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Fetal growth and the lifetime risk of generalized anxiety disorder

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Abstract

Background—Anxiety disorders are thought to have their origins in early childhood, though they have not yet been studied as a potential outcome of impaired fetal growth, which has been implicated in the developmental etiologies of many psychopathologies. This study investigated the association between indicators of fetal growth and the development of generalized anxiety disorder (GAD).

Methods—Indicators of fetal growth, including birth weight (BW) and ponderal index (PI), were assessed among 682 offspring of participants in the Providence, RI, site of the Collaborative Perinatal Project. Participants were interviewed as adults, and their lifetime histories of GAD were assessed using the Diagnostic Interview Schedule. We used Cox regression to estimate the association between fetal growth indicators and the development of GAD.

Results—The lifetime risk of GAD differed between infants in the highest category of BW and PI and all others. Newborns with birth weights below 3.5 kg (hazard ratio, HR: 2.38; CI=1.25, 4.55), in the lowest four BW z-score quintiles (HR=2.49; CI=1.14, 5.45) or a PI in the lowest four quintiles (HR=2.33; CI=1.04, 5.00) had higher lifetime risks of GAD.

Conclusion—In contrast to prior studies on psychiatric outcomes in relation to fetal growth, there was not a linear relationship between birth weight and GAD. While these results generally support the hypothesis that a healthy nutritional fetal uptake, as indicated by BW and PI, is associated with better lifetime mental health, further work is needed to characterize the nature of the association between fetal growth and subsequent psychopathology.

Keywords

generalized anxiety disorder; birth weight; gestational age; ponderal index

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INTRODUCTION

Compelling evidence suggests that depression is, in part, a neurodevelopmental disorder. Results from the Dutch hunger winter studies demonstrated elevated risks for depression among adults exposed to maternal famine prenatally, suggesting adverse psychiatric consequences of fetal growth restriction [1,2]. Results of long-term follow-up studies of established birth cohorts demonstrate associations between low birth weight and adult affective illness [3–11] as well as between maternal infection during pregnancy and adult affective illness [12]. Deficits in early childhood cognitive development also suggest the importance of neurodevelopment in the etiology of depression [13,14].

Despite this supporting evidence [3–11], not all studies have reported a link between indicators of fetal growth restriction and the development of depression [15–18]. Inconsistent findings across studies may suggest that the neurodevelopmental pathways to psychopathology are not diagnostically specific, but instead represent a more generalized vulnerability. The objective of the current study is therefore to investigate the association between multiple indicators of fetal growth restriction and the lifetime risk of Generalized Anxiety Disorder (GAD).

We focus on GAD as a potential outcome of fetal growth restriction for three reasons. First, epidemiologic evidence demonstrates a high degree of comorbidity between depression and GAD [19,20]. The comorbidity between depression and GAD may be due in part to a shared vulnerability to both disorders [21], as well as to the overlap that exists in the conceptualization of diagnostic criteria for both disorders [22–24]. Second, adverse prenatal experiences have been hypothesized to influence lifelong patterns of activation of the hypothalamic-pituitary-adrenal (HPA) axis [25,26], which is thought to be involved in the etiology of both depression and anxiety disorders. However, there appear to be different patterns of activation of the HPA axis between anxiety and depression, suggesting that there are also distinct neurobiological pathways involved in each condition. In major depression, the dysregulation of the HPA axis is due to a hypersecretion of cortisol [27–32]. In GAD, the activation of the HPA axis is less influenced by cortisol [33] and it is thought that HPA activation is due to a decrease in inhibitory signaling of GABA or the increased excitatory neurotransmission of glutamate [27]. Third, we are unaware of studies on the adverse psychiatric consequences of fetal growth restriction that have focused specifically on GAD or other anxiety disorders more broadly. We therefore seek to extend the knowledge base on the fetal origins of psychopathology by examining whether birth weight and ponderal index, two indirect indicators of fetal growth, are associated with the lifetime risk of GAD.

METHODS

Study participants

The current investigation is based on a long-term follow-up study of adults who were offspring of participants in the Providence, Rhode Island cohort of the Collaborative Perinatal Project (CPP), which enrolled over 53,000 pregnant women between 1959 and 1966 at 12 U.S. academic medical centers. Women were enrolled during pregnancy and followed during labor and delivery. Information was collected on women's past reproductive and gynecological history, past and recent medical history, socioeconomic status as well as medical family history. During labor and delivery an obstetric summary and delivery report was filled out by a trained observer. Examination of the neonate included anthropometric measurements, from which measures of birth size were constructed. Informed consent was obtained from all participants. Details on the CPP study design and methodology have been described previously [34,35].

The Providence, Rhode Island site enrolled 4,140 pregnancies. Of the 4,184 resulting births, a stratified random sample of offspring with Full Scale IQ $\geq$ 80 with and without learning disabilities (n=1,062), was selected in 1996 for participation in a study of the relation between childhood learning disabilities and adult psychiatric outcomes [36]. Of the 1,015 surviving cohort members (47 had died), 720 (70.9%) respondents were successfully located and interviewed. As reported by Martin et al., the interviewed and non-interviewed samples were similar with respect to childhood socioeconomic status and race/ethnicity, though a somewhat higher proportion of the interviewed sample was female [36]. In total, 682 subjects had complete information on all study variables and comprised the analytic sample for the current study. No significant differences were observed for respondents with complete versus missing information with regards to the following: female sex (38.7% among those with no missing data vs 39.5% among those with missing data); white race (76.4% vs 89.5%); GAD cases (10.7% vs 15.8%); preterm birth (14.1% vs 15.8%); low birth weight (9.2% vs 15.8%), small for gestational age (10.4%, 7.9%).

Measures

Fetal growth—We constructed measures of fetal growth using information on birth weight, birth length, and gestational age that was collected by CPP study personnel. We analyzed birth weight (in kilograms) as a 4 category variable (<2.5, 2.5–3.0, >3.0–3.5, >3.5) and as a dichotomous variable ($\leq$ 3.5 vs >3.5, corresponding to the median birth weight for U.S. singleton, full-term births). We also calculated birth weight Z-scores, standardized for sex and gestational age in the analytic sample, which was then split into quintiles and analyzed as an ordinal variable as well as a dichotomous variable (quintiles 1–4 vs. quintile 5). We categorized gestational age, measured by weeks from date of last menstrual period, as either preterm ($\leq$ 37 weeks [37,38]), term (38–41 weeks), or post-term ($\geq$ 42 weeks [39]). We created a measure of birth weight relative to gestational age, defined as either small (<10th percentile), appropriate (10th through 90th percentile), or large (>90th percentile). This was based on the sex, race, and gestational age-specific birth weight distribution of the full Providence CPP cohort. Finally, we computed the ponderal index, an indicator of thinness calculated as birth weight (kg) divided by birth length (m) cubed. We analyzed ponderal index as a 5 category variable (in quintiles) and as a dichotomous variable (quintiles 1–4 vs. quintile 5).

Generalized Anxiety Disorder—Lifetime diagnosis of GAD according to DSM-IV criteria [40] was determined using the Diagnostic Interview Schedule (DIS) [41]. The inter-rater (kappa=0.67) and test-retest (kappa=0.65) reliabilities of a DIS diagnosis of GAD are good [42–45]. Self-reported ages of onset of GAD have also been shown to have good reliability and validity when compared to clinical records [46].

Data analyses

We investigated the associations of multiple measures of fetal growth with the lifetime risk of GAD using Cox proportional hazards regression [47]. The dependent variable in these analyses was the self-reported age of onset of GAD; individuals who did not meet lifetime diagnostic criteria for GAD were censored at the age of adult interview.

Covariates in adjusted models included maternal factors at subjects' birth: age, marital status (single, either divorced/separated/widowed, or married/common law), self-reported history of treated mental illness (yes/no), and employment status (never worked, worked); and offspring sex, race (white vs. other) and age at interview. We also adjusted for potential learning disability at age 7 [36], which was used in the selection algorithm for participation in the adult re-interview study. The models were fitted for each measure of fetal growth separately. Sex specific analyses were also carried out to determine if there was a difference

in estimates of effect. The interactions between the different fetal growth parameters and sex were also tested. Additional sensitivity analyses were carried out in which subjects who had reported a major depressive episode prior to GAD onset were censored at age of onset of depression [40,41]. Analyses were carried out using the SAS statistical software version 9.1 (SAS Institute, Inc, Cary, NC, 2002–2003).

RESULTS

The characteristics of the study sample (n=682) are presented in Table 1. The sample was predominantly male (61.3%) and White (76.4%). The mean (SD) age of the sample was 33.3 (2.5) years. The lifetime prevalence of GAD was 10.7% (n=73). Among lifetime cases of GAD, 37% reported an onset by 15 years of age; 58% reported an onset by 21 years of age; 85% reported an onset by 28 years of age. There was a statistically significant difference in the lifetime risk of GAD across categories of two of the three measures of fetal growth (birth weight category and ponderal index category; Table 1). In each case, the heaviest-born infants had the lowest lifetime risks of GAD as adults.

Results of survival analyses of the lifetime risk of GAD are presented in Table 2. The unadjusted and adjusted hazard ratios demonstrate a significantly elevated risk of GAD among adults born lighter relative to adults in the heaviest and thinnest categories of birth weight and ponderal index, respectively. The results for birth weight are shown using two specifications. In the first specification which used four birth weight categories, GAD risk among adults born below 3.5 kg was approximately twice as high compared to adults born 3.5 or more kg (adjusted hazard ratios between 2.12–2.62 in the three lower categories of birth weight). When birth weight was dichotomized at 3.5 kg, the hazard ratio (HR) for GAD for the lighter born infants was 2.38 (CI=1.25, 4.55). A similar set of analyses was conducted for ponderal index. As with birth weight, lower ponderal index was associated with a higher risk of GAD. In the adjusted model, the hazard ratios for the lowest and fourth ponderal index quintiles were significantly different from the highest quintile (HR=3.40; CI=1.42, 8.15 and HR=2.59; CI=1.06, 6.30, respectively). The adjusted hazard ratio for the lower four quintiles vs. the highest ponderal index quintile indicates the magnitude of the difference between the highest vs. other quintiles (HR=2.33; CI=1.04, 5.00). Analyses stratified by sex revealed that the associations of birth weight and ponderal index with GAD were somewhat stronger among females than males. The only sex difference supported by a statistically significant interaction was for gestational age, indicating an increased risk of GAD among males born ≤ 37 weeks vs. males born 38–41 weeks (HR=4.66; CI=2.16, 10.04) but not among females (interaction between sex and preterm birth, $P=0.04$).

We conducted a sensitivity analyses in which person-time from individuals with a lifetime diagnosis of depression was censored at the age of depression onset, thereby removing cases of GAD that occurred subsequent to the diagnosis of depression. The results were essentially unchanged. In these analyses, the adjusted hazard ratio for GAD for birth weights below 3.5 kg vs. heavier born adults was 2.78 HR (CI= 1.23, 6.25), and for the lowest four ponderal index quintiles vs. the highest ponderal index quintile was 4.00 HR (CI=1.22 – 12.50). Also, further analyses of birth weight and ponderal index restricted to term births only yielded results that were similar to those observed in Table 2 for the full sample.

DISCUSSION

This is one of the first studies of the fetal origins of GAD assessed according to diagnostic criteria. We found that offspring born at higher birth weights (>3.5 kg and highest z-score quintile standardized for sex and gestational age) and ponderal index were at decreased risk for developing GAD adjusting for multiple potential confounding variables. In contrast,

males who were born preterm were at significantly increased risk for the development of GAD. Prior studies that are most similar to ours have focused on anxiety symptoms rather than a diagnosis of GAD. The first, based on a birth registry in Norway, investigated the association between fetal growth and symptoms of anxiety according to the Hospital Anxiety and Depression Rating Scale (HADS) [8], and found an association between being born small for gestational age at term and symptoms of anxiety/depression in adults aged between 20 and 30 years. A more recent study, based on an Australian birth cohort followed up to 14 years of age, showed that the young adolescents born in the lowest and highest birth weight z-score (standardized for sex and gestational age) quintiles had an increased risk of reporting symptoms of anxiety/depression and social problems [11].

Our results support the hypothesis that lower birth weight, an indirect indicator of fetal growth restriction, is a risk factor for multiple types of psychopathology. The nature of the association between the various measures derived from birth weight and adult psychopathology varies across studies, however. Thompson et al. reported higher risks of late life depression among males born in the lower birth weight categories than males born >3.9 kg, suggesting, as in our findings, that the heaviest babies were protected against psychopathology [4]. Alati et al. reported an association between lower birth weight and the depressive symptoms in early adulthood (age 21), although their results suggested a dose-response relationship between birth weight and depression that was only present among females [9]. Costello et al. also reported an association between birth weight and depression only among females during adolescence [10]. In the current study, lower birth weight and ponderal index were associated with an increased risk of GAD in the sample overall, though gender-specific analyses were consistent with somewhat stronger associations among females. We did not find any differences in the timing of GAD onset with respect to indicators of fetal growth (results not shown). The issue of gender and developmental differences in the fetal origins of mental disorders requires further work to resolve these inconsistencies across studies.

While a general pattern exists across studies that lower birth weights are associated with higher risks of psychiatric symptoms or disorders, it remains unclear whether there is an absolute threshold below which the risk for later psychopathology is increased, or whether there is a trend of decreasing risk of psychopathology with increasing birth weight. It is also important to note again that while several studies have reported an association between birth weight and psychopathology [3,5,6], others have not [15–18], and still others have found the associations only in one sex [7,8,10]. A previous study with the current sample found no association between birth weight, gestational age, born small for gestational age or ponderal index and a diagnosis of depression based on DSM criteria [18].

There are meaningful differences in aspects of study design that may partially account for the differences in findings across studies in the association between indicators of fetal growth and subsequent psychopathology. For example, some studies relied on symptom-based measures of depression or anxiety, whereas others focused on clinically defined syndromes. Our finding of an association between birth weight and GAD but not depression in this sample [18] highlights the importance of differentiating risks for multiple psychopathological outcomes. In addition, while our prior study on depression [18] and the current study on GAD controlled for the same set of potential confounders, the control variables that prior studies included differed across studies. Potential confounders of the association between indicators of fetal growth and later psychopathology should include factors that are suspected prior common causes of adverse pregnancy outcomes and of psychopathology. At a minimum, this would include social factors such as indicators of parental socioeconomic status, and clinical factors, such as a family history of psychopathology. While we controlled for socioeconomic status, there were other potential

confounding variables that were not measured in our study such as environmental adversities including exposure to violent neighborhoods, marital conflict, and maltreatment [48–50]. We controlled for the mother's past treatment of mental illness in order to account for the possibility that mothers who have anxiety during pregnancy are more prone to give birth to small babies [51], lead to lower cognitive abilities in adolescents [52] and that parental history of mental illness may be passed to the offspring and increase vulnerability to anxiety disorders [48,53–55]. A limitation of our measure of history of mental illness, however, is that it was based on the participants' reports of "nervous" problems that required hospitalization or psychiatric treatment. Therefore, this measure is not specific to GAD, may be subject to recall bias, and does not reflect the presence of untreated mental illness. Our results may therefore overstate the causal effects of fetal growth on GAD due to unmeasured confounding or to the imprecise measurement of potential confounders. Other limitations of our study include the selection of participants at a single site and period of time, which may not be representative of individuals born in other areas, and the lifetime assessment of GAD based on retrospective reports of symptoms.

The hypothesized mechanisms underlying the association between indicators of fetal growth and the development of psychopathology involve deficits in neurodevelopment due to reduced blood flow to the fetus and nutritional deficiency which are suspected to have a long-term impact on brain circuitry, specifically involving the HPA axis [25,26]. Dysregulation of the HPA axis is thought to increase vulnerability to mood and anxiety disorders [56–58] via heightened neurobiological responses to environmental stressors [59]. It remains important for future studies to investigate the importance of the timing of intrauterine stress or nutritional deficiency during gestation, as well as to obtain more direct measures of fetal growth than birth weight.

The results of this study demonstrate that a heavier birth weight and a higher ponderal index are protective against the future development of GAD, supporting the hypothesis that healthy nutritional fetal uptake and neuroregulatory functions contribute to better psychiatric outcomes. However, the associations we observed between birth weight and adult GAD were not characterized by an adverse effect of low birth weight, but rather a higher risk of GAD even among infants born at a "normal" birth weight relative to those born in the highest birth weight category. We speculate that understanding the etiologic mechanisms underlying our results, as well as the clinical implications of them, will necessitate research that examines the entire range of the birth weight distribution in relation to subsequent developmental and psychiatric outcomes, rather than focusing solely on the distinction between low birth weight and normal birth weight [60]. Moving beyond birth weight [61], work is needed to understand the developmental processes during gestation, early infancy, and in childhood that can explain the associations between indicators of fetal growth and adult disease that have been reported in epidemiologic studies; the clinical and public health implications of this work will be the identification of children with an elevated risk for future illness, and the identification of protective factors that can mitigate the adverse consequences of early life adversity.

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Table 1

Characteristics of Providence, Rhode Island CPP offspring in the adult follow-up sample (n=682), and the lifetime risk of generalized anxiety disorder (GAD) according to anthropomorphic characteristics at birth.

	Sample distribution		Participants with a lifetime diagnosis of GAD (N=73)	
	N	%	N	%
* Sex	Male	418	34	8.1%
	Female	264	39	14.7%
Race	White	521	61	11.7%
	Black/Other	161	12	7.5%
Gestational age	≤37 weeks	96	14	14.6%
	38–41 weeks	446	40	9.0%
	≥ 42 weeks	140	19	13.6%
* Birth weight (4 categories)	< 2.5 kg	63	9	14.3%
	2.5 – < 3.0 kg	156	19	12.2%
	3.0 kg – 3.5 kg	249	33	13.3%
	≥ 3.5 kg	214	12	5.6%
Birth weight Z-scores (Quintiles)	Q1 (0–20%)	134	15	11.2%
	Q2 (20–40%)	137	15	11.0%
	Q3 (40–60%)	139	21	15.1%
	Q4 (60–80%)	136	15	11.0%
	Q5 (80–100%)	136	7	5.2%
* Ponderal Index (Quintiles)	Q1 (0–20%)	134	22	16.4%
	Q2 (20–40%)	135	15	11.1%
	Q3 (40–60%)	136	10	7.4%
	Q4 (60–80%)	135	17	12.6%
	Q5 (80–100%)	135	7	5.2%
Size for gestational age	Small for GA (BW <10 th percentile)	73	7	9.6%
	Appropriate GA	541	63	11.7%

	Sample distribution		Participants with a lifetime diagnosis of GAD (N=73)	
	N	%	N	%
Large GA (BW > 90 th percentile)	68	10.0%	3	4.4%

* P < 0.05, tests for the difference in proportion of individuals with GAD.

Table 2

Results of survival analyses of the lifetime risk of generalized anxiety disorder according to anthropomorphic characteristics at birth.

	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Birth weight (4 CATEGORIES)		
< 2.5 kg	2.70 (1.14 – 6.42)	2.62 (1.01 – 6.78)
2.5 kg – 3.0 kg	2.23 (1.08 – 4.58)	2.12 (1.01 – 4.45)
>3.0 kg – 3.5 kg	2.43 (1.25 – 4.70)	2.47 (1.26 – 4.81)
> 3.5 kg	REFERENCE	REFERENCE
	$\chi^2_{(3)} = 9.43$; $p = 0.02$	$\chi^2_{(3)} = 8.50$, $p = 0.04$
Birth weight (2 CATEGORIES)		
≤ 3.5 kg	2.38 (1.28 – 4.55)	2.38 (1.25 – 4.55)
> 3.5 kg	REFERENCE	REFERENCE
	$\chi^2_{(1)} = 9.19$; $p = 0.002$	$\chi^2_{(1)} = 8.12$, $p = 0.004$
	Males	Males
≤ 3.5 kg	1.85 (0.83 – 4.00)	1.54 (0.67 – 3.57)
> 3.5 kg	REFERENCE	REFERENCE
	$\chi^2_{(1)} = 2.27$; $p = 0.13$	$\chi^2_{(1)} = 1.01$; $p = 0.32$
	Females	Females
≤ 3.5 kg	2.86 (1.03 – 8.33)	3.85 (1.37 – 11.11)
> 3.5 kg	REFERENCE	REFERENCE
	$\chi^2_{(1)} = 4.03$; $p = 0.04$	$\chi^2_{(1)} = 6.42$; $p = 0.01$
Birth weight Z-Scores (Quintiles)		
Q1	2.23 (0.91 – 5.47)	2.42 (0.98 – 5.96)
Q2	2.18 (0.89 – 5.36)	2.22 (0.90 – 5.47)
Q3	3.08 (1.31 – 7.25)	3.18 (1.34 – 7.52)
Q4	2.17 (0.89 – 5.33)	2.18 (0.88 – 5.39)
Q5	REFERENCE	REFERENCE
	$\chi^2_{(4)} = 7.82$; $p = 0.10$	$\chi^2_{(4)} = 8.27$; $p = 0.08$
Birth weight Z-Scores		
Q1 – Q4	2.42 (1.11 – 5.27)	2.49 (1.14 – 5.45)
Q5	REFERENCE	REFERENCE
	$\chi^2_{(1)} = 6.24$; $p = 0.01$	$\chi^2_{(1)} = 6.63$; $p = 0.01$
	Males	Males
Q1 – Q4	1.91 (0.67 – 5.40)	2.16 (0.76 – 6.20)
Q5	REFERENCE	REFERENCE
	$\chi^2_{(1)} = 1.72$; $p = 0.19$	$\chi^2_{(1)} = 2.49$; $p = 0.11$
	Females	Females
Q1 – Q4	3.08 (1.05 – 9.99)	3.43 (1.04 – 11.23)

	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Q5	REFERENCE $\chi^2_{(1)} = 4.83; p=0.03$	REFERENCE $\chi^2_{(1)} = 5.75; p=0.02$
Ponderal index (Quintiles)		
Q1	3.43 (1.46 – 8.03)	3.40 (1.42 – 8.15)
Q2	2.23 (0.91 – 5.48)	2.17 (0.88 – 5.36)
Q3	1.46 (0.55 – 3.82)	1.37 (0.52 – 3.62)
Q4	2.50 (1.04 – 6.04)	2.59 (1.06 – 6.30)
Q5	REFERENCE $\chi^2_{(4)} = 11.59; p=0.02$	REFERENCE $\chi^2_{(4)} = 11.52; p=0.02$
Ponderal index		
Q1– Q4	2.38 (1.10 – 5.26)	2.33 (1.04 – 5.00)
Q5	REFERENCE $\chi^2_{(1)} = 6.02; p=0.01$	REFERENCE $\chi^2_{(1)} = 5.24; p=0.02$
	Males	Males
Q1– Q4	2.13 (0.75 – 5.88)	1.72 (0.60 – 5.00)
Q5	REFERENCE $\chi^2_{(1)} = 2.01; p = 0.16$	REFERENCE $\chi^2_{(1)} = 1.03; p = 0.31$
	Females	Females
Q1– Q4	2.50 (0.76 – 8.33)	3.03 (0.92 – 10.00)
Q5	REFERENCE $\chi^2_{(1)} = 2.30; p = 0.13$	REFERENCE $\chi^2_{(1)} = 3.33; p = 0.07$
Gestational Age		
≤37 weeks	1.69 (0.92 – 3.10)	1.78 (0.96 – 3.28)
38–41 weeks	REFERENCE	REFERENCE
≥ 42 weeks	1.56 (0.78 – 3.11)	1.33 (0.76 – 2.32)
	$\chi^2_{(2)} = 4.06; p = 0.13$	$\chi^2_{(2)} = 3.45, p= 0.18$
	Males	Males
≤37 weeks	3.98 (1.86 – 8.50)	4.66 (2.16 – 10.04)
38–41 weeks	REFERENCE	REFERENCE
≥ 42 weeks	1.67 (0.68 – 4.08)	1.49 (0.59 – 3.71)
	$\chi^2_{(2)} = 11.35, p=0.003$	$\chi^2_{(2)} = 13.52, p=0.001$
	Females	Females
≤37 weeks	0.37 (0.09 – 1.57)	0.39 (0.09 – 1.67)
38–41 weeks	REFERENCE	REFERENCE
≥ 42 weeks	1.40 (0.70 – 2.79)	1.31 (0.64 – 2.66)
	$\chi^2_{(2)} = 4.03, p=0.13$	$\chi^2_{(2)} = 3.10, p=0.21$
Birth weight for gestational age		
Small for GA	0.82 (0.38 – 1.79)	0.75 (0.34 – 1.66)

	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Appropriate GA	REFERENCE	REFERENCE
Large GA	0.37 (0.12 – 1.17) $\chi^2_{(2)}=4.02$; p=0.13	0.41 (0.13 – 1.33) $\chi^2_{(2)}=3.25$, p=0.20

* Estimates adjusted for: sex, race, gestational age, mother's marital status and age at birth, history of treated mental illness, and employment status at birth, subject's age at interview and the presence of a probable learning disability.

χ^2 statistics correspond to the likelihood ratio of the model; χ^2 statistics for the adjusted variables were derived from the difference between the likelihood ratio of the full and reduced models.