Early development, stress and depression across the life course: pathways to depression in a national British birth cohort

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Background. The aetiology of depression is multifactorial, with biological, cognitive and environmental factors across the life course influencing risk of a depressive episode. There is inconsistent evidence linking early life development and later depression. The aim of this study was to investigate relationships between low birthweight (LBW), infant neurodevelopment, and acute and chronic stress as components in pathways to depression in adulthood.

Method. The sample included 4627 members of the National Survey of Health and Development (NSHD; the 1946 British birth cohort). Weight at birth, age of developmental milestones, economic deprivation in early childhood, acute stressors in childhood and adulthood, and socio-economic status (SES) in adulthood were assessed for their direct and indirect effects on adolescent (ages 13 and 15 years) and adult (ages 36, 43 and 53 years) measures of depressive symptoms in a structural equation modelling (SEM) framework. A structural equation model developed to incorporate all variables exhibited excellent model fit according to several indices.

Results. The path of prediction from birthweight to age of developmental milestones to adolescent depression/anxiety to adult depression/anxiety was significant (p<0.001). Notably, direct paths from birthweight (p=0.25) and age of developmental milestones (p=0.23) to adult depression were not significant. Childhood deprivation and stressors had important direct and indirect effects on depression. Stressors in adulthood were strongly associated with adult depression.

Conclusions. Depression in adulthood is influenced by an accumulation of stressors across the life course, including many that originate in the first years of life. Effects of early-life development on mental health appear by adolescence.

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Introduction

The aetiology of depression is thought to be multifactorial, with genetic, biological, cognitive and environmental factors interacting across the life course to influence the risk of a depressive episode among individuals of varying disposition. Historically, epidemiological research on depression has tended to focus on individual risk factors. However, to best understand the development of depression, such research must embrace the complex nature among various pathways to risk (Colman & Jones, 2004; Colman & Ataullahjan, 2010). Seminal work by Kendler et al. (2002, 2006) used twin registry data to study the development of depression in men and women, using structural equation modelling (SEM) of key determinants and their association over time. Eighteen key risk factors were considered, and the results indicated three key pathways that lead to an episode of major depression, with different periods of influence for each dimension: (1) internalizing behaviour and liability that manifests itself early in life, (2) externalizing behaviour from adolescence to adulthood, and (3) variation in adversity across the life course (Kendler et al. 2002, 2006).

Prenatal and infant development may be important in determining risk for depression later in life. Low birthweight (LBW) has been linked to depression in adolescence (Gale & Martyn, 2004; Costello et al. 2007; Colman et al. 2012) and adulthood (Thompson et al. 2001; Gale & Martyn, 2004; Hack et al. 2004; Alati et al. 2007; Colman et al. 2007a). This supports a fetal programming hypothesis in which prenatal stress at crucial periods of fetal brain development may elicit a maladaptive hyper-responsiveness to stress that could persist well into the life course (Weinstock, 2007).
However, LBW is also associated with other factors, such as poor cognitive development (Shenkin et al. 2004), which are in turn also risk factors for depression (Colman et al. 2007a; Gale et al. 2009; Koenen et al. 2009). Consequently, the intermediate causes on the pathway from LBW to depression are not clear.

Stress in early childhood is also associated with depression throughout life. Both chronic stress, such as prolonged poverty, and acute stressful events, such as parental divorce or being separated from the family, increase the risk of depression in later adult life (Kessler et al. 1997; Sadowski et al. 1999; Pesonen et al. 2007; Horesh et al. 2008). It has been suggested that the relationship between stress and depression varies across the life course. Furthermore, there is evidence from both animal (Weinstock, 2007) and human studies (Kuehner, 2003; Hammen, 2005; Costello et al. 2007) that aetiological mechanisms of depression may be different in men and women. Thus, large longitudinal studies that examine the different pathways from acute or chronic stress to depression are necessary to elucidate the mechanisms responsible (Hammen, 2005).

SEM approaches are increasingly used in psychiatric epidemiology to understand relationships between multiple measures over time, and time-dependent risk factors (Kendler et al. 2002, 2006). Such models can highlight temporal relationships between factors and identify key direct and indirect pathways that lead to depression, including moderation and also mediation effects (Colman & Jones, 2004; Colman & Ataullahian, 2010). The aim of this study was to use a SEM framework to investigate relationships between LBW, infant neurodevelopment, and acute and chronic stress as components in pathways to depression in members of a national British birth cohort. Given that both animal (Weinstock, 2007) and human studies (Kuehner, 2003; Hammen, 2005; Costello et al. 2007) have suggested that aetiological mechanisms in depression may differ by sex, structural equation models for males and females were explored/estimated separately.

Method

Subjects

Subjects were members of the Medical Research Council (MRC) National Survey of Health and Development (NSHD). This is an ongoing longitudinal study of 5362 individuals who formed a stratified sample of babies born in England, Scotland and Wales during 3–9 March 1946. The sample has been studied prospectively on 21 occasions up to age 53 years. Comparisons with census data show that those remaining in the cohort (n=3673 at age 53) are broadly representative of all native-born adults currently resident in England, Scotland and Wales (Wadsworth et al. 2003).

Neurodevelopment

Information on birthweight was obtained from the medical records or from mothers in 1946. Birthweight was recorded to the nearest quarter of a pound and converted to grams; the log of birthweight was used in the analysis. When the children were aged 2 years, mothers were asked to recall the age, in months, at which the child first sat up, stood unaided, walked, and first spoke words other than any derivation of ‘mother’ or ‘father’. Age of attainment (in months) for each domain was used as a measure of early neurodevelopment.

Acute and chronic stress

Two acute stressful events from childhood were assessed: parents divorcing before the age of 13, and being separated from the mother for more than 28 days before the age of 4. Parental divorce during childhood has been shown to be associated with depression in adulthood (Kessler et al. 1997). Similarly, separation from a parent during childhood for reasons other than divorce has been associated with depressive symptoms in adulthood (Kessler et al. 1997; Pesonen et al. 2007); presumably because of the importance of parent–child attachment for lifelong mental health (Jakobsen et al. 2012). In adulthood, numerous acute stressful events were recorded. Survey members were asked at age 36 about the occurrence of eight stressful life events in the previous 12 months, and at ages 43 and 53 the occurrence of 16 stressful life events in the previous 12 months was recorded (van Os et al. 2001). Events reported included being assaulted, death of a loved one and an employment crisis.

Chronic stress was measured using indices of low socio-economic status (SES), as lower SES is linked to numerous ongoing adverse social and environmental conditions (Baum et al. 1999). In childhood, crowding in the home was used as an indication of economic deprivation (Wadsworth et al. 2002). Survey members who were born into a home that housed two or more persons per room were considered to be deprived (Wadsworth et al. 2002). Social class of the survey members in adulthood was based on the British Registrar General’s social class classification according to the current or last occupation of the survey member (Kuh et al. 2005); members were grouped into manual versus non-manual social classes. Individuals with a manual job were considered to be of lower SES.
Depression

Symptoms of depression/anxiety were assessed at ages 13 and 15 using multi-item, teacher-rated psychiatric screening questionnaires. These questionnaires have previously been analysed using SEM to provide continuous latent variable measures for ages 13 and 15 from categorical (two- and three-point rating scales) data. Measurement models included the following items: ‘always tired and washed out’, ‘usually gloomy and sad’, ‘avoids attention’, ‘very anxious’, ‘timid child’, ‘rather frightened of rough games’, ‘extremely fearful’, ‘unable to make friends’, ‘diffident about competing’, ‘frequently day dreams in class’ and ‘becomes unduly miserable or worried in response to criticism’ (Colman et al. 2007a).

Depressive symptoms at age 36 were recorded using a short version of the Present State Examination (PSE; Wing et al. 1974), a clinically validated instrument administered here by research nurses trained to assess the frequency and severity of neurotic and affective symptoms in the preceding month. At age 43, the Psychiatric Symptom Frequency (PSF) scale developed for the survey (Lindelow et al. 1997) was administered. This is a 20-item scale where cohort members self-report the frequency and intensity of common symptoms of depression and anxiety experienced in the preceding year. At age 53, the survey members completed the 28-item ‘scaled’ General Health Questionnaire (GHQ; Goldberg & Hillier, 1979), a popular dimensional measure of psychological distress that focuses on the experience and impact of symptoms of anxiety and depression in the preceding 4 weeks. We have previously analysed these questionnaires using latent variable techniques (unidimensional item response theory) to create single measures at each age for depressive and anxious symptomatology (Colman et al. 2007a).

Statistical analysis

We used an SEM approach to investigate relationships between the developmental and stress variables and their effect on symptoms of depression in adolescence and adulthood. To reduce the number of variables and pathways in the model, we created four latent variables: (1) neurodevelopment, which loaded all four ages of attainment of developmental milestones; (2) acute stress in adulthood, which loaded the number of stressful events at ages 36, 43 and 53; (3) symptoms of depression in adolescence from the teacher ratings, which loaded the two measures of depressive and anxious symptoms at ages 13 and 15; and (4) symptoms of depression in adulthood, which loaded the three measures of depressive and anxious symptoms at ages 36, 43 and 53. These four latent variables provided dimensional summaries of relevant observed variables for use as continuous measures in the structural equation model, and offer some correction for measurement error in the observed variables themselves. The two acute stressors in childhood, in addition to early childhood deprivation and low SES in adulthood, were included as binary predictors (dummy variables) in the model. Finally, the natural logarithm of birthweight, a more normally distributed measure of development, was also used as a continuous measure.

The proposed structural model, outlining the candidate mechanisms linking development to affective risk, included direct pathways from all childhood factors to symptoms of depression in adolescence and adulthood (see Fig. 1). In addition, we included pathways from early childhood deprivation to early development, acute stress in childhood and low SES in adulthood to examine indirect pathways from early deprivation to depressive symptoms in adolescence and adulthood. Similarly, a path from birthweight to neurodevelopment was included. Finally, a path from adolescent depressive symptoms to adult depressive symptoms was included to assess indirect pathways from childhood variables to adult mental health through adolescent mental health.

This latent variable path analysis was implemented as a structural equation model in MPlus version 5.1 (Muthén & Muthén, 1998–2007) using robust weighted least squares estimation, under a missing completely at random (MCAR) assumption for missing data. The sample included all individuals who had at least one assessment of symptoms of depression (n=4627). Separate models were explored for males and females.

Although our focus was on direct and indirect pathways to symptoms of depression, and hence on the magnitude of the residuals that remained after estimation of the model, given the proposed pathways we also report model fit using several popular indices: the Tucker–Lewis index (TLI; Tucker & Lewis, 1973) and the Root Mean Square Error of Approximation (RMSEA; Steiger & Lind, 1980). TLI values >0.96 are indicative of good model fit, as are RMSEA values <0.06. However, it is also important to consider the relative saturation of the model, which was necessary to operationalize and estimate the set of candidate effects within our SEM.

Results

Table 1 shows the prevalence of acute and chronic stressors in childhood and adulthood. Economic deprivation in childhood affected approximately 15% of survey members. In adulthood, men were more likely than women to have lower SES. Acute stressful events were rare in childhood; however, approximately one
quarter of survey members reported three or more stressful events in the previous 12 months at age 36, 43 or 53 years.

Indices of model fit for the proposed structural equation model for females and males were very favourable, both having a TLI of 0.99 and an RMSEA of 0.017. In the remainder of the results we have focused our text to describe the paths in the model that were statistically reliable. Effect sizes can be gauged from the model estimates shown in the figures (standardized coefficients are shown) as these are in the metric of correlation coefficients.

Table 1. Prevalence of acute and chronic stressors in childhood and adulthood

<table>
<thead>
<tr>
<th>Stressful events</th>
<th>Males (%) (n=2401)</th>
<th>Females (%) (n=2262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic deprivation in childhood</td>
<td>14.4</td>
<td>15.7</td>
</tr>
<tr>
<td>Separated from mother for more than 28 days before age 4 years</td>
<td>7.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Parental divorce before age 13 years</td>
<td>5.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Lower social class in adulthood</td>
<td>38.0</td>
<td>26.8</td>
</tr>
<tr>
<td>Stressful events at age 36 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18.5</td>
<td>16.6</td>
</tr>
<tr>
<td>1</td>
<td>25.7</td>
<td>22.4</td>
</tr>
<tr>
<td>2</td>
<td>25.1</td>
<td>25.6</td>
</tr>
<tr>
<td>≥3</td>
<td>30.7</td>
<td>35.3</td>
</tr>
<tr>
<td>Stressful events at age 43 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25.3</td>
<td>24.0</td>
</tr>
<tr>
<td>1</td>
<td>29.3</td>
<td>30.4</td>
</tr>
<tr>
<td>2</td>
<td>22.2</td>
<td>20.4</td>
</tr>
<tr>
<td>≥3</td>
<td>23.2</td>
<td>25.1</td>
</tr>
<tr>
<td>Stressful events at age 53 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21.5</td>
<td>20.5</td>
</tr>
<tr>
<td>1</td>
<td>29.1</td>
<td>26.9</td>
</tr>
<tr>
<td>2</td>
<td>22.2</td>
<td>20.3</td>
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<tr>
<td>≥3</td>
<td>27.2</td>
<td>32.3</td>
</tr>
</tbody>
</table>

Fig. 1. Proposed developmental model for symptoms of depression and anxiety across the life course.
Pathways to adolescent depression in girls

Lower birthweight and delay in reaching neurodevelopmental milestones were both associated (direct effects) with adolescent depression in females (Fig. 2). There was also an indirect pathway from birthweight to adolescent depression through neurodevelopment, whereby lower birthweight girls were more likely to reach milestones later and consequently were more likely to become depressed in adolescence ($z = -2.2, p = 0.03$). Neither economic deprivation nor acute stressors in childhood were associated with adolescent depression. However, there was an indirect effect of economic deprivation in childhood on adolescent depression whereby children in economically deprived families were more likely to be larger at birth and reached developmental milestones earlier, dampening the direct effect of economic deprivation on their mental health in adolescence ($z = -2.6, p = 0.008$ for ED-ND-CD; $z = -2.1, p = 0.04$ for ED-BW-ND-CD).

Pathways to depression in adult females

Adolescent depression was directly associated with depression in adult females (Fig. 2). Birthweight and neurodevelopment were not directly associated with adult depression but indirect pathways through adolescent depression were identified ($z = -2.4, p = 0.01$ for BW-CD-AD; $z = -2.0, p = 0.04$ for BW-ND-CD-AD; $z = 2.2, p = 0.03$ for ND-CD-AD). Stressors were strongly associated with depression in adult females. Parental divorce in childhood, low SES in adulthood and acute stressful events in adulthood were directly associated with depression in adult females. In addition, economic deprivation had significant indirect effects on depression in adulthood by increasing the likelihood of parental divorce in childhood and lower SES in adulthood.
Pathways to depression in adult males

Adolescent depression was also directly associated with depression in adulthood for males (Fig. 3). Birthweight and neurodevelopment were not directly associated with depression in adult males but the indirect pathway from birthweight to neurodevelopment through adolescent depression was also present, as in females ($z = -2.3, p = 0.02$), as was the pathway from neurodevelopment to adolescent depression to depression in adulthood ($z = 2.5, p = 0.01$). Acute stressful events in adulthood were also strongly associated with depression in adult males. Being separated from the mother early in childhood was also directly associated with depression in adult males. Economic deprivation in childhood had an indirect effect on depression in adulthood, which involved dampening the effect of neurodevelopment on adolescent depression and subsequent adult depression ($z = -2.3, p = 0.02$).

Discussion

The findings and related research

This study used data from 4627 members of a birth cohort to identify several pathways to symptoms of depression in adulthood. Notably, we found that indicators of deprivation early in life, both economic and biological, were not directly associated with depression in adulthood but were associated with intermediate risk factors that subsequently increase the risk of depression later in life. Crowding in the home in the first years of life, a marker of economic deprivation, was associated with both increased risk of acute stressful events in childhood and economic deprivation in adulthood, which were subsequently associated with a greater risk of adult depression. Indeed, others have also observed that the association between low SES in childhood and depression in adulthood may be mediated by SES in adulthood (Stansfeld et al. 2008b).

Surprisingly, our results suggest that more household crowding is related to faster neurological development (i.e. earlier attainment of developmental milestones). Overcrowding has been linked to lower IQ scores (Wachs, 1978) and less complex verbal communication with parents (Evans et al. 1999), and psychological development, particularly in boys (Wachs, 1979), although other research suggests that physical development is not strongly associated with overcrowding (Booth & Johnson, 1975; Gulliford et al. 1991). One possible explanation for our results is that our measure of overcrowding does not reflect the extent to which crowding may interfere with versus enable children’s development, particularly with respect to physical development. More crowded homes are often those with more siblings, and young children with more siblings may reach developmental milestones at an earlier age, as these children potentially have more opportunities for imitation of older siblings’ behaviours. In accordance with the ideas of certain theorists (Piaget, 1926; Festinger, 1954), toddlers have
Indeed been shown to preferentially imitate the behaviours of other children over those of parents (Ryalls et al. 2000).

LBW, a marker of prenatal adversity, was not directly associated with depression in adulthood. It was, however, associated with development delay in infancy, which was associated with adolescent depression and a subsequent increased risk of depression in adulthood. This suggests that the influence of impaired development on lifelong mental health is apparent by adolescence, as has been observed in other birth cohorts (Jaffee et al. 2002).

Consistent with the majority of other epidemiological studies, we found a direct association between LBW and adolescent depressive symptoms in girls, but not boys (Hack et al. 2004; Alati et al. 2007; Costello et al. 2007). These findings are supported by laboratory evidence showing that female offspring of prenatally stressed rats have an increased response to stress compared to male offspring, suggesting that the developing hypothalamic-pituitary-adrenal (HPA) axis of female fetuses may have an increased sensitivity to maternal circulating stress hormones (Weinstock, 2007). Of note, we found an indirect significant association between LBW and adolescent depressive symptoms among males, whereby males of lower birthweights were at an increased risk of delay in reaching developmental milestones; those with delay in reaching milestones were at an increased risk of adolescent depression. Numerous studies have shown that prenatal maternal stress impairs learning and memory to a greater extent in the male rat brain than the female rat brain (Weinstock, 2007); epidemiological studies have shown an association between impaired cognitive ability early in life and later symptoms of depression (Colman et al. 2007a; Gale et al. 2009; Koenen et al. 2009). This pathway from prenatal stress to impaired cognitive development to adolescent depression may explain why some studies show a stronger association between LBW and depression among males (Thompson et al. 2001; Colman et al. 2012).

An important finding from this study is the relative influence on adult depression of stressful events in adulthood compared to childhood factors. Although much evidence points to the long-term effect of adolescent mental disorder on adult mental health (Kim-Cohen et al. 2003; Rutter et al. 2006; Colman et al. 2007b), our findings suggest that stressful events in adulthood may make a larger contribution towards depression than adolescent mental disorder. This may partially be due to differences in the measurement of stressful events in the current study. Indeed, stressful events in childhood included two specific events (separation from the mother, parent divorce) whereas the measure in adulthood included several stressful events. However, studies of a British cohort followed from birth to age 45 have reported more modest effects of childhood disorders on adult depression (Clark et al. 2007), in addition to a magnitude of effect of childhood disorder comparable to stress in the adult workplace (Stansfeld et al. 2008a). These findings, along with ours, suggest that the influence of childhood adversity may be strong for a subset of adults with depression and may be more evident early in adulthood; however, as cohorts age and some adults experience a first onset of depression, it is increasingly likely that stress in adult life is a contributing factor and less likely that the depressive episode can be traced to childhood. Nevertheless, even if the effect is smaller than previously reported, it is clear that deprivation, stress and impaired development in early life have important effects on the life course of mental health problems. Moreover, we only examined two acute stressors in childhood, which may have contributed to a potential underestimation of direct or indirect influence of these stressors on adult depression.

Similarly, it is of interest that acute stressful events in childhood (parental divorce or long separation from the mother) were not associated with adolescent depressive symptoms but were instead directly associated with adult symptoms. These findings suggest that the accumulation of stressors across the life course, or their consequences, may have an important influence on depression in adulthood, supporting other research showing that increased numbers of adverse factors in childhood and adolescence increase the risk of depression in adulthood (Sadowski et al. 1999; Clark et al. 2010). However, this finding was only true for males. In support of this finding, some research suggests that stressors such as parental divorce may only increase the risk of depression and suicide attempts for females (Cooney & Smith, 1996; Lizardi et al. 2009; Wintre et al. 2011).

**Methodological considerations**

This study has some limitations that deserve mention. We only focused on a limited number of factors associated with depression; however, the aetiology of depression is multifactorial in nature, including many factors that are present in early life (Colman & Ataullahjan, 2010), and this may influence the pathways observed in this study. For example, we considered neither personality traits nor child temperament, and there are numerous intermediate health risks that are associated with depression such as poor childhood physical health, substance abuse, lower cognitive ability and childhood abuse, all of which are associated with socio-economic deprivation early in
life (Melchior et al. 2007). Although our analysis may be improved by adding further factors such as these, we sought to focus on selected key variables to present an initial but comprehensive model of some candidate pathways. Similarly, prospective data are not available in the NSHD on some potentially relevant factors, such as maternal prenatal smoking, maternal depression and family history of depression, that may be associated with both early development and psychopathology.

Our measures were psychometric latent factors/dimensions and we did not use a clinically validated assessment of depression such as a categorical diagnosis. However, elevated symptoms of depression and anxiety have been shown to be associated with previous and future severe disorder (Kessler et al. 2003; Merikangas et al. 2003; Fergusson et al. 2005). Moreover, questionnaire studies such as ours, which use psychiatric screens or symptom severity measures that are able to capture important variation in illness (or illness risk) on a continuous dimension, have reported associations between LBW and symptoms of depression and anxiety (Cheung, 2002; Cheung et al. 2002) whereas, importantly, studies that have used categorical classifications have not (Osler et al. 2005). Consequently, we consider the use of scales that measure a wider range of severity of symptoms on a continuous scale a strength, as it maximizes power in SEM. Similarly, the only available rating of adolescent depressive symptoms was teacher rated. It is possible that the results could have differed with a self-report measure. However, studies using the Rutter B2 scale (Rutter, 1967), which is similar in method and items to our measure, found that teachers identified mental disorder more accurately than parents or children themselves (Kresanov et al. 1998), and also predicted future mental disorder more accurately than parents or children themselves (Sourander et al. 2004).

A pathway from depressive symptoms in adolescence to stressful events in adulthood was not included in our proposed model. However, previous episodes of depression have been shown to predict subsequent stressful life events, and also subsequent major depression (Kendler et al. 2003). Consequently, we conducted a post-hoc analysis that examined a model that included a direct path from adolescent depressive symptoms to adult stressful events. This path was not statistically significant and therefore not retained in the model.

Lastly, our decision to stratify analyses by sex was based on the evidence for sex-specific mechanisms in the development of depression (Kuehner, 2003; Hammen, 2005; Costello et al. 2007; Weinstock, 2007). However, some of the sex differences across models may be attributable to the reduced sample size (compared to the pooled sample) and a resulting lack of power to detect significant pathways for each sex-specific group.

These limitations, however, are offset by some notable study strengths. We used a large population-based sample and data collections that covered the life-span well into mid-adulthood on relevant aetiological prognostic factors. We were able to use several indicators of acute and chronic stress, and prenatal and infant development, as predictors or variables on the pathway to symptoms of depression in adolescence and adulthood. These strengths underscore the important findings of our structural model, which suggest that depression in adulthood is influenced by an accumulation of stressors across the life course, including many that originate in the first years of life.

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Declaration of Interest

None.

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