American Journal of Epidemiology 2007 165(5):575-582; doi:10.1093/aje/kwk036

Is There a Fetal Origin of Depression? Evidence from the Mater University Study of Pregnancy and Its Outcomes

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Received for publication March 29, 2006. Accepted for publication July 26, 2006.

ABSTRACT

It is unclear whether there is a fetal origin of adult depression. In particular, previous studies have been unable to adjust for the potential effect of maternal depression during pregnancy on any association. The association of birth weight with adult symptoms of depression was examined in an Australian prospective birth cohort, the Mater University Study of Pregnancy and its outcomes. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale among 3,719 participants at the 21-year follow-up in 2002–2005. In multivariable analyses, there were a weak inverse association between birth weight and symptoms of depression in the whole cohort and some evidence of sex differences in this association. Among females, there was a graded inverse association: In the fully adjusted model, the odds ratio for a high level of depressive symptoms for a 1-standard deviation increase in birth weight (gestational age-standardized *z* score) was 0.82 (95% confidence interval: 0.73, 0.92). Among males, there was no association (with sex in all models: $p_{\text{interaction}} < 0.004$). Study results provide some support for a fetal origin of adult depression and suggest that the association is not explained by maternal mental health characteristics during pregnancy. Further research is needed to better understand the mechanisms underlying the association.

Keywords: Australia; birth weight; cohort studies; depression; maternal-fetal relations; pregnant women

Abbreviations: CES-D, Center for Epidemiologic Studies Depression; CI, confidence interval; DSSI, Delusions-Symptoms-States Inventory; MUSP, Mater University Study of Pregnancy

INTRODUCTION

The fetal origins hypothesis (also known as the developmental origins) of adult disease suggests that a

number of adult diseases have their origins in prenatal exposures (1–3). There is now a considerable body of evidence that supports a role for fetal exposures in the development of cardiovascular disease and diabetes (1, 4). There is also increasing evidence that the fetal environment may be important in the development of the central nervous system and in the etiology of mental ill health. Low birth weight has been found in a number of studies to be a risk factor for schizophrenia (5), and there has been recent interest in the association between birth weight and common affective disorders. Most (6–11), though not all (12, 13), studies have found an inverse association between birth weight adjusted for gestational age and depression (7–11). However, the mechanism underlying the association remains unclear. One possible explanation for the association between birth weight and depression is that it is explained by maternal factors that were not accounted for in previous studies. Maternal depression during pregnancy is associated with low birth weight (14) and with future depression in her offspring (15, 16). Thus, maternal mental health problems may lead to both lower birth weight and the offspring's increased risk of depression, but to our knowledge no previous study has examined the effect of maternal depression during pregnancy on the association of birth weight with depression.

The aim of this study is to examine the association of birth weight with adult symptoms of depression and to determine whether any association can be explained by symptoms of maternal depression and anxiety or other maternal pregnancy characteristics.

MATERIALS AND METHODS

The study

The Mater University Study of Pregnancy (MUSP) is a birth cohort study of mothers and children enrolled at the first antenatal visit at the Mater Misericordiae Hospital (Brisbane, Australia) between 1981 and 1984. Participants were followed up at 3–5 days, 6 months, and 5, 14, and 21 years after the birth. A total of 7,223 live singleton babies (52 percent males) constitute the MUSP birth cohort.

Measures—depressive symptoms at age 21 years

Our measurement of depressive symptoms was the 20-item version of the Center for Epidemiologic Studies Depression (CES-D) Scale (17). This measurement of depression was assessed on the 3,843 MUSP participants (53 percent of the original cohort) who attended the 21-year follow-up. The CES-D Scale does not constitute a clinical diagnosis of depression. However, it has been constructed using well-known items from existing depression scales, and it measures the severity and persistence of depressive symptoms over a 1-week period (17). The Scale is one of the most widely used screening questionnaires for the detection of depressive symptoms; it correlates well with other depression scales, and it has been found to have good internal consistency across diverse population groups and good short-term test-retest reliability (17–19). The score is calculated by reversing four positive mood items and then summing the item scores. A score of 16 or more out of 20 indicates current increased symptoms of depression and/or psychological distress (17). Of the 3,843 participants in this study, 124 had at least one item on the CES-D Scale missing and were excluded from further study. Of the 3,719 participants included in the study, the CES-D score ranged from 0 to 57, and 891 (24 percent) participants had high scores of 16 or more. In addition to examining the association of birth weight with the predefined and validated cutpoint of 16 used for defining those at high risk of moderate-severe depression (17), we also examined the association of birth weight with having a CES-D score of 25 or more (a level that has been associated with high risk of being diagnosed with major depression (20, 21)) and used the score as a continuous scale, examining the mean change in CES-D score per change in birth weight standard deviation. Finally, we used a three-endpoint outcome measure with scores ranging between 0 and 15 ("no depressive symptoms"), 16–24, and 25–57 to assess whether there was a greater affect particularly among females in the group of women with more severe depressive symptoms. Of the 891 who had scores higher than 16, 15.2 percent (n = 565) reported depressive symptoms lower than 24, and 8.8 (n = 326) reported depressive symptoms greater than 25.

The antenatal visit and birth records

Information on birth weight (to the nearest gram), gestational age (nearest week), and maternal parity (zero, one or two, three or more) was obtained from the obstetric records. Socioeconomic status was measured with maternal age (13–19, 20–34, and 35 or more), mother's education (did not complete secondary school, completed secondary school, completed further/higher education), marital status (married, cohabiting, and single), and ethnic status (White, Asian, and Aboriginal/Torres Strait Islander) obtained at the antenatal visit. Maternal lifestyle behavior in pregnancy included tobacco and alcohol use during pregnancy. Mothers were asked to recall the frequency and quantity of tobacco use in the previous week. Smoking status was categorized as none, 1–19, and 20 or more cigarettes per day. Maternal alcohol consumption was also assessed using two frequency/quantity items. Drinking status was categorized as abstainers, less than one drink per day, and one or more drinks per day.

At the antenatal visit, maternal depression and anxiety symptoms were assessed using the Delusions-Symptoms-States Inventory (DSSI) (22). The DSSI was developed by clinicians and validated against a clinical sample (23). It contains two seven-item subscales measuring depression and anxiety, which have been found to correlate strongly with other scales of depression including the Beck Depression Inventory (24). In this study, maternal symptoms of depression and anxiety were defined as reporting four or more of the seven symptoms in the DSSI depression and anxiety subscales. The anxiety and depression assessments used in this study were obtained at the first antenatal visit (first trimester for most women), around the time of birth, and at 6 months after the birth.

Data analyses

Logistic regression was used to assess the association between birth weight and two binary outcomes (our main outcome of a CES-D score of 16 or more vs. less than 16 and a CES-D score of 25 or more vs. less than 25). Linear regression was used to assess the association of birth weight and CES-D score as a continuous outcome. Birth weight was entered into these models in two ways. First, we examined the association using the following birth weight categories: 2.50 kg or less, 2.51–3.00 kg, 3.01–3.50 kg, and greater than 3.50 kg. These categories were chosen to replicate those from a similar paper that used data from the 1970 British Birth Cohort Study (10). These categories enabled us to examine whether the association was linear across the categories or whether there was any evidence of a threshold or nonlinear effect. We then examined the association with birth weight entered as a continuous gestational age-standardized *z* score. This enabled us to examine the linear association of intrauterine growth with depressive symptoms. The participant's intrauterine growth rate was estimated by calculating internally standardized sex and gestational age *z* (standard deviation) scores, by subtracting the mean birth weight for all other cohort participants with the same gestational age and of the same sex from the actual birth weight of the participant and dividing by the standard deviation of the sex- and gestational age-specific means. Means and standard deviations of birth weight were calculated for participants by sex and gestational age (in weeks) categories.

We fitted a series of multivariable regression models to examine the effect of potential confounders. After examining the crude association, we first adjusted for gestational age (in weeks) in the analyses using birth weight categories (but not that with gestational age-standardized *z* scores). Subsequent models adjusted for the following: maternal age (three-level categorical variable), education (three-level categorical variable), marital status (three-level categorical variable), and ethnicity (three-level categorical variable); maternal smoking (three-level categorical variable); maternal alcohol consumption (three-level categorical variable); maternal anxiety in pregnancy (binary); and maternal depression in pregnancy (binary). All of the multivariable regression models were fitted on a restricted sample of 3,493 youth with complete data available for all covariates included in any model. Statistical evidence for a difference in effect between males and females was assessed by computing a likelihood ratio test of the interaction term with sex. In the main analyses, we adjusted for the potential confounding effect of maternal smoking, alcohol consumption, and symptoms of depression and anxiety during early pregnancy. There was a strong correlation between these measurements in early pregnancy and corresponding assessments of anxiety and depression measured

around the time of birth and at 6 months; if all were included in the same model, there was evidence of collinearity. We therefore repeated all of our main analyses, replacing the maternal factors measured in early pregnancy with those measured around the time of birth (in one set of repeat analyses) and at 6 months' follow-up (in a second set of repeat analyses). The results from these two sets of repeated analyses did not differ from our main analyses presented here. Finally, we generated a variable that was coded 1 if a mother scored four or more on the DSSI at any time (early pregnancy or birth or 6 months) and 0 if she never scored four or more on these assessments. When we adjusted for this variable in the analyses, we found no attenuation of the association, and results were essentially the same as those presented here where we adjust for depression/anxiety symptoms in early pregnancy.

Dealing with loss to follow-up

Because of loss to follow-up and hence missing data on the outcome variable, the main analyses were conducted on 53 percent of the original birth cohort. Participants lost to follow-up were more likely to weigh 2.50 kg or less, to be males, and to be of Asian and Aboriginal/Torres Strait Islander background (for all: $p < 0.001$). Their mothers were more likely to be teenagers, less educated, and single or cohabiting; to have three or more children; to use tobacco and alcohol during pregnancy; and to be anxious and depressed at their first antenatal visit (for all: $p < 0.001$).

To determine whether this affected the validity of our findings, we undertook a weighted analysis using inverse probability (of having missing outcome data) weights (25, 26). The probability weights were computed by using a logistic regression model with the outcome being depression data or not. The influence of all other covariates used in our primary analyses on having depression data or not was assessed in combination in a logistic regression model. The regression coefficients from this model were then used to determine probability weights for the covariates in the main analyses. For example, if we found the probability of nonresponse for a mother who was depressed to be 0.65, then a weighting of 1.54 for all mothers with depression was entered into the main analyses. We then compared the results from the weighted and unweighted analyses. The results from the inverse probability weighted analyses did not differ from the unweighted analyses presented here, suggesting that our results were not substantively affected by selection bias due to loss to follow-up. All analyses were conducted using STATA, version 8, software (StataCorp LP, College Station, Texas).

RESULTS

Table 1 shows the univariable associations of birth weight with depressive symptoms and potential confounding factors. Birth weight was inversely associated with depressive symptoms, but there was no association between prematurity and depression. Maternal symptoms of anxiety and depression were also both importantly associated with offspring's depressive symptoms in these univariable analyses. Young people with current depressive symptoms at the 21-year follow-up were also more likely to be female, and their mothers were more likely to have been cohabiting or single rather than married at baseline and to have smoked during their pregnancy.

TABLE 1. Univariable associations of birth weight and potential confounding factors with depressive symptoms at age 21 years in 2002–2005, Mater University Study of Pregnancy (*n* = 3,493)[*]

	Sample size (no.)	Depressed at age 21 years			
		%	*p* value	Odds ratio	95% confidence interval (unadjusted)
Birth weight (kg)					
>3.50	1,433	21.6		1	
3.01–3.50	1,351	24.4		1.17	0.98, 1.39
2.51–3.00	569	26.1		1.28	1.02, 1.60
≤2.50	140	30.0	0.04	1.52	1.03, 2.23
Gender					
Male	1,651	18.5		1	
Female	1,842	28.5	0.02	1.76	1.50, 2.06
Gestation					
Normal	3,163	23.93		1	
Preterm	330	24.44	0.9	0.99	0.79, 1.29
Maternal education					
Post-high school	712	22.4		1	
Complete high school	2,249	23.2		1.05	0.86, 1.28
Incomplete high school	532	27.8	0.05	1.34	1.03, 1.73
Maternal age (years)					
≥35	161	25.6		1	
20–34	2,866	23.2		0.88	0.61, 1.26
13–19	466	26.5	0.3	1.04	0.69, 1.57
Maternal marital status					
Married	2,857	22.8		1	
Cohabiting	307	22.8		1.00	0.76, 1.32
Single	329	32.7	0.001	1.65	1.29, 2.10
Maternal smoking in pregnancy					
Nonsmoker	2,327	22.3		1	
Smoker	931	25.9		1.22	1.02, 1.45
Heavy smoker	239	29.3	0.01	1.44	1.07, 1.93
Maternal alcohol use in pregnancy					
Nondrinker	1,588	24.1		1	
Light drinker	1,674	23.2		0.95	0.81, 1.11
≥1 drink per day	131	27.5	0.3	1.51	0.81, 2.82
Parity (previous births)					
None	1,446	22.2		1	
1 or 2	1,698	25.2		1.18	1.00, 1.40
≥3	349	23.0	0.1	1.05	0.79, 1.39
Maternal anxiety in pregnancy					
Nonanxious	3,144	22.7		1	
Anxious	349	33.5	0.001	1.72	1.36, 2.18
Race					
Caucasian	3,234	23.5		1	
Asian	125	26.0		1.14	0.76, 1.72
Aboriginal and Torres Strait Islander	134	28.4	0.4	1.29	0.88, 1.90
Maternal depression in pregnancy					
Nondepressed	3,354	23.3		1	
Depressed	139	34.5	0.002	1.74	1.21, 2.49

[*] Depressive symptoms are defined as Center for Epidemiologic Studies Depression scores of greater than 16.

Table 2 shows the multivariable associations between birth weight and current symptoms of depression (CES-D score of 16 or more) at the age of 21 years. Among females, there was a strong graded inverse association with birth weight, which persisted with adjustment for all potential confounding factors. In the fully adjusted model, the odds ratio for depression for a 1-standard deviation increase in birth weight (gestational age-standardized *z* score) was 0.82 (95 percent confidence interval (CI): 0.73, 0.92) among females. Among males, there was no association between birth weight and depression (for sex in all models: $p_{\text{interaction}} < 0.004$). When we repeated our analyses with more stringent criteria for defining a case with greater symptoms (CES-D score of 25 or more), we found a similar inverse association between birth weight

and this outcome in women (for a 1-standard deviation increase in birth weight: odds ratio = 0.87, 95 percent CI: 0.75, 1.02 in the fully adjusted model), although the association was less precisely estimated because of fewer participants' having this higher score. Among men, there appeared to be a positive association between birth weight and greater symptoms of depression (odds ratio = 1.22, 95 percent CI: 0.96, 1.53) (for interaction with sex: $p = 0.048$). Moreover, the results using the CES-D score as a continuous outcome were consistent with those presented in the table. Among women, the fully adjusted mean difference in CES-D score per standard deviation increase in birth weight was –0.51 (95 percent CI: –0.97, –0.063) and, among men, it was 0.16 (95 percent CI: –0.24, 0.56), with statistical evidence of a sex difference ($p_{interaction} = 0.045$). Finally, when we compared those in the 16–24 and those in the 25–57 score groups with the 0–15 score group, we found that in the fully adjusted model the odds ratio for a 1-standard deviation increase in birth weight (gestational age-standardized *z* score) was 0.81 (95 percent CI: 0.71, 0.93) for the 16–24 score symptoms and 0.84 (95 percent CI: 0.71, 0.99) for those in the 25–57 score groups (in females). Among those in the lowest birth weight category (2.50 kg or less), the odds ratio of more severe symptoms was 2.22 (95 percent CI: 1.05, 4.71), and that of milder symptoms was 2.04 (95 percent CI: 1.07, 3.92), when each of these was compared with the 0–15 score group.

TABLE 2. Associations between birth weight and depressive symptoms at age 21 years in 2002–2005, Mater University Study of Pregnancy (*n* = 3,493)*

Birth weight (kg)	Sample size (no.)	Unadjusted		Model 1†		Model 2‡		Model 3§		Model 4¶		Model 5#		Model 6**	
		Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Overall sample (n = 3,493)															
>3.50	1,433	1		1		1		1		1		1		1	
3.01–3.50	1,351	1.17	0.98, 1.39	1.19	1.00, 1.43	1.14	0.95, 1.37	1.12	0.93, 1.35	1.12	0.93, 1.35	1.12	0.93, 1.35	1.12	0.93, 1.35
2.51–3.00	571	1.28	1.02, 1.60	1.35	1.07, 1.72	1.26	0.99, 1.61	1.22	0.96, 1.56	1.22	0.95, 1.55	1.22	0.95, 1.56	1.22	0.95, 1.56
≤2.50	142	1.52	1.04, 2.23	1.69	1.13, 2.52	1.63	1.08, 2.46	1.58	1.05, 2.39	1.58	1.05, 2.39	1.55	1.02, 2.34	1.55	1.03, 2.35
Risk of depression with birth weight *z* score				0.91	0.84, 0.99	0.9	0.83, 0.98	0.91	0.83, 0.99	0.91	0.83, 0.99	0.91	0.83, 0.99	0.91	0.83, 0.99
Males (n = 1,651)															
>3.50	752	1		1		1		1		1		1		1	
3.01–3.50	594	0.88	0.67, 1.17	0.9	0.67, 1.19	0.9	0.68, 1.20	0.89	0.67, 1.19	0.89	0.67, 1.19	0.89	0.67, 1.20	0.89	0.67, 1.20
2.51–3.00	238	0.95	0.65, 1.38	0.98	0.66, 1.46	0.98	0.66, 1.46	0.97	0.64, 1.45	0.95	0.63, 1.42	0.95	0.63, 1.42	0.95	0.63, 1.42
≤2.50	67	0.99	0.53, 1.86	1.06	0.54, 2.05	1.09	0.56, 2.12	1.07	0.55, 2.10	1.06	0.54, 2.09	1.05	0.54, 2.09	1.06	0.54, 2.09
Risk of depression with birth weight *z* score				1.03	0.91, 1.18	1.03	0.91, 1.18	1.03	0.90, 1.18	1.04	0.91, 1.19	1.04	0.91, 1.19	1.04	0.91, 1.19
Females (n = 1,842)															
>3.50	681	1		1		1		1		1		1		1	
3.01–3.50	757	1.33	1.05, 1.68	1.34	1.06, 1.70	1.36	1.07, 1.73	1.33	1.05, 1.70	1.35	1.06, 1.72	1.35	1.06, 1.72	1.35	1.06, 1.72
2.51–3.00	331	1.44	1.08, 1.93	1.49	1.10, 2.02	1.54	1.13, 2.10	1.47	1.07, 2.01	1.48	1.08, 2.02	1.47	1.07, 2.02	1.47	1.07, 2.02
≤2.50	73	2.01	1.22, 3.31	2.15	1.27, 3.63	2.23	1.30, 3.82	2.16	1.26, 3.71	2.16	1.26, 3.71	2.05	1.20, 3.55	2.07	1.20, 3.56
Risk of depression with birth weight *z* score				0.83	0.74, 0.93	0.81	0.73, 0.91	0.83	0.74, 0.92	0.83	0.74, 0.93	0.82	0.73, 0.92	0.82	0.73, 0.92

* Depressive symptoms are defined as Center for Epidemiologic Studies Depression scores of greater than 15.
† Model 1: adjusted for gestational age. When the main exposure variable was gestational age, the standardized *z* score was not adjusted for gestational age since the birth weight exposure variable was standardized for this.
‡ Model 2: as model 1 and, in addition, adjusted for maternal age at birth, maternal education, marital status, and ethnic background.
§ Model 3: as model 2 and, in addition, adjusted for maternal smoking in pregnancy.
¶ Model 4: as model 3 and, in addition, adjusted for maternal drinking in pregnancy.
# Model 5: as model 4 and, in addition, adjusted for maternal anxiety in pregnancy.
** Model 6: as model 5 and, in addition, adjusted for maternal depression in pregnancy.

DISCUSSION

This study aimed to further explore emerging evidence of a relation between fetal growth and depression in early adulthood, with particular attention to whether maternal symptoms of mental health problems during pregnancy confounded the effect of low birth weight standardized for gestational age (a proxy indicator for

poor intrauterine growth) on offspring's current depressive symptoms in early adulthood. We have found a graded inverse association between birth weight and depressive symptoms at age 21 years among females but not males. This association persisted with adjustment for a range of potential confounding factors, including maternal depressive and anxiety symptoms, smoking, and alcohol consumption during pregnancy. Our findings thus provide some support for a fetal origin of adult psychological distress.

Study strengths and limitations

An important strength of our study is that it is the first to be able to assess the impact of the maternal symptoms of anxiety and depression during pregnancy on the association between birth weight and depressive symptoms. We had repeated assessments of these symptoms in the mother, taken in early pregnancy and around the time of birth of the study child and when the infant was 6 months of age and, whichever of these repeated measures (which were highly correlated) was entered individually in the regression models or when a composite of all three was entered, the association between birth weight and depressive symptoms in females remained. The main limitation of our study is loss to follow-up, with those who completed the 21-year assessment being different for several of our explanatory factors compared with those who did not attend. However, when we took this into account using inverse probability weights, we found that the results were essentially unaltered from those presented, suggesting that the associations we have demonstrated are not explained by selection bias resulting from loss to follow-up. We used a well-validated depression scale as our outcome measure although the CES-D Scale is not a clinical diagnosis of depression, and some investigators have argued that this scale is more accurately described as representing more general psychological distress than specific depressive symptoms (18, 27). In addition, the CES-D Scale measures current depressive symptoms and may not be sensitive to detecting clinical cases who may have been under medication and, thus, asymptomatic at the time of the interview. On the other hand, as a standardized assessment across all participants, the CES-D Scale has the advantage of identifying all individuals reporting symptoms of depression, some of whom might otherwise be labeled as nondepressed. Other studies, using a variety of validated scales of depression and/or psychological distress, have reported linear inverse associations between birth weight and these outcomes (7–11). This is consistent with our findings that remained robust to changes when we used the score as a continuous outcome and when we compared women with scores of 16 or more and 25 or more with women with scores of less than 16. Taken together, this body of evidence suggests that birth weight is inversely associated with symptoms of depression.

Possible mechanisms for the association

The association between birth weight and later depression may be explained by residual confounding. In this study, we have been able to adjust for repeated assessments of maternal symptoms of depression/anxiety, smoking, alcohol consumption during pregnancy, and socioeconomic position and found that these have very little impact on the association. These findings are consistent with those of other studies, where adjustment for tobacco use and alcohol use in pregnancy (8–10), as well as socioeconomic position (6, 10, 11, 13, 28), did not appear to explain the association. Genetic variants that affect both fetal growth and later risk of depression might explain the link between birth weight and later depression. Although we cannot directly assess this in MUSP, to some extent any genetic variants linking these two would be accounted for by adjustment for maternal depression, and we see no effect on adjustment for this. To our knowledge, no candidate genes linking birth size and depression have been found.

The fetal or developmental origins of adult disease hypothesis suggests that poor fetal nutrition during key periods of development results in permanent changes to the structure of developing organs and/or hormonal systems and that these permanent changes result in increased risk of adult disease outcomes. Changes in the developing neuroendocrine system have been suggested as explaining the association. These include damage to the hypothalamic-pituitary-adrenal axis (6, 10, 11), the growth hormone axis (6, 11), or the thyroid hormone axis (6, 11). These theories are not mutually exclusive and, indeed, the overlap in function of these systems means that they could all be involved. Although there is some evidence for an

association between poor fetal growth and effects on the hypothalamic-pituitary-adrenal axis (29), there is limited direct evidence that these hormonal pathways are responsible for the association between low birth weight for gestational age and psychological distress in adulthood. There is evidence of an inverse association between birth weight and insulin resistance and diabetes in adulthood, and insulin resistance and diabetes may be related to depression (30). However, the direction and nature of the association between insulin resistance and depression are unclear (30–32), and again there is no direct evidence that the pathway between poor fetal growth and adult psychological distress involves insulin resistance. A direct effect of intrauterine growth on neurocognitive development is implicated by the association in several studies of birth weight with childhood intelligence, but a recent study found that adjustment for the childhood intelligence quotient and behavioral problems had very little impact on the association between birth weight and adult depressive symptoms (11).

Although our work adds to previous work in this area by demonstrating that the association between an indicator of poor fetal growth and future depressive symptoms is not explained by maternal symptoms of depression or anxiety during pregnancy, we are unable to determine the specific mechanisms linking poor fetal growth to future mental health problems. Further research in studies with detailed and repeated measurements of markers for these different hormonal pathways is required to determine the underlying mechanisms.

Sex differences in the association

With development of the fetal origins hypothesis, it has been suggested that the investigation of sex differences in associations is important (33). Male and female fetuses have different growth trajectories and some differences in the timing of organ development (33). Thus, one might expect sex differences in the associations of some prenatal exposures with adult diseases. On the other hand, all subgroup analyses should be treated with some caution, and there is evidence that investigators tend to report results by sex when the overall results are null or weak (34). In the area of research assessing the association between birth weight and adult psychological distress, there have been conflicting results, with most studies not reporting a sex difference (8, 9), one suggesting a stronger effect in females compared with males (10), and two with a stronger effect in males compared with females (6, 11). These reports of sex differences have not always been supported by statistical evidence. We found an effect only in females, with statistical evidence of a sex difference. The inconsistencies in sex differences across studies may be because the reported differences are due to chance, or they may reflect differences in the ways that males and females respond to different questionnaires of psychological symptoms and, hence, sex differences in the levels of measurements for some of the different scales used in each study. The risk of current depressive symptoms was greater in women than men in our study, consistent with evidence from other studies showing depression to be more common in females than males in early adulthood (35), and it is possible that in this age group the small number of men with depressive symptoms makes it difficult to detect an association. Further research is required that establishes whether there are true sex differences in the rate and timing of the development of the neuroendocrine pathways that might underlie this association.

Conclusions and implications

Consistent with several previous studies, this study found an inverse association between birth weight for gestational age and current depressive symptoms in early adults. There was some evidence that the association was present only in females. Unlike previous studies, this study was able to assess whether this association was importantly confounded by maternal factors, such as depressive symptoms during pregnancy, and we found that it was not. Thus, our results provide some support for the theory of a fetal origin of adult depression. Further research is required to understand the biologic mechanisms responsible for this association.

ACKNOWLEDGEMENTS

The study has been funded primarily by the National Health and Medical Research Council (NHMRC), Queensland Health, Queensland Treasury, the Centre for Accident Research and Road Safety—Queensland, the Australian Institute of Criminology, and the Telstra Foundation. R A. is funded by a NHMRC Public Health Fellowship (grant 301298). A. A. M. is funded by NHMRC Capacity Building (grant 252834). D. A. L. is funded by a Department of Health Career Scientist Award from the United Kingdom.

The authors thank the MUSP Team, the Mater Misericordiae Hospital, and the Schools of Social Science, Population Health, and Medicine, University of Queensland, for their support. Special thanks go to the MUSP 21-Year Follow-up Team who collected the 21-year follow-up data: Rosemary Aird, Stacey Allerton, Ruth Armstrong, Samantha Batchelor, Pauline Bonnici, Rachael Bor, Emma Brown, Justine Butcher, Fiona Cameron, Narelle Constantine, Sophie Gudgeon, Jatinder Kaur, Jane Maclean, Amanda Margerison, Kobie Mulligan, Kelly Quinlan, Marie Seeman, and Jennifer Winn.

The views expressed in this paper are those of the authors and not necessarily those of any funding body.

Conflict of interest: none declared.

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