Birth weight and psychological distress at age 45–51 years

Results from the Aberdeen Children of the 1950s cohort study

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Background It is unclear whether the effect of low birth weight on common affective disorders in later life is direct or mediated through childhood factors.

Aims To determine whether birth weight has a direct effect on psychological distress in adulthood not mediated by childhood IQ or behavioural problems.

Method Participants (n=5572) of the Aberdeen Children of the 1950s study had data on birth weight for gestational age and adult psychological distress. Logistic regression was used to examine the association between these factors, with adjustment for confounders and potential childhood mediators.

Results Children born full term but weighing less than 5.5 lb had increased odds of psychological distress in later life after adjustment for potential confounders (OR=1.49, 95% CI 1.01–2.20). Further adjustment for childhood IQ and behaviour did not attenuate the association. A 1 s.d. decrease in birth weight for gestational age was associated with a 4% increased odds of psychological distress in adulthood (OR=1.04, 95% CI 0.97–1.12).

Conclusions Low birth weight for gestational age, particularly at term, was associated with adult psychological distress. This was not mediated by childhood factors, suggesting a direct effect of early life factors on adult mental health. A neurodevelopmental pathway may therefore be implicated.

Declaration of interest None.

The foetal origins hypothesis (Barker *et al*, 1989; Barker, 1998) has suggested a link between early life factors and adult health. Often quoted are studies showing a relationship between low birth weight and coronary heart disease (Leon *et al*, 1998) or non-insulin-dependent diabetes mellitus (Lithell *et al*, 1996). There is also evidence suggesting a link between markers of foetal growth and hypoxic brain damage, most notably low birth weight and schizophrenia (Cannon *et al*, 2002). Evidence from three birth cohorts has suggested that low birth weight may act as a risk factor for common affective disorder across a range of ages (26 years (Gale & Martyn, 2004); 23, 33 and 42 years (Cheung *et al*, 2002); and 68 years (Thompson *et al*, 2001)), but disparity exists. Thompson *et al* (2001) reported an increased risk of depression at age 68 years for men born of low birth weight but not women, whereas Gale & Martyn (2004) reported an increased risk of depression in women at 26 years, but not men.

Early life factors, such as birth weight, influence cognition (Breslau, 1995; Richards *et al*, 2001) and behaviour (Kelly *et al*, 2001) in childhood, and childhood cognitive deficit and psychiatric disorders are associated with psychiatric disorder in adulthood (van Os *et al*, 1997). An indirect pathway linking low birth weight and adult psychiatric morbidity via childhood cognition and/or behavioural problems may therefore be proposed, but it is possible that, in addition to or instead of this indirect effect, early life factors may have a direct effect on the occurrence of common affective disorder in later life. Using data from the Aberdeen Children of the 1950s study (Batty *et al*, 2004), we examined the association between birth weight and adult psychological distress at age 45–51 years. Our aim was to determine whether childhood factors (specifically, cognition and behavioural problems) mediate the association between early life factors and adult psychological distress.

METHOD

The Aberdeen Children of the 1950s cohort study

Full details of the Aberdeen Children of the 1950s study have been described elsewhere (Batty *et al*, 2004). In brief, this cohort comprises children born in Aberdeen, Scotland, UK between 1950 and 1956 who participated in the Aberdeen Child Development Survey (ACDS). This was a cross-sectional survey of learning disability in all children attending a primary school in Aberdeen in December 1962. Obstetric and perinatal data (including pre-eclampsia, birth weight and length of gestation) were available by reference to the Aberdeen Maternal and Neonatal Databank (AMND), established in 1948. Father's social class at the time of birth was derived from the occupational status listed on obstetric records. Details of maternal age, parity and whether the child was a singleton birth were also available from AMND records. At baseline, data were available for 12 150 children.

Results of IQ tests (assessed using the Moray House Picture Intelligence Test; Birch *et al*, 1970) routinely administered in Aberdeen schools at 7 years of age were extracted from school records for children taking part in the ACDS. Teachers also completed the Rutter Scale B (Rutter, 1967) of behaviour disorder for each child. On the Rutter scale, a score of 9 or more is indicative of a childhood behavioural disorder. Further classification into neurotic or antisocial disorder can be made using the sub-scale scores. If neither sub-scale score dominates, the disorder is deemed 'undifferentiated'.

In 1998 over 97% of the original cohort were traced and the majority still resided in Scotland. In May 2001, a questionnaire was mailed to surviving cohort members who were believed to be resident in the UK (n=11 282); 7183 cohort members responded (63.7% participation rate). A variety of socio-demographic data were recorded as part of this questionnaire, including marital status and current occupation, from which social class (I, II, III, IV or V) was assigned using the Standard Occupational Classification (Office of Population Censuses and Surveys, 1991).

In addition, participants were asked about psychological distress using 4 items from the 12-item General Health Questionnaire (GHQ; Goldberg & Williams, 1988).

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These items were: have you (i) been able to enjoy your day-to-day activities; (ii) been feeling unhappy and depressed; (iii) been losing confidence in yourself; and (iv) been feeling reasonably happy, all things considered. It is known that long questionnaires reduce response rates (Edwards *et al*, 2002). Such practical considerations were behind the decision to limit the number of GHQ items included. Previous work has shown that the difference in the percentage of variation explained by any subset of four GHQ questions was less than 5% (Jacobsen *et al*, 1995). Therefore, the four items included were based on an unrotated principal-components analysis of the data from the first sweep of the British Household Panel Survey (Weich & Lewis, 1998). The total score for the GHQ4 was derived using the GHQ scoring method (0, 0, 1, 1), giving total scores between 0 and 4. A score of 1 or more was taken to indicate adult psychological distress.

Data-set available for analysis

Of the 7183 participants who completed the 2001 follow-up questionnaire, data from 80 proxy respondents were excluded. Of the remaining 7103 individuals, 7033 had completed all four GHQ questions and, of these, 5572 had information recorded on AMND data: maternal age, father's social class at the time of birth, parity, whether the child was a singleton, pre-eclampsia during pregnancy, length of gestation and birth weight; ACDS reading survey data: gender, IQ at age 7 years and Rutter B scores; 2001 follow-up questionnaire data: marital status and adult social class.

Statistical analysis

All analyses were conducted using Stata version 8 for PC. Logistic regression was used to examine the relationship between obstetric and perinatal factors (birth weight for gestational age and pre-eclampsia) and adult psychological distress (GHQ4 $\geqslant$1). Odds ratios (ORs) and their 95% confidence intervals (95% CIs) are reported. Because of the presence of siblings within the data-set, the cluster option for logistic regression was used in all analyses.

Associations were initially adjusted for multiple birth, with subsequent adjustment for other potential confounding factors (gender, father's social class, parity and maternal age). Additional adjustment was then made for potential confounders identified in adulthood (marital status and social class recorded on the 2001 survey questionnaire).

The primary analysis dichotomised birth weight (using a cut-point of 5.5 lb or approximately 2500 g) and gestational age ($\geqslant$38 weeks' gestation) in order to determine the effect of low birth weight by gestational age. However, in an attempt to provide a more sensitive estimate of the association, *Z*-scores (Armitage *et al*, 2002) were calculated. The *Z*-score expresses birth weight in standard deviation units according to gestational age. Within the Aberdeen data-set, each completed week of gestation is recorded, with the exception of the extremes of the distribution ($\leqslant$33 weeks and $\geqslant$43 weeks), similarly birth weight is recorded in categories of 0.5 lb except for extreme values (<2.5 lb and $\geqslant$9.5 lb). *Z*-scores were therefore calculated by estimating the mean birth weight category for each completed week of gestation, and the estimate of variance was adjusted using Sheppard's correction (Armitage *et al*, 2002) to allow for the use of grouped data.

In order to test the hypothesis that early life factors have a direct effect on adult psychological distress, the logistic regression models were further adjusted for cognition (IQ at age 7 years) and Rutter neurotic and antisocial sub-scale scores. If the effect of early life factors on adult mental health was mediated through such intermediaries, then any association between early life factors and adult mental health would be attenuated.

Finally, given that missing data on the GHQ outcome variable meant that the above analyses involved just under half the original cohort, the validity of the study findings might be in doubt. To address this, a weighted analysis using probability weights (Brick & Kalton, 1996) was conducted. Probability weights were constructed using a logistic regression model where the outcome was having or not having GHQ4 data. The influence of father's social class, maternal age, parity, multiple birth and gender were assessed individually and then combined in a multivariable model. The results of unweighted and weighted analyses were then compared to assess whether exclusion of subjects (because of missing data) had influenced the study findings. Further discussion of the representativeness of the study cohort can be found elsewhere (Batty *et al*, 2004).

RESULTS

Description of the study cohort

Of the 5572 participants, 2890 (51.9%) were female and 2682 (48.1%) were male. The majority of fathers (60.3%) were in social class III at the time of their child's birth (Table 1). Mothers were most commonly between the ages of 25 and 29 years at the birth of their child. This was the first child for just over a third of women (n=1901). Almost all the children (98%) were singletons.

Prevalence of pre-eclampsia, pre-term birth and low birth weight

Table 1 shows that 18.2% of mothers had problems with hypertension, pre-eclampsia or eclampsia during pregnancy; 371 children (6.7%) were born before 38 weeks of gestation and almost 5% were born weighing less than 5.5 lb (or 2537 g).

Table 1 Characteristics of the study cohort

Characteristic	*n*	%
Father's social class		
I/II	613	11.0
III	3359	60.3
IV/V	1600	28.7
Maternal age (years)		
15–19	163	2.9
20–24	1681	30.2
25–29	1838	33.0
30–34	1232	22.1
35–39	506	9.1
40+	152	2.7
Pre-eclampsia		
None	4557	81.8
Other hypertension (including mild pre-eclampsia)	837	15.0
Moderate pre-eclampsia	121	2.2
Severe pre-eclampsia	57	1.0
Length of gestation		
<38 weeks	371	6.7
Low birth weight		
<5.5 lb	266	4.8
Birth weight according to gestational age		
Normal weight[1], full term[2]	5058	90.8
Normal weight, pre-term	248	4.5
Low weight, pre-term	123	2.2
Low weight, full-term	143	2.6

1. Normal weight=birth weight of 5.5 lb or more.
2. Full-term=gestational length of 38 weeks or longer.

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Table 2 Childhood and adult factors and psychological distress in adulthood

Variable	Total	GHQ4 ⩾1		*P*
	n	*n*	%	
Father's social class				
I/II	613	114	18.6	0.024[1]
III	3359	618	18.4	
IV/V	1600	345	21.6	
Parity				
1	1901	375	19.7	0.57[1]
2	1719	331	19.3	
3+	1952	371	19.0	
Maternal age (years)				
15–19	163	42	25.8	0.019[1]
20–24	1681	352	20.9	
25–29	1838	335	18.2	
30–34	1232	230	18.7	
35–39	506	91	18.0	
40+	152	27	17.8	
Gender				
Male	2682	459	17.1	<0.001[2]
Female	2890	618	21.4	
Adult marital status				
Single	453	112	24.7	<0.001[2]
Married	4094	673	16.4	
Widowed	88	26	29.6	
Divorced	720	192	26.7	
Separated	217	74	34.1	
Adult social class				
I/II	2369	399	16.8	<0.001[1]
III	2408	452	18.8	
IV/V	795	226	28.4	

1. χ^2 test for trend.
2. χ^2 test for association.

Almost 3% of children were born at full term (⩾38 weeks) but were of low weight (<5.5 lb) (Table 1).

Adult psychological distress

Nineteen per cent of the cohort (95% CI 18.3–20.4%) (*n*=1077) were categorised as having psychological distress (GHQ4⩾1) at the time of the follow-up survey; 434 participants (7.8%) scored above two on the GHQ4 and 193 (3.5%) answered positively to all four questions. As expected, women were more likely to be distressed (21.4%) than men (17.1%) (Table 2). Furthermore, those whose fathers or who were themselves in social class IV or V were more likely to be distressed. Those who were married at the time of the 2001 survey were less likely to be distressed. There was also a tendency for those children born to young mothers to be more likely to report psychological distress in adulthood (Table 2).

Associations between obstetric and perinatal factors and childhood IQ and behavioural disorder

As in previous studies, low birth weight (<5.5 lb) was associated with an increased odds of cognitive deficit (IQ <100) at age 7 years and childhood behavioural disorder (Table 3). This effect was observed among both those born early (<38 weeks' gestation) and those born at term. There was no such increase for the children of mothers who had severe pre-eclampsia during pregnancy, although this was based on small numbers.

Table 3 Associations between obstetric and perinatal factors and childhood IQ and behavioural disorder

Variable	*n*	Outcome=IQ<100 at age 7 years		Outcome=childhood behavioural disorder (Rutter score ⩾9)	
		OR[1]	95% CI	OR[1]	95% CI
Length of gestation					
⩾38 weeks	5201	1.00		1.00	
<38 weeks	371	1.14	0.89–1.47	1.55	1.06–2.27
Birth weight					
⩾5.5 lb	5306	1.00		1.00	
<5.5 lb	266	1.86	1.40–2.49	1.98	1.28–3.07
Birth weight according to gestational age[2]					
Normal weight, full-term	5058	1.00		1.00	
Normal weight, pre-term	248	1.03	0.76–1.40	1.39	0.87–2.23
Low weight, pre-term	123	1.60	1.05–2.44	2.10	1.14–3.85
Low weight, full-term	143	2.12	1.45–3.10	1.96	1.08–3.54
Pre-eclampsia					
None	4557	1.00		1.00	
Other hypertension (including mild pre-eclampsia)	837	0.85	0.70–1.04	1.07	0.77–1.48
Moderate pre-eclampsia	121	0.60	0.36–1.01	0.87	0.37–2.08
Severe pre-eclampsia	57	1.43	0.77–2.66	1.33	0.47–3.78

OR, odds ratio; CI, confidence interval.
1. Adjusted for father's social class, multiple birth, parity, maternal age, gender.
2. Normal weight means birth weight of 5.5 lb or more and full-term means gestational length of 38 weeks or longer.

Associations between childhood IQ and behavioural disorder and adult psychological distress

IQ <100 at age 7 years was associated with an increased odds of psychological distress in adulthood (Table 4). A score of 9 or above on the Rutter scale was associated with a 40% increased odds of adult psychological distress (Table 4).

Table 4 Associations between childhood IQ and behavioural disorder and adult psychological distress (GHQ4⩾1)

Variable	*n*	OR[1]	95% CI
IQ at age 7 years			
⩾100	4247	1.00	
<100	1325	1.22	1.05–1.43
Rutter score			
<9	5238	1.00	
⩾9	334	1.41	1.08–1.83

OR, odds ratio; CI, confidence interval.
1. Adjusted for father's social class, gender, multiple birth, parity, maternal age.

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Associations between obstetric and perinatal factors and adult psychological distress

Neither pre-term delivery (<38 weeks' gestation) nor low birth weight (<5.5 lb) was associated with an increased odds of psychological distress in adulthood (Table 5). However, those children who were born weighing less than 5.5 lb but at full term (i.e. born after at least 38 weeks of gestation) had an increased odds (1.65 (95% CI 1.14–2.41)) of experiencing psychological distress at age 45–51 years (Table 5). After adjustment for potential confounders (father's social class, parity, maternal age, gender, adult social class and adult marital status), this association persisted (OR=1.49 (95% CI 1.01–2.21)). No increase in odds was observed for those of low birth weight who were born early (before 38 weeks). Similarly, pre-term delivery was not associated with an increased odds of psychological distress in adulthood among those of normal birth weight (Table 5).

Excluding the multiple births from the data-set would result in significant loss of power for our analysis as this group has greater exposure. However, we have undertaken a stratified analysis by multiplicity and found that the low weight at term category was at greatest risk of adult psychological distress among both singletons and multiple-birth infants (data not shown). Moreover, there was no evidence of an interaction between birth weight by gestational age and multiplicity (P=0.19).

After adjustment for confounders, the children of those mothers who had experienced severe pre-eclampsia or eclampsia during pregnancy also had an increased odds of psychological distress in adulthood. However, this may be due to chance (Table 5).

Additional modelling demonstrated that the observed association between low birth weight at full term and adult psychological distress was independent of pre-eclampsia (data not shown). While a formal test of interaction was inconclusive (P=0.25), analysis stratified by gender showed stronger associations for men than women for low birth weight at full term (OR_{men}=2.85 (95% CI 1.40–5.78) *v.* OR_{women}=1.16 (95% CI 0.72–1.88)).

The direct effect of low birth weight at full term on adult psychological distress was examined by further adjusting the logistic regression models for IQ at age 7 years and Rutter sub-scale scores (Table 5). Little change in the size of the effect estimates following this adjustment was observed, suggesting that low birth weight at full term has a direct effect on adult mental health. Although we have examined the mediating role of childhood IQ and behaviour in this data-set, we cannot exclude the possibility that other factors may mediate this relationship.

Using Z-scores, an increased odds of adult psychological distress was observed for those of low birth weight for gestational age. For a standard deviation decrease in birth weight for gestational age, there was a 4% increased odds of psychological distress in adulthood (OR=1.04, 95% CI

Table 5 Associations between obstetric and perinatal factors and adult psychological distress (GHQ4⩾1)

Variable	*n*	Adjustment for:									
		Multiple birth		plus father's social class, parity, maternal age, gender		plus adult social class		plus adult marital status		plus IQ and Rutter neurotic and antisocial sub-scale scores	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Length of gestation											
⩾38 weeks	5201	1.00		1.00		1.00		1.00		1.00	
<38 weeks	371	1.07	0.82–1.40	1.05	0.80–1.38	1.04	0.79–1.37	1.03	0.78–1.35	1.02	0.78–1.34
Birth weight											
⩾5.5 lb	5306	1.00		1.00		1.00		1.00		1.00	
<5.5 lb	266	1.32	0.97–1.79	1.25	0.92–1.70	1.23	0.90–1.67	1.20	0.88–1.65	1.20	0.88–1.65
Birth weight according to gestational age[1]											
Normal weight, full-term	5058	1.00		1.00		1.00		1.00		1.00	
Normal weight, pre-term	248	1.16	0.85–1.59	1.14	0.83–1.57	1.13	0.82–1.56	1.12	0.81–1.55	1.11	0.81–1.54
Low weight, pre-term	123	0.98	0.60–1.58	0.94	0.58–1.52	0.93	0.57–1.52	0.91	0.56–1.48	0.91	0.56–1.47
Low weight, full-term	143	1.65	1.14–2.41	1.56	1.06–2.28	1.50	1.03–2.21	1.49	1.01–2.20	1.49	1.01–2.21
Pre-eclampsia											
None	4557	1.00		1.00		1.00		1.00		1.00	
Other hypertension[2]	837	1.02	0.85–1.23	1.07	0.88–1.30	1.08	0.89–1.31	1.09	0.89–1.32	1.09	0.90–1.32
Moderate pre-eclampsia	121	1.10	0.71–1.70	1.15	0.73–1.79	1.15	0.74–1.80	1.17	0.74–1.84	1.17	0.74–1.85
Severe pre-eclampsia	57	1.63	0.88–3.01	1.66	0.90–3.09	1.65	0.89–3.07	1.58	0.85–2.94	1.59	0.86–2.97

OR, odds ratio; CI, confidence interval.
1. Normal weight means birth weight of 5.5 lb or more and full-term means gestational length of 38 weeks or longer.
2. Includes mild pre-eclampsia.

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Table 6 Comparison of characteristics of those with and without GHQ outcome data

Variable	GHQ outcome data available (*n*=7033)		No GHQ outcome data (*n*=5117)		*P*
	n	%	*n*	%	
Father's social class					<0.001[1]
I/II	776	11.6	387	8.1	
III	3945	59.0	2709	56.7	
IV/V	1971	29.5	1681	35.2	
Missing	341		340		
Parity					<0.001[1]
1	2358	33.5	1633	31.9	
2	2096	29.8	1409	27.5	
3+	2579	36.7	2074	40.5	
Missing	0		1		
Maternal age (years)					<0.001[1]
15–19	259	3.7	308	6.0	
20–24	2129	30.3	1669	32.6	
25–29	2261	32.2	1516	29.6	
30–34	1518	21.6	1028	20.1	
35–39	656	9.3	452	8.8	
40+	207	2.9	141	2.8	
Missing	3		3		
Gender					<0.001[2]
Male	3359	47.8	2923	57.1	
Female	3674	52.2	2194	42.9	
Birth weight according to gestational age					0.019[2]
Normal weight, full-term	5759	90.5	4039	89.7	
Normal weight, pre-term	286	4.5	196	4.4	
Low weight, pre-term	152	2.4	120	2.7	
Low weight, full-term	169	2.7	148	3.3	
Missing[3]	667		614		

1. χ^2 test for trend.
2. χ^2 test for association.
3. Primarily due to missing data on gestational age.

0.97–1.12). The strength of this association increased when restricted to infants born at term (OR=1.06 (95% CI 0.98, 1.14)). Again, additional adjustment for childhood IQ and behavioural disorder (Rutter scores) did not attenuate this association (data not shown).

Differences between those with and without GHQ outcome data

There were a number of differences in the baseline characteristics among those who did and did not complete the GHQ items included in the 2001 follow-up questionnaire (Table 6). Those who did not complete the GHQ were more likely to be male and have fathers of lower social class. However, there was no difference in the birth weight for gestational age profile among those who did or did not have GHQ outcome data.

Adjustment using probability weights (to account for the observed differences) did not substantially alter the size of the effect estimates when compared with the results obtained for the unweighted analysis (data not shown). Exclusion of subjects from the cohort being analysed (because of missing outcome data) was therefore unlikely to have biased the effect estimates obtained.

DISCUSSION

The aim of this study was to investigate the association between obstetric and perinatal factors and psychological distress at ages 45–51 years and, in particular, to investigate the pathway through which these early life factors may act on adult mental health. We found that children born at full term but of low birth weight (<5.5 lb) had an increased odds of psychological distress in later life, which persisted after adjustment for potential confounders. No such increase was seen for those of low birth weight who were born early. Further adjustment for childhood factors (IQ and behavioural problems) did not alter the strength of the association between low birth weight at full term and adult psychological distress. This suggests that low birth weight at full term has a direct effect on adult mental health rather than simply reflecting a pathway through childhood cognition and/or behaviour.

Severe pre-eclampsia/eclampsia was also associated with an increased odds of psychological distress in adulthood, although this may be due to chance given the small numbers with this condition. As others have suggested (Cannon *et al*, 2002), notwithstanding the large sample size there still may be limits on the factors that can be explored given the low prevalence of obstetric complications.

In line with the finding of an earlier case–control study (Preti *et al*, 2000), more recent results from birth cohort studies have shown that low birth weight is associated with affective disorder in adulthood (Thompson *et al*, 2001; Cheung *et al*, 2002; Gale & Martyn, 2004). Gale & Martyn (2004) also reported that the effect of low birth weight on depression at age 26 years was stronger among those born at full term, which is in agreement with our findings. Studies of the Dutch Hunger Winter and subsequent linkage with the Dutch psychiatric registry (Brown *et al*, 2000) have also shown an association between prenatal famine (in the second and third trimester) and hospitalisation for major affective disorder. However, the study of hospitalised patients (Brown *et al*, 2000; Preti *et al*, 2000) is likely to introduce selection bias. Adjustment for confounding factors was also lacking (Brown *et al*, 2000) or limited (Thompson *et al*, 2001) in previous investigations.

Using data from the 1970 birth cohort, Gale & Martyn (2004) conducted separate analyses to examine the relationship between birth weight and psychological distress at age 16 years, history of depression between 16 and 26 years and depression

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at 26 years. However, the relationship between birth weight, psychological distress in late childhood (age 16 years) and adult depression was not explored. Similarly, data on childhood behavioural problems and cognition were available for participants of the 1958 birth cohort, but the influence of these factors was not examined by Cheung *et al* (2002). We are not aware of any previous study investigating the mechanism by which birth weight, childhood factors and adult mental health are linked and we have found that term low birth weight has a direct effect on psychological distress in adulthood.

Strengths and limitations

The Aberdeen Children of the 1950s cohort covers residents of a specific geographical area, whereas the 1946, 1958 and 1970 cohorts include births from across the entire UK. IQ scores of ACDS participants are known to be comparable with other studies (Birch *et al*, 1970), but fathers of children participating in ACDS were of lower social class compared with figures for Scotland or other birth cohorts (Batty *et al*, 2004).

The Aberdeen Children of the 1950s study has the advantage of having detailed obstetric data recorded prior to the onset of psychological distress (via the AMND). Furthermore, detailed information was available on potential confounders. The only major omissions were the lack of data on maternal smoking and parental mental health. Studies have suggested links between maternal psychosocial factors and low birth weight for gestational age (Paarlberg *et al*, 1999) and between parental mental health and child cognition and/or behaviour (Ramchandani & Stein, 2003). However, for primary cases of major depression, heritability has been estimated at approximately 20% (Kendler *et al*, 1992), a relatively small figure. Having adjusted for major confounders (paternal social class, maternal age, parity, gender, adult social class and adult marital status), confounding is therefore unlikely to explain the observed association between term low birth weight and psychological distress in adulthood, although we cannot exclude such a possibility.

One potential limitation of our study is the measurement of adult psychological distress using the GHQ rather than a standardised psychiatric interview. However, the GHQ has been used widely in population studies and is a valid and reliable instrument (Goldberg & Williams, 1988). A shortened version of the GHQ was used for practical reasons and the four items derived from a principal-components analysis of data from a large (n=7726) nationwide prospective cohort study (Weich & Lewis, 1998). Using these four items, the prevalence of psychological distress was similar to that observed in other population studies (Weich & Lewis, 1998). Furthermore, we conducted a sensitivity analysis (data not shown) to examine the effect of different methods of scoring the GHQ on the results. This supported our findings of an association between term low birth weight and adult psychological distress.

In common with other birth cohorts (Gale & Martyn, 2004), those not responding to the follow-up questionnaire were more likely to be born to younger mothers, to have fathers of lower social class and to be male. However, there were no differences in the profile of birth weight according to gestational age among respondents and non-respondents. In order to address the potential impact of the above differences, a weighted analysis was conducted; the results differed little from the unweighted figures. Attrition is therefore unlikely to have biased the study findings.

Possible aetiological mechanisms

Low birth weight for gestational age is a marker of impaired foetal growth. The observed association with adult psychological distress provides further evidence for the theory that adult psychiatric morbidity may be a consequence of impaired neurodevelopment. In infants born at full-term, this is usually attributed to placental insufficiency (which leads to a reduction in oxygen and nutrients to the developing foetus), whereas in pre-term infants there are many other potential pathophysiological processes that might affect the brain. Studies of the Dutch Hunger Winter (Brown *et al*, 2000) noted that the effect of birth weight was confined to the second or third trimester, which suggests that there may be a 'critical' period (Ben Shlomo & Kuh, 2002) during which neuroimpairment occurs, thereby increasing the later susceptibility to psychological distress. In addition, the fact that low birth weight had a direct effect on adult health (rather than acting via effects on childhood cognition and/or behaviour) implies that an environmental trigger in later life may result in psychological distress in vulnerable individuals. As has been proposed for schizophrenia (Keshavan & Hogarty, 1999), this delayed effect may also reflect a maturational developmental process. This theory is supported by work in rats where neonatal excitotoxic hippocampal damage resulted in abnormal behaviour in adulthood (Lipska & Weinberger, 1994).

Structural changes relating to a number of biological mechanisms have been implicated. These include the hypothalamic–pituitary–adrenal axis (Thompson *et al*, 2001; Gale & Martyn, 2004), the growth hormone axis (Thompson *et al*, 2001) and thyroid function (Thompson *et al*, 2001). However, understanding the involvement of such mechanisms is complicated by the overlap between these systems and cognitive function. Alternatively, neuropathological abnormalities in areas that are involved with emotional response (observed in structural imaging studies (Manji *et al*, 2001)) may reflect the influence of early life factors.

Others have suggested that low levels of maternal insulin-like growth factor (IGF-1) during pregnancy are associated with restricted foetal growth (Holmes *et al*, 1998). There is also experimental evidence that mice deficient in liver IGF-1 have reduced insulin sensitivity (Haluzik *et al*, 2003). The modulatory role of IGF-1 is further supported by recent work showing an inverse relationship between insulin resistance and depression (Lawlor *et al*, 2003). Recently, IGF has been implicated in the association of markers of foetal growth impairment with schizophrenia (Gunnell & Holly, 2004). IGF-1 can cross the blood–brain barrier and has been suggested to directly influence brain development (Gunnell & Holly, 2004). While the trend for an increased odds of psychological distress in adulthood across the entire spectrum of birth weight for gestational age (Z-score analysis) suggests that hormonal effects may be involved, it is unlikely that there is a sole aetiological factor underlying low birth weight (Soothill *et al*, 1999).

In conclusion, low birth weight babies, particularly at term, were more likely to experience psychological distress in adulthood. This appears to be a direct relationship, rather than being mediated by childhood factors. A neurodevelopmental pathway is thus implicated in the development of common affective disorder. Further work is required to elucidate the biological mechanism underlying this relationship.

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CLINICAL IMPLICATIONS

- **Children born at full term but of low birth weight (< 5.5 lb) are more likely to experience psychological distress in adulthood. This association appears to be direct, not mediated by childhood factors.**
- **This delayed effect may reflect a maturational developmental process.**
- **A neurodevelopmental pathway is implicated in the development of common affective disorder, not just schizophrenia.**

LIMITATIONS

- **Psychological distress was based on self-report rather than clinical interview.**
- **No data were available on parental mental health, which may be a possible confounder.**
- **Results are based on a cohort of individuals from one geographical region of the UK.**

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