59  
60 378 environmental) that contribute to both lower blood pressure and depression that are especially enriched

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2  
3 379 in those offspring most at risk of developing depressive disorder in the near future. Another possibility  
4 380 is that low blood pressure, in those who are familiarly/genetically vulnerable to depression, represents  
5  
6 381 an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major  
7  
8 382 depressive disorder. There is strikingly limited research on biological links between early mental health  
9  
10 383 problems and physical health as well as on autonomic system function in young people who are  
11  
12 384 familiarly vulnerable to depression [22]. Our findings highlight the need for further research on links  
13  
14 385 between mental and physical health in young people.

### 16 17 386 **Strengths and Limitations**

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19  
20 387 This is the first study we are aware of to report on the longitudinal relationship between blood pressure  
21  
22 388 and depressive disorder in adolescents, an important period for the onset of depression. In the main  
23  
24 389 sample, children and adolescents were followed up at three points over a four year period with a high  
25  
26 390 retention rate of over 80%. A similar pattern of results was found in a large community based cohort  
27  
28 391 study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples,  
29  
30 392 diagnoses were systematically ascertained using interview and blood pressure readings were measured  
31  
32 393 according to standardised protocol. In addition, potential confounders of the relationship were taken  
33  
34 394 account of. There were also possible limitations of the study. Blood pressures were measured using an  
35  
36 395 electronic device which uses an oscillometric technique rather than the auscultatory technique that most  
37  
38 396 population norms are based on and it has been noted that these readings are not equivalent. However  
39  
40 397 there is a lack of consensus as to whether using different methods leads to any systematic bias and  
41  
42 398 inaccuracies seem more related to not using a standardised technique rather than the instrument.[23] In  
43  
44 399 addition, the cut off values identified in the high risk and replication samples differed slightly. This  
45  
46 400 may have been because of differences in measurement techniques in the two studies. These results need  
47  
48 401 to be replicated in other samples in order to establish more precise cut off for low systolic blood  
49  
50 402 pressure. There was also relatively a high false positive rate for the cut offs identified in both the high  
51  
52 403 risk and the replication sample (34% and 39% respectively). However the aim of this analysis was not  
53  
54 404 to develop a screening tool for depression but to use ROC curve analysis as a method to maximise both  
55  
56 405 sensitivity and specificity in determining the optimal cut off value for low blood pressure. Moreover  
57  
58 406 some of the individuals labelled as “false positives” will have sub-threshold depression which has been  
59  
60 407 found to be associated with impairment, and to predict escalation to future disorder;[24, 25]. Despite



1  
2  
3 408 being a high-risk sample, the number of children with depressive disorder was small and many of the  
4 409 sample had not been though the age of maximum risk for developing a depressive disorder so this  
5  
6 410 could lead to an underestimate of the effects of risk factors. In addition, the number of children with  
7  
8 411 depressive disorder was also low in the replication sample, partly because only a self-report measure of  
9  
10 412 depressive disorder was available at age 15, and partly because of selective attrition over time.  
11  
12 413 Previous studies have reported that although attrition has affected prevalence rates of depression in the  
13  
14 414 mother and internalising disorders in the children, the associations between risks and outcomes  
15  
16 415 remained intact, although conservative estimates of the likely true effects.[26, 27] Lastly, the  
17  
18 416 subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe  
19  
20 417 group as maternal self-report of depression was used as opposed to defining episodes of depression  
21  
22 418 using DSM-IV criteria as was done in the main dataset.  
23  
24 419 In summary, in our study of adolescents at high risk of depression we found that low blood pressure  
25  
26 420 was associated with major depressive disorder. This finding was replicated in an independent cohort.  
27  
28 421 Future research is needed using different populations to confirm this relationship as it is a novel finding  
29  
30 422 and to investigate the mechanisms by which the relationship between low blood pressure and  
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32 423 depressive disorder in children at risk for depression may arise.  
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3 424 **Acknowledgments**  
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5

6 425 Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable  
7 426 Trust and the National Institute for Social Care and Health Research Academic Health Science  
8  
9 427 Collaboration (AHSC) fellowship.  
10

11  
12 428 We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for  
13 429 their help with recruiting them and the whole EPAD team. We thank the other investigators involved in  
14  
15 430 the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael  
16  
17 431 Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the  
18  
19 432 families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the  
20  
21 433 whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical  
22  
23 434 workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research  
24  
25 435 Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support  
26  
27 436 for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar,  
28  
29 437 Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research  
30  
31 438 was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules  
32  
33 439 Thorn Charitable Trust.  
34

35  
36 440 **Conflict of interest**  
37

38  
39 441 None of the authors have conflict of interest/financial disclosures.  
40

41  
42 442 **Role of funding source**  
43

44  
45 443 Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant  
46  
47 444 and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research  
48  
49 445 Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors  
50  
51 446 (AKT). The funders had no further role in the study design, the collection, analysis and interpretation  
52  
53 447 of data, the writing of the report, or in the decision to submit the paper for publication.  
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3 1 **Title:** Depression and blood pressure in high-risk children and adolescents: an investigation using two  
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5 2 longitudinal cohorts.

6  
7  
8 3 **Abstract**

9 4 *Objective* – To examine the relationship between blood pressure and depressive disorder in children  
10  
11 5 and adolescents at high-risk for depression.

12 6 *Design* – Multi-sample longitudinal design including a prospective longitudinal 3-wave high-risk study  
13  
14 7 of offspring of parents with recurrent depression and an on-going birth cohort for replication.

15 8 *Setting* – Community based studies.

16 9 *Participants* – High-risk sample includes 281 families where children were aged 9-17 years at baseline  
17  
18 10 and 10-19 years at the final data point. Replication cohort includes 4830 families where children were  
19  
20 11 aged 11-14 years at baseline and 14-17 years at follow up and a high-risk subsample of 612 offspring  
21  
22 12 with mothers that had reported recurrent depression.

23 13 *Main outcome measures* –New onset DSM-IV defined depressive disorder in the offspring using  
24  
25 14 established research diagnostic assessments - the Child and Adolescent Psychiatric Assessment  
26  
27 15 (CAPA) in the high risk sample and the Development and Wellbeing Assessment (DAWBA) in the  
28  
29 16 replication sample.

30 17 *Results* – Blood pressure was standardised for age and gender to create standard deviation scores and  
31  
32 18 child's weight was statistically controlled in all analyses. In the high-risk sample, lower systolic blood  
33  
34 19 pressure at wave 1 significantly predicted new onset depressive disorder in children (OR=.65, 95% CI  
35  
36 20 .44 to .96; p=.029) but diastolic blood pressure did not. Depressive disorder at Wave 1 did not predict  
37  
38 21 systolic blood pressure at Wave 3. A significant association between lower systolic blood pressure and  
39  
40 22 future depression was also found in the replication cohort in the second subset of high-risk children  
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42 23 whose mothers had experienced recurrent depression in the past.

43 24 *Conclusion* – Lower systolic blood pressure predicts new onset depressive disorder in the offspring of  
44  
45 25 parents with depression. Further studies are needed to investigate how this association arises.

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51 26 **Key words**

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53 27 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.

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2  
3 29 **Introduction**

4 30 The two leading causes of death and disability in the developed world are depression and  
5  
6 31 cardiovascular disease. The association between depression and cardiovascular disease is well  
7  
8 32 established in adults,[1] although the mechanisms by which it arises are still not clear. It has been  
9  
10 33 suggested that these links reflect early associations between depression and cardiovascular risk factors.  
11  
12 34 High blood pressure is an important cardiovascular risk factor and it has also been linked to depression  
13  
14 35 in adults in some studies.[2] Other studies, however, have found the converse. They suggest that  
15  
16 36 depression is associated with low blood pressure and that it is only depression treated with certain  
17  
18 37 antidepressants which is associated with high blood pressure.[3] To guide the study of mechanisms by  
19  
20 38 which the links between cardiovascular risk factors, notably blood pressure and depression may arise, it  
21  
22 39 is important to first ascertain the direction of effects. In the few longitudinal studies in this area, the  
23  
24 40 findings are inconsistent, with some studies finding depression as a predictor of either high blood  
25  
26 41 pressure,[4] or low blood pressure,[5] whilst others have found the converse, with low blood pressure  
27  
28 42 predicting depression.[6]

29 43  
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31 44 Although both depression and the early indicators of cardiovascular disease have been found to have  
32  
33 45 onset in childhood and adolescence,[7, 8] very few studies have focused on these links in younger  
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35 46 populations. In this study, the main aim was to investigate the relationship between blood pressure and  
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37 47 subsequent first onset episode of depression in a prospective cohort of children and adolescents at high  
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39 48 risk of depression. The secondary aim was to replicate findings in an independent cohort.  
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3 50 **Method**  
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5 51 Data were derived from a prospective longitudinal study of offspring of parents with recurrent  
6 52 depression—‘The Early Prediction of Adolescent Depression (EPAD) study’. At baseline, the sample  
7 53 included 337 families (315 mothers and 22 fathers) that were recruited from general practices across  
8 54 South Wales, by writing to eligible families, and from a database of adults with previously identified  
9 55 unipolar depression. A sample size of 300 families was calculated to provide sufficient power to test  
10 56 the main hypotheses of the original project whilst allowing detailed assessments at each time point.  
11 57 Recurrent depression is defined as the presence of least two episodes of DSM-IV major depressive  
12 58 disorder. Diagnosis in the index parent was confirmed at baseline using a research diagnostic interview  
13 59 that is widely used to assess adult psychiatric disorder, the SCAN (Schedules for Clinical Assessment  
14 60 in Neuropsychiatry). This was undertaken by researchers who were trained and supervised by an  
15 61 experienced academic clinician. The youngest child within the age range of 9 to 17 years was selected  
16 62 for inclusion (197 girls and 140 boys, mean age = 12.4 years). All children were biologically related to  
17 63 and currently living with the affected parent. Additional exclusion criteria included children with  
18 64 moderate-severe intellectual disability (IQ<50) and parents with bipolar disorder, mania/hypomania or  
19 65 psychosis at time of interview. Two families were consequently excluded from waves 2 and 3 of the  
20 66 study because the depressed parent had been diagnosed as suffering from bipolar disorder since the  
21 67 wave 1 assessment. Symptoms of psychiatric disorder in parents and offspring were separately assessed  
22 68 using age-appropriate standard research diagnostic interviews independently by two trained research  
23 69 psychologists on three occasions over the course of the study which began in April 2007 and finished  
24 70 in April 2011. The average time between the baseline and second assessment was 16.2 months and  
25 71 between the second and third assessment was 12.5 months. Further details on the sample characteristics  
26 72 and methodology have been described previously.[9]

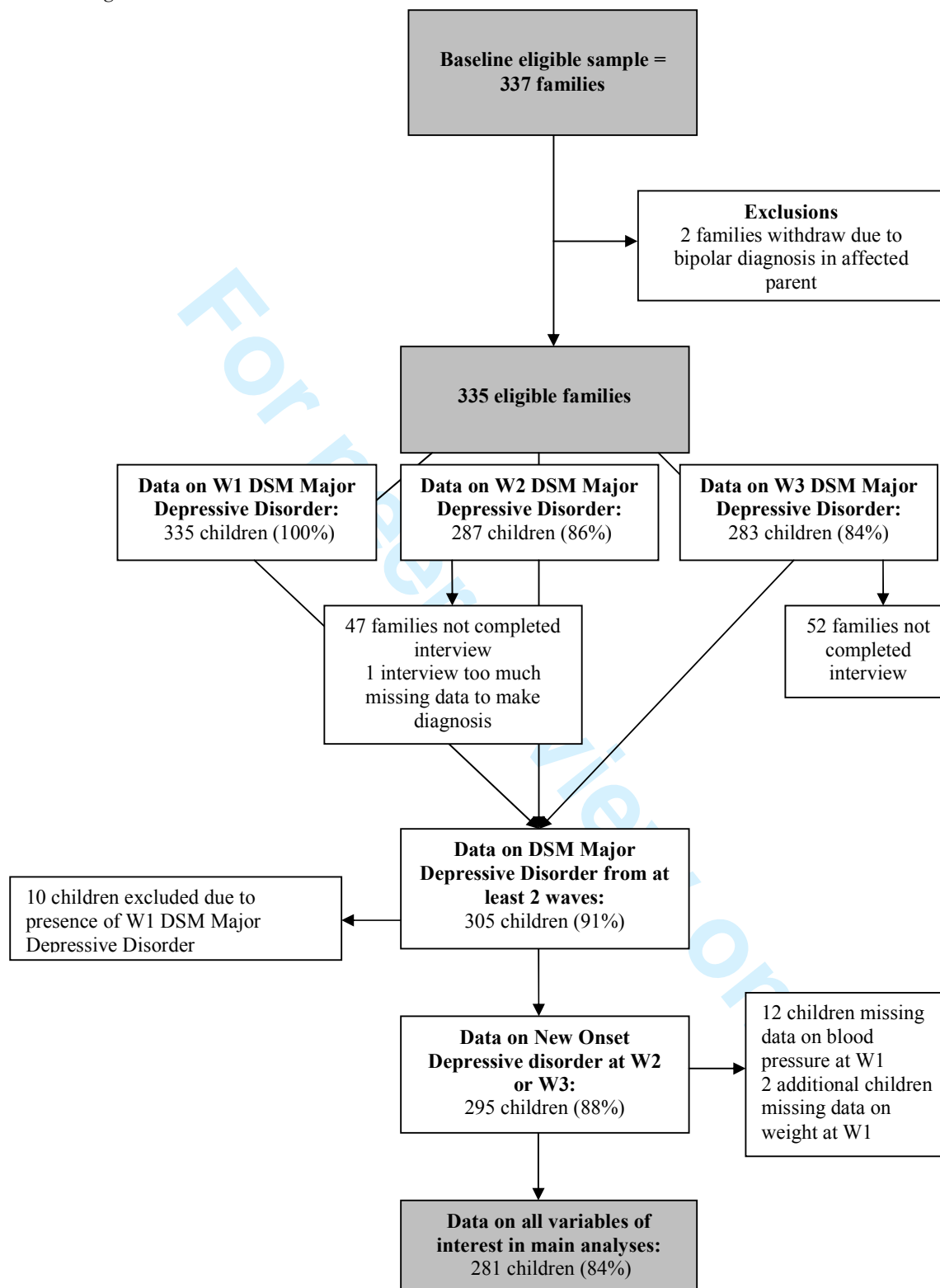
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46 73 For the main analyses, 30 families were excluded because they had not completed at least two waves of  
47 74 data. A further 10 children were excluded from main analyses because they already met criteria for  
48 75 DSM-IV major depressive disorder at baseline and thus the blood pressure assessment did not precede  
49 76 onset. Lastly 14 children were excluded because a measure of blood pressure and/or weight had not  
50 77 been completed at baseline either because there had been a fault in the equipment or the child had  
51 78 refused. This resulted in a final sample of 281 families (see Figure 1 for more details). Psychiatric data  
52 79 were collected from parents and children via semi-structured research diagnostic interviews and blood  
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80 pressure and weight were assessed by the interviewer. Additional data on physical health problems,  
81 maternal education and social class were collected from parents and children from self-completed  
82 questionnaires that were mailed to the families two weeks before their interview. Ethical approval for  
83 the study was obtained from the Multi-centre Research Ethics Committee for Wales.  
84

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85 Figure 1



Flow chart of retention at each assessment in the EPAD sample

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3 86 Data were also utilised from a birth cohort study ‘The Avon Longitudinal Study of Parents and  
4 87 Children (ALSPAC)’ to allow replication of findings from the first high-risk sample. The cohort was  
5 88 set up to examine genetic and environmental determinants of health and development.[10] The initial  
6 89 cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date  
7 90 of delivery between 1<sup>st</sup> April 1991 and 31<sup>st</sup> December 1992 ([www.alspac.bris.ac.uk](http://www.alspac.bris.ac.uk)). All pregnant  
8 91 women resident in three health districts in the old administrative county of Avon who had an estimated  
9 92 delivery between the above dates were eligible to participate. In addition, pregnant women that had  
10 93 migrated into the catchment area before the point of delivery were eligible. Recruitment was carried  
11 94 out by attempting to make contact with eligible women through ALSPAC staff visiting community  
12 95 locations and through using antenatal and maternity health services and media information to  
13 96 encourage contact and promote the study.[10] The parents completed regular postal questionnaires  
14 97 concerning their child’s health and development since birth. The children have completed  
15 98 questionnaires and attended annual assessment clinics since age 7 years. For analyses using the whole  
16 99 sample, 4830 children had data on both blood pressure and weight at age 12 years (2515 females and  
17 100 2315 males; age range: 11-14 years; mean age = 12.8 years) and depression at age 15 years (age range:  
18 101 14-17 years; mean age = 15.4 years). Main replication analyses focused on the sub-sample of children  
19 102 whose mothers had experienced recurrent depression (at least two episodes); 612 children were  
20 103 included in these analyses (347 females and 265 males). Ethical approval for the study was obtained  
21 104 from the ALSPAC Ethics and Law committee and the Local Research Ethics Committees.

## 105 **Measures**

106 EPAD study:

107 *Assessment of depression in the offspring of parents with recurrent depression*

108 The Child and Adolescent Psychiatric Assessment (CAPA) is a semi-structured research diagnostic  
109 interview that has high reliability and that is used to assess children's psychiatric symptoms [11].

110 Parents are asked about their children's psychopathology and children are independently interviewed  
111 using the interview schedules (parent and child versions). The presence of any given symptom has to  
112 be rigorously assessed and only endorsed by the interviewer when it achieves the CAPA defined  
113 symptom threshold. Interviewers were trained by the team that developed the CAPA and all interviews  
114 were recorded. Interview fidelity was checked through inter-rater reliability checks of 20 randomly

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3 115 selected recordings at each time point (10 parent report and 10 child report) and through weekly  
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5 116 supervision by an academic clinician with extensive experience in using the interview. Average  
6  
7 117 agreement between raters for DSM-IV psychiatric disorder was excellent ( $\kappa=0.92$ ), as was average  
8  
9 118 agreement for depression symptoms ( $\kappa=0.93$ ). CAPA was used at each assessment and assesses the  
10  
11 119 presence of a major depressive disorder in the child over the preceding three months. The parent and  
12  
13 120 child versions were completed independently, with interviews conducted in separate rooms where  
14  
15 121 possible and in 99 percent of cases, by separate researchers. Child diagnoses were generated using  
16  
17 122 DSM-IV criteria, based on CAPA symptoms. The presence of a diagnosis was endorsed if either  
18  
19 123 parent (reporting on the child) or child reported it as being present. Fidelity of the diagnostic algorithms  
20  
21 124 was further checked as all those meeting diagnostic criteria and subthreshold cases were reviewed  
22  
23 125 weekly by two senior clinical and academic child and adolescent psychiatrists. The total number of  
24  
25 126 DSM-IV major depressive disorder symptoms was also computed from the CAPA.

26  
27 127 *New onset major depressive disorder* - The presence of a new onset DSM-IV diagnosis of major  
28  
29 128 depressive disorder at either the second or third assessment was defined by excluding children that had  
30  
31 129 a baseline diagnosis of DSM-IV major depressive disorder.

32  
33 130 *Blood pressure* –An Omron 705IT sphygmomanometer was used to measure blood pressure at each  
34  
35 131 assessment whilst the child was in a seated position with their arm resting on a flat surface. A standard  
36  
37 132 cuff was used to measure blood pressure in children aged 11 years and over and a small adult cuff was  
38  
39 133 used for children under 11 years, unless overweight. Systolic and diastolic blood pressures were  
40  
41 134 measured using standardised guidelines set out by the American Heart association.[12] At least two  
42  
43 135 readings were taken at least one minute apart using the right arm. When the difference between two  
44  
45 136 readings was 5mmHg or less an average was taken.

46  
47 137 *Weight and other potential confounders* – Weight was considered to be a confounder of the relationship  
48  
49 138 between blood pressure and depression due to its potential association with both.[13, 14] Interviewers  
50  
51 139 measured the weight of the children without shoes to the nearest 0.1 kg using Seca scales. We also  
52  
53 140 examined whether the results were affected by the presence of physical health problems (parent  
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55 141 reported), any medication use (child or parent reported) and using body mass index (BMI) instead of  
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57 142 weight.  
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3 143 *Demographics* – The mother and father questionnaires completed at baseline were used to assess  
4 144 maternal education and highest parental social class. Maternal education was categorised according to  
5 145 whether the mother had completed higher education (A-Levels, degree or postgraduate qualification).  
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7 146 Parental social class was categorised according to whether either parent reported having a non-manual  
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9 147 occupation.

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13 148 ALSPAC:

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15 149 *Maternal history of recurrent depression* – Mothers completed regular questionnaires from pregnancy  
16  
17 150 to when the child was aged 12 years including the questions ‘Have you had depression in the last year/  
18  
19 151 last two years/ since your child was born/ever’. The mother was also asked ‘Have you ever had severe  
20  
21 152 depression’ on three occasions over this time period. Research diagnostic interview generated  
22  
23 153 psychiatric data on parents are not available in ALSPAC. Recurrent depression in the replication data  
24  
25 154 set thus had to be defined where mother had reported having depression on at least two separate  
26  
27 155 occasions, and if at least one of these occasions was reported as being severe. These criteria were used  
28  
29 156 to create a subsample that was as similar as possible to the primary high-risk sample.

30  
31 157 *Child depressive disorder* – Parent reports on their child's symptoms were obtained using a structured  
32  
33 158 diagnostic schedule (the Development and Wellbeing Assessment; DAWBA [15]) that, like the CAPA,  
34  
35 159 has been used widely for large scale population studies. The parent-rated DAWBA was completed  
36  
37 160 when the target age of the children was 13 years. Children were directly interviewed using the  
38  
39 161 DAWBA at age 15 years. The DAWBA assesses the presence of a depressive disorder over the  
40  
41 162 preceding month. DSM-IV diagnoses of depression were generated at each time point using a well-  
42  
43 163 defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a  
44  
45 164 DSM-IV diagnosis of depression and generates diagnoses (see [www.DAWBA.com](http://www.DAWBA.com) for more  
46  
47 165 information). A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part  
48  
49 166 of the ALSPAC data collection process. [16]

50  
51 167 *Blood pressure* – Systolic and diastolic blood pressure were measured at the clinic assessments when  
52  
53 168 the target ages of the children were 12 years and 15 years. Blood pressure was measured twice at each  
54  
55 169 assessment with a Dinamap 9301 Vital Signs Monitor and a mean of both readings was taken.

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3 170 *Weight and other potential confounders* – Interviewers measured the weight and height of the children  
4  
5 171 in light clothing and without shoes at the clinic assessments when the target age of the children was 12  
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7 172 years. Weight was measured to the nearest 0.1 kg using Tanita scales (Tanita; Illinois, USA) and height  
8  
9 173 was measured to the nearest 0.1 cm using a Harpenden stadiometer (Tarti; Turkey). BMI was then  
10  
11 174 calculated (kg/m<sup>2</sup>). Maternal systolic blood pressure at 8 weeks gestation was abstracted from antenatal  
12  
13 175 medical records.

14  
15 176 *Demographics* – The mother and father questionnaires completed during pregnancy were used to assess  
16  
17 177 maternal education and highest parental social class. Maternal education was categorised according to  
18  
19 178 whether the mother had completed higher education (A-Levels or degree). Parental social class was  
20  
21 179 categorised according to whether either parent reported having a non-manual occupation.

### 22 23 180 **Statistical methods**

24  
25 181 Each set of analyses were conducted in two steps. First, descriptive statistics were examined in the  
26  
27 182 high-risk sample and then in the replication cohort using the subsample of children with mothers that  
28  
29 183 have experienced recurrent depression in the past. Next, regression analyses were performed to  
30  
31 184 examine the association between blood pressure and depression in the high-risk sample and then in the  
32  
33 185 subsample from the replication cohort. Logistic regression analyses were used when the dependent  
34  
35 186 variable was dichotomous and ordinary least squares linear regression analysis was used when the  
36  
37 187 dependent variable was continuous. Continuous outcome data that were not normally distributed were  
38  
39 188 transformed prior to analysis using a natural log transformation. Next, the linearity of the relationship  
40  
41 189 between systolic blood pressure and future depressive disorder was examined by investigating the  
42  
43 190 percentage of children with future depressive disorder by blood pressure quintiles, again in both  
44  
45 191 samples. Next, receiver operating characteristic (ROC) analysis was performed to establish a cut off for  
46  
47 192 blood pressure in both samples that showed adequate sensitivity and specificity for detecting future  
48  
49 193 depressive disorder. Lastly, the association between systolic blood pressure and future depressive  
50  
51 194 disorder was investigated in the general population by using the entire ALSPAC sample and the  
52  
53 195 presence of a multiplicative interaction between maternal depression and systolic blood pressure on  
54  
55 196 future depressive disorder was examined. Listwise deletion was used to deal with missing data in all  
56  
57 197 analyses and data were analysed using SPSS (v20).

198 **Results**199 **Demographic comparability of the EPAD high-risk sample (offspring of parents with recurrent**  
200 **depression), the ALSPAC replication subsample of children with mothers that have experienced**  
201 **recurrent depression and the whole ALSPAC sample**

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

204 *Table 1*

|   | <b>EPAD</b><br>(n=281) | <b>ALSPAC</b><br>(subsample of offspring<br>of recurrently<br>depressed mothers;<br>n=612) | <b>ALSPAC</b><br>(whole sample;<br>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                                       |

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

207 **Descriptives from EPAD high-risk sample**

208 Mean systolic and diastolic blood pressure in the EPAD sample at baseline were 117.26 mmHg and  
209 70.88 mmHg and standard deviations were 13.18 and 11.39 respectively. There were no significant  
210 differences between males and females for systolic or diastolic blood pressure at baseline. Systolic  
211 blood pressure at baseline was significantly correlated with age ( $r=.23$ ,  $p<.001$ ), but diastolic blood  
212 pressure was not ( $r=.02$ ,  $p=.728$ ). Systolic blood pressure was thus standardised for age and gender to  
213 create standard deviation scores and all analyses for systolic blood pressure were run with the  
214 standardised variable.[17] Mean blood pressures for each age group in this sample were generally  
215 higher than population norms.[17,18] Systolic blood pressure at baseline was significantly associated  
216 with weight ( $r=.25$ ,  $p<.001$ ), but diastolic blood pressure was not ( $r=.07$ ,  $p=.236$ ). Given this finding  
217 all analyses with systolic blood pressure are reported controlling for weight.



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3 218 Twenty-four children (5 boys, 19 girls) in the sample developed a new onset depressive disorder  
4  
5 219 (8.54%).

6  
7  
8 220 **Descriptives from ALSPAC dataset – using the subsample of children with mothers that have**  
9  
10 221 **experienced recurrent depression in the past**

11 222 Mean systolic and diastolic blood pressure in this sample at age 12 years were 111.10 mmHg and 56.61  
12  
13 223 mmHg and standard deviations were 9.44 and 8.16 respectively. There were no significant differences  
14  
15 224 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
16  
17 225 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
18  
19 226 systolic blood pressure were run with the standardised variable. The association between blood  
20  
21 227 pressure and weight at age 12 was significant for both systolic ( $r=.45$ ,  $p<.001$ ) and diastolic blood  
22  
23 228 pressure ( $r=.18$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

24  
25 229 Eighteen children (5 boys, 13 girls) in the sample reported a depressive disorder over the last month at  
26  
27 230 age 15 (2.94%).

28  
29  
30 231 **Initial analyses in EPAD high-risk sample**

31 232 Logistic regression analyses were performed to investigate the association between blood pressure and  
32  
33 233 new onset depressive disorder in the EPAD sample of children. It was found that as systolic blood  
34  
35 234 pressure increased, risk for new onset depressive disorder decreased, when adjusting for child's weight  
36  
37 235 at baseline (OR = .65, 95% CI .44 to .96;  $p=.029$ ), i.e. lower systolic blood pressure at baseline  
38  
39 236 significantly predicted new onset depressive disorder. Diastolic blood pressure at baseline did not  
40  
41 237 significantly predict new onset depressive disorder (OR = .97, 95% CI .92 to 1.01;  $p=.120$ ).

42  
43  
44 238 Results remained the same when the outcome was expanded to include the new onset of more broadly  
45  
46 239 defined mood-related diagnoses (primary diagnosis: major depressive disorder  $n=22$ , dysthymia  $n=1$ ,  
47  
48 240 cyclothymia  $n=1$ , bipolar disorder  $n=3$ , adjustment disorder with depressed mood  $n=4$  and depressive  
49  
50 241 disorder not otherwise specified  $n=5$ ). Results also remained similar when separately adjusting for  
51  
52 242 medication use and physical health problems in the child and when adjusting for BMI instead of  
53  
54 243 weight. The association was not significantly moderated by gender ( $p=.769$ ).

55  
56 244 Given few adolescents developed new onset depressive disorder, the analysis was repeated using total  
57  
58 245 depression symptom scores at wave 3 as the outcome. Linear regression analysis with systolic blood

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

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

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

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

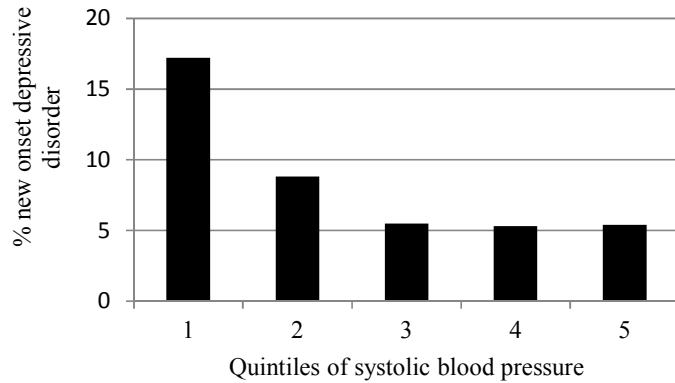
264 To examine whether depressive disorder was a predictor of blood pressure, a linear regression analyses  
265 was performed with a diagnosis of depressive disorder at age 13 as a predictor and systolic blood  
266 pressure at age 15 as the outcome, again controlling for child's weight. This was non-significant ( $\beta = -$   
267 .04;  $p = .378$ ).

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

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

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

275 *Figure 2*



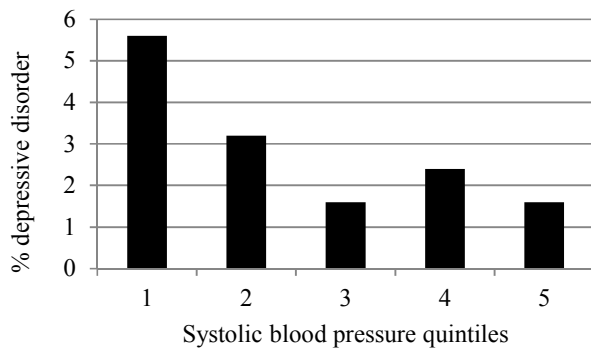
276  
 277 *Figure to show percentage of children with new onset depressive disorder at follow-up by quintiles of*  
 278 *systolic blood pressure at baseline in the EPAD sample*

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

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

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

287 *Figure 3*



288

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

291 Analyses so far have highlighted a significant association between lower systolic blood pressure and  
 292 future depression in two different samples of offspring of parents with recurrent depression. Next, ROC  
 293 analysis was performed to establish a cut off for blood pressure in both samples that **maximised both**  
 294 **sensitivity and specificity** for detection of future depressive disorder. A cut off point of below 0.025  
 295 standard deviations above the mean using standardised systolic blood pressure [17] showed a  
 296 sensitivity of 63% and a specificity of 66% for the high risk EPAD sample (this would approximately  
 297 equate to systolic blood pressure below 112mmHg for a 12 year old boy and below 113mmHg for a 12  
 298 year old girl). A cut off point of below 0.485 standard deviations below the mean using standardised  
 299 systolic blood pressure [17] showed a sensitivity of 61% and a specificity of 61% for the ALSPAC  
 300 replication sample (this would approximately equate to systolic blood pressure below 108mmHg for a  
 301 12 year old boy or girl). Logistic regression analyses were performed to examine the strength of the  
 302 association between low blood pressure and future depressive disorder using each of the cut offs  
 303 identified in each sample (Table 2).

304 *Table 2*

|               | OR (95% CI) <sup>1</sup>                   |   |
|---------------|--|---|
|               | Optimal cut off in EPAD<br>sample (< .025) | Optimal cut off in<br>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)                            |

306 <sup>1</sup>Adjusted for child weight at W1

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

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

1  
2  
3 312 Lastly, supplementary analyses were performed to examine the association between blood pressure and  
4  
5 313 future depression in the general population using the entire ALSPAC sample.  
6  
7

8 314 **Supplementary analyses using entire ALSPAC sample:**

9  
10 315 **1) Testing the relationship between depressive disorder and blood pressure in the general**  
11  
12 316 **population (not limiting analysis to those adolescents with a parental history of recurrent**  
13  
14 317 **depression)**

15  
16 318 **Descriptives**

17  
18 319 Mean systolic and diastolic blood pressure in the sample at age 12 were 111.01 mmHg and 56.53  
19  
20 320 mmHg and standard deviations were 9.54 and 7.88 respectively. There were no significant differences  
21  
22 321 between males and females for systolic or diastolic blood pressure at age 12. Again, systolic blood  
23  
24 322 pressure was standardised for age and gender to create standard deviation scores and all analyses for  
25  
26 323 systolic blood pressure were run with the standardised variable. The association between blood  
27  
28 324 pressure and weight at age 12 was significant for both systolic ( $r=.44$ ,  $p<.001$ ) and diastolic blood  
29  
30 325 pressure ( $r=.19$ ,  $p<.001$ ), therefore all results are reported controlling for weight.

31  
32 326 Seventy five children (22 boys, 53 girls) in the sample reported a depressive disorder over the last  
33  
34 327 month at age 15 (1.55%).

35  
36 328 **Preliminary analyses**

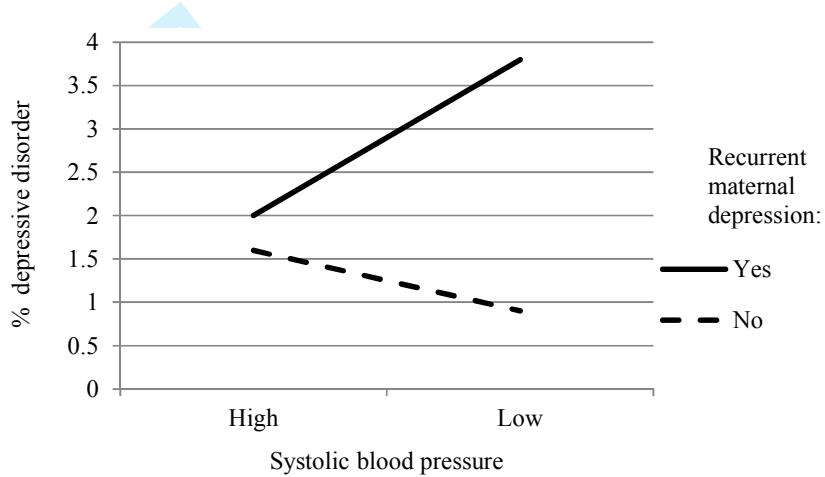
37  
38 329 Logistic regression analyses were performed to investigate the association between blood pressure and  
39  
40 330 depressive disorder. Systolic blood pressure at age 12 did not significantly predict depressive disorder  
41  
42 331 at age 15 (OR = .98, 95% CI .76 to 1.27;  $p=.875$ ). Diastolic blood pressure at age 12 did not  
43  
44 332 significantly predict depressive disorder at age 15 (OR = 1.01, 95% CI .98 to 1.04;  $p=.604$ ).

45  
46 333 **2) Examining whether a history of recurrent maternal depression moderated the**  
47  
48 334 **relationship between systolic blood pressure and depression**

49  
50 335 Logistic regression analyses were then performed to test if recurrent maternal depression moderated the  
51  
52 336 relationship between systolic blood pressure and depressive disorder. The predictor variables, systolic  
53  
54 337 blood pressure and maternal recurrent depression were centred to convert them to their deviation form  
55  
56 338 to remove non-essential multicollinearity. The interaction was found to be significant (OR = .49, 95%  
57  
58 339 CI .27 to .89;  $p=.019$ ).

1  
2  
3 340 Systolic blood pressure was then categorised into 'high' and 'low' by splitting at the median, so that  
4 341 the interaction could be displayed graphically. As can be seen in Figure 4, when recurrent maternal  
5 342 depression was present, children with low blood pressure showed the highest percentage of depressive  
6 343 disorder. However, when recurrent maternal depression was not present, children with high blood  
7 344 pressure showed the highest percentage of depressive disorder.

13 345 *Figure 4*



28  
29 346  
30 347 *Figure to show percentage of children with depressive disorder at age 15 years within 'high' and 'low'*  
31 348 *systolic blood pressure groups at age 12 years by maternal depression status in the ALSPAC sample*

1  
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3 349 **Discussion**

4 350 In this study we found that lower systolic blood pressure significantly predicted future new onset  
5  
6 351 depressive disorder amongst a sample of children and adolescents at high risk of developing depression  
7  
8 352 because of a parental history of recurrent depression. This finding was replicated in a large community  
9  
10 353 based cohort study (ALSPAC) for children whose mothers reported a history of recurrent depression  
11  
12 354 (replication sample). When investigating this relationship in more detail, it seemed that those with the  
13  
14 355 lowest systolic blood pressure were most at risk of developing a depressive disorder in the future. A cut  
15  
16 356 off value for systolic blood pressure in 12 year old children was identified as being within the range of  
17  
18 357 108 and 113mmHg. Finally when investigating this relationship in the entire population cohort  
19  
20 358 (ALSPAC), the association between blood pressure and major depressive disorder was no longer  
21  
22 359 significant. There was no evidence for an association in the opposite direction (depression predicting  
23  
24 360 future blood pressure levels) either in the study sample or in the replication cohort nor was there an  
25  
26 361 association between diastolic blood pressure and future depression in either dataset.

27  
28 362 In our study, whilst the average blood pressure in the offspring of parents with recurrent depressive  
29  
30 363 disorder was slightly higher than population norms, it was those whose blood pressure was lower who  
31  
32 364 were at most risk of developing depressive disorder. This was not true in adolescents from the general  
33  
34 365 population. In adolescents from the general population who did not have a parent with recurrent  
35  
36 366 depressive disorder, higher blood pressure showed some association with a higher risk of future  
37  
38 367 depressive disorder. There have been no previously published longitudinal studies examining the  
39  
40 368 relationship between blood pressure and depression in children from the general population or children  
41  
42 369 at high-risk of depression. In adults a “vascular depression” hypothesis has been proposed to explain  
43  
44 370 links between elevated blood pressure and depression [19] but some adult studies have found cross-  
45  
46 371 sectional links between low blood pressure and depression.[20, 21] In addition, a study on elderly  
47  
48 372 patients reported a fall in systolic blood pressure predicted the onset of depression.[6] The aim in our  
49  
50 373 study was however to look at links between blood pressure and depression prior to the usual age of  
51  
52 374 onset of hypertensive disease to examine developmental changes. Given the limited scientific literature  
53  
54 375 on this topic, the mechanisms by which low blood pressure might precede depression for adolescent  
55  
56 376 offspring of individuals with recurrent depressive disorder are unclear and we can at present only  
57  
58 377 speculate as to what these might be. Possible mechanisms include shared risks (genetic and/or  
59  
60 378 environmental) that contribute to both lower blood pressure and depression that are especially enriched

1  
2  
3 379 in those offspring most at risk of developing depressive disorder in the near future. Another possibility  
4 380 is that low blood pressure, in those who are familially/genetically vulnerable to depression, represents  
5  
6 381 an early manifestation (possibly through autonomic system dysregulation) or prodromal phase of major  
7  
8 382 depressive disorder. There is strikingly limited research on biological links between early mental health  
9  
10 383 problems and physical health as well as on autonomic system function in young people who are  
11  
12 384 familially vulnerable to depression [22]. Our findings highlight the need for further research on links  
13  
14 385 between mental and physical health in young people.

### 16 17 386 **Strengths and Limitations**

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19  
20 387 This is the first study we are aware of to report on the longitudinal relationship between blood pressure  
21  
22 388 and depressive disorder in adolescents, an important period for the onset of depression. In the main  
23  
24 389 sample, children and adolescents were followed up at three points over a four year period with a high  
25  
26 390 retention rate of over 80%. A similar pattern of results was found in a large community based cohort  
27  
28 391 study (ALSPAC) for those children of mothers with a history of recurrent depression. In both samples,  
29  
30 392 diagnoses were systematically ascertained using interview and blood pressure readings were measured  
31  
32 393 according to standardised protocol. In addition, potential confounders of the relationship were taken  
33  
34 394 account of. There were also possible limitations of the study. Blood pressures were measured using an  
35  
36 395 electronic device which uses an oscillometric technique rather than the auscultatory technique that most  
37  
38 396 population norms are based on and it has been noted that these readings are not equivalent. However  
39  
40 397 there is a lack of consensus as to whether using different methods leads to any systematic bias and  
41  
42 398 inaccuracies seem more related to not using a standardised technique rather than the instrument.[23] In  
43  
44 399 addition, the cut off values identified in the high risk and replication samples differed slightly. This  
45  
46 400 may have been because of differences in measurement techniques in the two studies. These results need  
47  
48 401 to be replicated in other samples in order to establish more precise cut off for low systolic blood  
49  
50 402 pressure. There was also relatively a high false positive rate for the cut offs identified in both the high  
51  
52 403 risk and the replication sample (34% and 39% respectively). However the aim of this analysis was not  
53  
54 404 to develop a screening tool for depression but to use ROC curve analysis as a method to maximise both  
55  
56 405 sensitivity and specificity in determining the optimal cut off value for low blood pressure. Moreover  
57  
58 406 some of the individuals labelled as “false positives” will have sub-threshold depression which has been  
59  
60 407 found to be associated with impairment, and to predict escalation to future disorder;[24, 25] Despite



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2  
3 408 being a high-risk sample, the number of children with depressive disorder was small and many of the  
4 409 sample had not been though the age of maximum risk for developing a depressive disorder so this  
5  
6 410 could lead to an underestimate of the effects of risk factors. In addition, the number of children with  
7  
8 411 depressive disorder was also low in the replication sample, partly because only a self-report measure of  
9  
10 412 depressive disorder was available at age 15, and partly because of selective attrition over time.  
11  
12 413 Previous studies have reported that although attrition has affected prevalence rates of depression in the  
13  
14 414 mother and internalising disorders in the children, the associations between risks and outcomes  
15  
16 415 remained intact, although conservative estimates of the likely true effects.[26, 27] Lastly, the  
17  
18 416 subsample of recurrently depressed mothers in the replication dataset is likely to index a less severe  
19  
20 417 group as maternal self-report of depression was used as opposed to defining episodes of depression  
21  
22 418 using DSM-IV criteria as was done in the main dataset.  
23  
24 419 In summary, in our study of adolescents at high risk of depression we found that low blood pressure  
25  
26 420 was associated with major depressive disorder. This finding was replicated in an independent cohort.  
27  
28 421 Future research is needed using different populations to confirm this relationship as it is a novel finding  
29  
30 422 and to investigate the mechanisms by which the relationship between low blood pressure and  
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32 423 depressive disorder in children at risk for depression may arise.  
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3 424 **Acknowledgments**  
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6 425 Funding support: British Medical Association (Strutt and Harper) Grant, the Sir Jules Thorn Charitable  
7 426 Trust and the National Institute for Social Care and Health Research Academic Health Science  
8  
9 427 Collaboration (AHSC) fellowship.  
10

11  
12 428 We are extremely grateful to all the families who took part in the EPAD study, the GP surgeries for  
13 429 their help with recruiting them and the whole EPAD team. We thank the other investigators involved in  
14  
15 430 the original EPAD study, Dr. Robert Potter, Dr. Stephan Collishaw, Dr. Daniel Smith, Prof. Michael  
16  
17 431 Owen, Dr. Frances Rice and Prof. Nick Craddock. In addition, we are also extremely grateful to all the  
18  
19 432 families who took part in the ALSPAC study, the midwives for their help with recruiting them, and the  
20  
21 433 whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical  
22  
23 434 workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research  
24  
25 435 Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support  
26  
27 436 for ALSPAC. This publication is the work of the authors and Gemma Hammerton, Ajay Thapar,  
28  
29 437 Gordon Harold and Anita Thapar will serve as guarantors for the contents of this paper. This research  
30  
31 438 was specifically funded by the British Medical Association (Strutt and Harper Grant) and the Sir Jules  
32  
33 439 Thorn Charitable Trust.  
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35  
36 440 **Conflict of interest**  
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38  
39 441 None of the authors have conflict of interest/financial disclosures.  
40

41  
42 442 **Role of funding source**  
43

44  
45 443 Initial funding for this study was provided by the British Medical Association (Strutt and Harper) Grant  
46  
47 444 and the Sir Jules Thorn Charitable Trust. The National Institute for Social Care and Health Research  
48  
49 445 Academic Health Science Collaboration (AHSC) fellowship provided funding for one of the authors  
50  
51 446 (AKT). The funders had no further role in the study design, the collection, analysis and interpretation  
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53 447 of data, the writing of the report, or in the decision to submit the paper for publication.  
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For peer review only

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

|                              | Item No | Recommendation  |
|------------------------------|---------|---|
| <b>Title and abstract</b>    | 1       | (a) Indicate the study's design with a commonly used term in the title or the abstract<br><b>page 1</b><br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found<br><b>page 1</b>   |
| <b>Introduction</b>          |         |   |
| Background/rationale         | 2       | Explain the scientific background and rationale for the investigation being reported<br><b>page 3</b>   |
| Objectives                   | 3       | State specific objectives, including any prespecified hypotheses<br><b>page 3</b>   |
| <b>Methods</b>               |         |   |
| Study design                 | 4       | Present key elements of study design early in the paper<br><b>page 4 &amp; 7</b>  |
| Setting                      | 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection<br><b>page 4 &amp; 7</b>  |
| Participants                 | 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br><b>page 4 &amp; 7</b><br>(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<br><b>pages 7, 8, 9 &amp; 10</b>   |
| Data sources/<br>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<br><b>pages 7, 8, 9 &amp; 10</b>   |
| Bias                         | 9       | Describe any efforts to address potential sources of bias<br><b>page 3, pages 8 &amp; 10 (addressing confounders), and pages 19</b>   |
| Study size                   | 10      | Explain how the study size was arrived at<br><b>pages 4, 6 &amp; 7</b>  |
| Quantitative variables       | 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why<br><b>pages 7, 8, 9 &amp; 10</b>   |
| Statistical methods          | 12      | (a) Describe all statistical methods, including those used to control for confounding<br><b>pages 8, 10, 11 &amp; 12</b><br>(b) Describe any methods used to examine subgroups and interactions<br><b>pages 10, 16 &amp; 17</b><br>(c) Explain how missing data were addressed<br><b>page 10</b><br>(d) If applicable, explain how loss to follow-up was addressed<br>(e) Describe any sensitivity analyses<br><b>pages 10, 12, 13 &amp; 15</b> |

## Results

|    |                          |     |   |
|----|--------------------------|-----|---|
| 1  | 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<br><b>pages 4, 6 &amp; 7</b>                          |
| 2  |                          |     | (b) Give reasons for non-participation at each stage<br><b>pages 4, 6 &amp; 7</b>   |
| 3  |                          |     | (c) Consider use of a flow diagram<br><b>page 6</b>   |
| 4  | Descriptive data         | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br><b>page 11, 12 &amp; 16</b>   |
| 5  |                          |     | (b) Indicate number of participants with missing data for each variable of interest<br><b>pages 4, 6 &amp; 7</b>  |
| 6  |                          |     | (c) Summarise follow-up time (eg, average and total amount)<br><b>page 4</b>  |
| 7  | Outcome data             | 15* | Report numbers of outcome events or summary measures over time<br><b>page 11, 12 &amp; 16</b>   |
| 8  | 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<br><b>pages 8, 10, 12, 13, 15 &amp; 16</b> |
| 9  |                          |     | (b) Report category boundaries when continuous variables were categorized<br><b>page 13, 14 &amp; 15</b>  |
| 10 |                          |     | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period  |
| 11 | Other analyses           | 17  | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses<br><b>pages 11-17</b>  |
| 12 | <b>Discussion</b>        |     |   |
| 13 | Key results              | 18  | Summarise key results with reference to study objectives<br><b>page 18</b>  |
| 14 | 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<br><b>pages 19 &amp; 20</b>  |
| 15 | Interpretation           | 20  | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence<br><b>page 18</b>  |
| 16 | Generalisability         | 21  | Discuss the generalisability (external validity) of the study results<br><b>pages 18 &amp; 19</b>   |
| 17 | <b>Other information</b> |     |   |
| 18 | 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<br><b>page 21</b>   |

\*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>.