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Fetal and Infancy Growth Pattern, Cord and Early Childhood Plasma Leptin, and Development of Autism Spectrum Disorder in the Boston Birth Cohort

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Abstract

Leptin is a pro-inflammatory cytokine that plays an important role in energy homeostasis. Emerging evidence suggests that leptin levels are altered in children with autism spectrum disorder (ASD); however this has not been studied prospectively. Rapid growth during infancy and early childhood has been implicated in ASD, but the evidence is inconsistent. Since leptin is involved in growth and is a potential risk factor for ASD, we explored the associations between 1) cord, early childhood leptin and ASD; and 2) birth weight for gestational age, early childhood weight gain and ASD. We also assessed the mediating role of leptin in the relationship between weight gain during infancy and ASD. This study was conducted in a sample of 822 subjects from the Boston Birth Cohort. ASD was defined from diagnostic codes in electronic medical records. Extremely rapid weight gain during infancy was associated with a greater ASD risk and this persisted after adjusting for potential confounders (aOR: 3.11; 95% CI: 1.37, 7.07). Similarly, children that had higher plasma leptin levels, prior to ASD diagnosis, had an increased ASD risk in both unadjusted

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and adjusted models (aOR: 7.87; 95% CI: 2.06, 30.04). Further, early childhood leptin indirectly mediated the relationship between rapid weight gain and ASD. No associations were found between birth weight for gestational age, cord leptin and risk of ASD. Our findings provide a basis to further explore whether the combination of early life growth pattern and a biomarker such as leptin can predict ASD earlier.

Lay Summary:

Is early life growth and a biomarker leptin related to ASD risk? To answer this question, we followed 822 children from birth and found that those who gained weight very quickly in infancy, had higher leptin levels in early childhood, had a greater chance of later ASD diagnosis. More research is needed to see if infant's weight gain pattern along with a biomarker (such as leptin) can be used to identify children with ASD sooner.

Keywords

Leptin; rapid weight gain in infancy; autism

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental conditions characterized by impairments in sociability and communication, as well as increased repetitive and/or restrictive behaviors and interests (Jeste, 2015; Leitner, 2014; Murray, 2010; Schaevitz, Berger-Sweeney, & Ricceri, 2014; Zhubi, Cook, Guidotti, & Grayson, 2014). ASD prevalence in the U.S. has increased dramatically since 1996 and now, 1 in 68 children are diagnosed with ASD (Krakowiak et al., 2012; Van Naarden Braun et al., 2015). The precise cause of ASD is largely unknown (Moore, Kneitel, Walker, Gilbert, & Xing, 2012). Numerous studies have demonstrated associations with genetic, environmental, perinatal and immunological risk factors, leading to a hypothesis that ASD likely has a multifactorial pathogenesis or is a common end point of multiple causal pathways (Limperopoulos, 2009; Moore et al., 2012).

Among the perinatal risk factors, preterm birth and small for gestational age (SGA) have been studied extensively in the context of ASD (Joseph et al., 2017; Moore et al., 2012; Padilla et al., 2017; Schieve et al., 2014). SGA is a proxy for intrauterine growth restriction (Hunter et al., 2016) and studies have reported that SGA children are at increased risk of ASD (Lampi et al., 2012; Larsson et al., 2005; Moore et al., 2012); however, the results are inconsistent (Glasson et al., 2004; Larsson et al., 2005; Schendel & Bhasin, 2008). Many children that are small at birth tend to have rapid catch-up growth during early postnatal period (Castanys-Munoz et al., 2017; Ong, 2007). Rapid growth during first year of life has been shown to be associated with ASD (Dementieva et al., 2005; Dissanayake, Bui, Huggins, & Loesch, 2006; Torrey, Dhavale, Lawlor, & Yolken, 2004), although not all studies have confirmed these findings (Courchesne, Carper, & Akshoomoff, 2003; Rommelse et al., 2011). While abnormal birth weight percentiles and rapid early growth have been identified as independent risk factors of ASD, the combined effect of SGA with rapid postnatal weight gain has not been explored. Most studies previously conducted on

SGA infants have not accounted for the rate of postnatal growth, and vice versa. Further, the biological mechanisms behind SGA and rapid weight gain and ASD risk have not been clearly elucidated (Sacco et al., 2007; Suren et al., 2013).

Leptin is a peptide hormone that is predominantly secreted by the white adipose tissue and has been studied in the context of fetal growth and early childhood weight gain (Blardi et al., 2010; Karakosta et al., 2011). Studies have found that children with SGA have lower leptin levels possibly reflecting a lower fat mass as a result of intrauterine restricted fetal weight gain (Catov et al., 2007; Harigaya, Nagashima, Nako, & Morikawa, 1997; Koistinen et al., 1997; Pighetti et al., 2003). Metabolically, lower cord blood leptin levels are known to predict rapid weight gain in infancy (Kettaneh et al., 2007; S. Li et al., 2016; Ong et al., 1999; Perng et al., 2016). Beyond leptin's role in prenatal and postnatal weight gain, this pleiotropic cytokine has been shown to be important in the regulation of the immune system, neurodevelopment including neuron excitability, synaptic plasticity, neural differentiation and promoting migration of neuronal lineage cells to the cortical plate (Ashwood et al., 2008; Blardi et al., 2010; Harvey, 2007; Harvey, Solovyova, & Irving, 2006; Paz-Filho et al., 2008). Emerging evidence suggests that children (2–15 years) with ASD have significantly higher plasma leptin levels than controls (Al-Zaid, Alhader, & Al-Ayadhi, 2014; Ashwood et al., 2008; Blardi et al., 2010; Essa M.M. et al., 2011; Rodrigues et al., 2014). Among a few studies that have researched leptin-ASD association in children, most were done after ASD diagnosis (Ashwood et al., 2008; Blardi et al., 2010), thus unable to assess the temporal relationship. To our knowledge, none of the studies have assessed cord and early childhood leptin levels independently and simultaneously in relation to ASD in a prospective birth cohort.

Despite studies observing cytokine involvement in ASD (Krakowiak et al., 2017; Masi, Glozier, Dale, & Guastella, 2017; Rodrigues et al., 2014; N. Xu, Li, & Zhong, 2015) and the knowledge about the role of fetal and infant growth and ASD (Dementieva et al., 2005; Dissanayake et al., 2006; Torrey et al., 2004), existing studies have not evaluated the potential link between growth and leptin levels related to ASD. We set out to understand whether elevated leptin levels observed in people with ASD are related to rapid weight gain during infancy, and whether leptin has a mechanistic role in explaining the early growth-ASD relationship. Specifically, in this report we sought to explore the relationship between – 1) birth weight for gestational age, weight gain during first year of life and ASD risk; 2) cord and early childhood leptin and ASD risk; and 3) the potential of leptin mediating the relationship between weight gain during first year and ASD risk. We analyzed the longitudinal data from the Boston Birth Cohort (BBC), a predominantly urban low-income minority population.

Methods

Participation and data collection procedure

As illustrated in supplemental figure 1, this study included 822 children from the BBC, who were recruited at birth (between 1998 and 2009), were followed prospectively until 2015 and had a median length of follow-up of 7.5 years (interquartile range: 5.2 – 9.8 years). Mothers of newborns were invited to participate in the study 24–72 hours after birth. Over 90% of

those that were approached agreed to participate and were initiated into the study (G. Wang et al., 2014; X. Wang et al., 2002). For every preterm (defined as <37 weeks of gestation) and/or low birth weight baby (defined as <2,500 g), approximately two term and normal birth weight babies (and their mothers) were enrolled in the study (X. Wang et al., 2002). The exclusion criterion for initial enrolment was multiple-gestation pregnancies and newborns with major birth defects. Participants and non-participants did not differ on characteristics such as infant birth weight, maternal ethnicity, or other sociodemographic characteristics (X. Wang et al., 2002). A sub-set of the participants were enrolled in the follow-up study that began in 2003 and children not planning to receive pediatric care at the Boston Medical Center were not included in the postnatal follow-up. There were no major differences in baseline demographic characteristics between those with and without postnatal follow-up (M. Li et al., 2016).

Of 2,932 that were eligible for postnatal follow-up, 2,110 were excluded for the following reasons: 1,589 did not have at least one of the exposure variables (cord leptin, early childhood leptin) and 521 had other competing diagnosis such as ADHD, intellectual disabilities (ID) or other developmental disabilities (DD). Electronic Medical Records (EMR) containing clinicians' primary and secondary diagnoses using ICD-9 codes were obtained for every postnatal clinical visit since 2003. The study was approved by the Institutional Review Boards of the Johns Hopkins Bloomberg School of Public Health and Boston University Medical Center.

Identification of children with ASD

Based on EMR, children that were ever diagnosed with autism (ICD-9 code 299.00), Asperger syndrome (299.80) and/or pervasive developmental disorder not otherwise specified (299.90) were categorized as having ASD. Neurotypical children were those that were never diagnosed with ASD, ADHD, ID and other DD. When children had concurrent diagnosis, such as ASD and ADHD or ASD and ID or ASD and other DD, they were classified as having ASD. Two separate sensitivity analyses were conducted - 1) using a stringent criteria, defined as having ASD diagnosis on more than two separate occasions in the EMR and one visit to specialists such as behavioral pediatrician, pediatric neurologist or child psychologist; and 2) using a stringent control that additionally excluded children who did not have other competing diagnoses (Conduct disorder (312.0 – 312.9), Emotional disturbances of childhood or adolescence including Oppositional Defiant Disorder (313.0 – 313.9), Congenital Anomalies (740 – 759.9)).

Exposure variables

Birth weight for gestational age was defined as follows: SGA (<10^{th} percentile), appropriate for gestational age (AGA) (≥10^{th} – 90^{th} percentile) and large for gestational age (LGA) (>90^{th} percentile) (G. Wang et al., 2014). Child's length (<2 years) and height and weight were measured during the well-child visits at the Boston Medical Center. WHO reference values was used to calculate weight-for-age *z*-scores and was defined as the change in weight-for-age *z*-scores from birth until the target time-point. Weight-for-age *z*-score was categorized into the following groups: slow (weight gain *z*-score <−0.67), on track (−0.67 to 0.67), rapid (>0.67 to 1.28), and extremely rapid (>1.28) (G. Wang, Johnson, et al., 2016).

Umbilical cord blood sample was collected at delivery and non-fasting early childhood venous blood sample were collected during subsequent follow-up visits. The median age of early childhood leptin measurement was 18.4 months (IQR: 10.3–49.2 months). All the blood samples were processed immediately after collection and plasma samples were stored in a freezer at −80°C. Only children with blood samples obtained prior to ASD diagnosis were included in the early childhood biomarker analysis. As mentioned elsewhere, plasma leptin levels were measured in duplicates using a sandwich immunoassay based on flow metric xMAP technology on Luminex 200 machines (Luminex Corp., Austin, TX). The interassay coefficient of variation was 4.5% (G. Wang, Johnson, et al., 2016). Unlikely leptin levels, defined as greater than 3 SD, were observed in 8 and 7 subjects for cord and early childhood leptin, respectively and were re-assigned a value of 3SD (G. Wang, Hu, et al., 2016).

Statistical Analyses

The outcome variable was ASD and major exposure variables were 1) birth weight for gestational age and weight gain during first year of life and 2) cord blood and early childhood leptin levels. Correlation between cord and early childhood leptin was minimal (0.02). Normality of the data was assessed using Shapiro-Wilk test and both cord and early childhood leptin levels were log transformed because of the skewed distribution. Data analyses were performed to compare neurotypical children and those with ASD using chi-square tests for categorical variables and ANOVA for continuous variables. Logistic regression models were applied to estimate the crude and adjusted associations between weight gain during first year of life, log-transformed leptin levels at birth and early childhood (X, independent variables) and ASD (Y, dependent variable). All results are presented as odds ratio. Throughout, we used 2-sided statistical tests with a significance level of 0.05. Data were analyzed using STATA version 13.0 (StataCorp, College Station, TX).

Mediation analysis: The role of leptin as a potential mediator of the association between weight gain during infancy and ASD risk was examined. KHB command in STATA was used to decompose the total effect of weight gain in infancy into natural direct and indirect effects, mediated by early childhood leptin levels (Breen, Karlson, & Holm, 2013). The total effect (defined as the effect of weight gain during infancy on ASD without the mediating variable early childhood leptin) was decomposed into direct effect (the effect of weight gain during infancy on ASD when controlling for early childhood leptin, the mediator) and indirect effect (the effect of weight gain during infancy on ASD through early childhood leptin, the mediator). The proportion of mediating effect among the total effect was calculated as indirect effect divided by the total effect.

Other covariates

Covariates were selected *a priori* based on the existing literature, including our own work in the BBC (M. Li et al., 2016; Raghavan et al., 2017; G. Wang et al., 2014; G. Wang, Hu, et al., 2016). Following covariates were adjusted in the analysis: maternal age at delivery, smoking during pregnancy (ever smoked 3 months before pregnancy/during pregnancy vs. not smoked before pregnancy/during pregnancy), parity (not including the index pregnancy),

maternal education (high school or less vs. some college or more), maternal pre-pregnancy BMI, maternal diabetes status (defined below), maternal age at delivery, race/ethnicity, child's sex (female vs. male), gestational age at birth (defined below), year of the baby's birth (1998–2006 vs. 2007–2013), mode of feeding (defined below), age at which early childhood blood was drawn and follow-up time for each subject.

Maternal diabetes status was classified into the following: 1) no preexisting diabetes mellitus (DM) or gestational diabetes mellitus (GDM), 2) preexisting DM, and 3) GDM. Subjects were categorized as having preexisting DM if any of the following criteria were met before pregnancy: (a) diabetes diagnosis by a physician; (b) received a ICD-9 code of "250.x" or "648.0x"; (c) fasting plasma glucose level ≥126 mg/dl (7.0 mmol/l) or a casual plasma glucose≥200 mg/dl (11.1 mmol/l); (d) treatment with anti-diabetes medicines (oral medicines or insulin). Subjects were categorized as having GDM if there was no evidence of preexisting diabetes (as defined above) and met any of the following criteria: (a) physician diagnoses of GDM; (b) received a ICD code of "648.8x"; (c) fasting plasma glucose level ≥126 mg/dl (7.0 mmol/l) or casual plasma glucose≥200 mg/dl (11.1 mmol/l); (d) two or more of the following plasma glucose values in oral glucose tolerance test (OGTT) were met or exceeded: i) Fasting: 95 mg/dL (5.3 mmol/L); ii) 1 h: 180 mg/dL (10.0 mmol/L); iii) 2 h: 155 mg/dL (8.6 mmol/L); iv) 3-h 140mg/dL (7.8mmol/L); v) treatment with anti-diabetes medicines (oral medicines or insulin) (American Diabetes, 2003, 2016; Organization).

Neonates who were delivered ≥ 37 completed weeks of gestation were categorized as term, while those delivered <34 weeks, and ≥34 but <37 weeks of gestation were considered early and late preterm, respectively. Race/ethnicity was categorized into black, white, Hispanic and Other. Data on mode of feeding was collected from mothers using a standardized questionnaire during a follow-up visit in the first few years of life. Mode of feeding was categorized into the following: 1) formula only, 2) both formula and breastfeeding, and 3) breastfeeding only. When mothers had multiple follow-up visits, data collected during the first visit was used (Hong et al., 2011).

Results

Table 1 describes the characteristics of mothers and children by child's case status (neurotypical vs. ASD). As expected, previously recognized risk factors were more prevalent among children with ASD compared to neurotypical children, including male sex, advanced maternal age, preterm birth and lower birth weight. Consistent with the literature (Mantzoros et al., 2009; Tome et al., 1997), girls had higher cord and early childhood plasma leptin levels than boys (Supplemental Table 1). Children that were SGA had lower cord leptin levels and were more likely to have extremely rapid weight gain (Supplemental tables 1 and 2). Children with most rapid weight gain during infancy were also likely to have higher early childhood leptin levels, but the latter did not differ by birth weight for gestational age (Supplemental table 1).

Birth weight for gestational age and ASD risk

A total of 599 children had birth weight for gestational age data, of which 47 were later diagnosed with ASD (Supplemental Figure 1). Five of these 47 ASD subjects had co-

occurring ID. Compared to children with AGA, neither SGA children nor LGA children were at a greater risk of ASD, before or after the adjustment of covariates including maternal age at delivery, parity, smoking status, education, race, maternal BMI, maternal diabetes, child's sex, follow-up time and gestational age (Table 2).

Weight gain during infancy and ASD risk

A total of 573 children had weight gain during infancy data, of which 46 were later diagnosed with ASD (Supplemental Figure 1). Five of these 46 subjects had co-occurring ID. Prenatal determinants of weight gain during infancy are presented in Supplemental Table 2, and preterm birth was a major determinant of infant excessive weight gain. When compared to children whose growth was on track based on weight gain *z*-scores, children that had slow weight gain or rapid weight gain did not have an increased ASD risk (OR_{slow}: 1.52; 95% CI: 0.49, 4.71, OR_{rapid}: 1.33; 95% CI: 0.46, 3.86) (Table 2). However, extremely rapid weight gain during infancy was associated with an increased risk of ASD ($OR_{extremely\ rapid}$: 2.64; 95% CI: 1.20, 5.78). This association persisted after adjusting for covariates (child's sex, race, follow-up time and breastfeeding status) in model 3 ($aOR_{extremely\ rapid}$: 3.11; 95% CI: 1.37, 7.07). Next, we sequentially added birth weight for gestational age to model 3 covariates and observed a consistent association (Table 2). However, the significance attenuated after adjusting for gestational age in addition to model 3 covariates (aOR: 2.08; 95% CI: 0.84, 5.13). The association did not attenuate after adjusting for prenatal determinants such as maternal BMI, diabetes status and age at the time of delivery, in addition to covariates specified in model 3 (Table 2). Sensitivity analyses using stringent comparators or cases showed a consistent association between birth weight for gestational age, weight gain during infancy and risk of ASD (supplemental tables 3 and 4).

Cord leptin and ASD risk

A total of 655 children had data on cord leptin levels, of which 39 were later diagnosed with ASD (Supplemental Figure 1). Two of these 39 ASD subjects had co-occurring ID. Prenatal and perinatal determinants of cord leptin are presented in Supplemental Table 1. The mean cord leptin levels were 38.23 pg/mL in children with neurotypical development and 27.37 pg/mL in children with ASD (Table 1). As observed in other cohorts (Mantzoros et al., 2009), higher cord blood leptin levels correlated with increase in gestational age. In the unadjusted model, cord leptin levels (stratified into quartiles) were not associated with the risk of ASD (Table 3). Similarly, no associations were observed after adjusting for covariates in models 1 and 2. The relationship between cord leptin and ASD was not altered, irrespective of whether cord leptin was assessed as a continuous or a categorical variable (Supplement table 5).

Early childhood leptin and ASD risk

A total of 652 children were included in the analyses, of which 36 were later diagnosed with ASD (Supplemental Figure 1). Four of these 36 ASD subjects had co-occurring ID. Figure 1 provides a distribution of early childhood leptin levels among neurotypical children and those with ASD, showing a shift in distribution towards right for children with ASD. Supplemental figure 2 provides a distribution of when early childhood leptin levels were

measured. When compared to children that had the lowest leptin levels (quartile 1), children with highest leptin levels (quartile 4) had an increased ASD risk (OR: 5.41; 95% CI: 1.53, 19.05) (Table 3). The association remained significant after adjusting for covariates (model 3) including child's sex, race, child's age when leptin was measured, follow-up time and breastfeeding status (aOR: 7.87; 95% CI: 2.06, 30.04). Further adjusting for gestational age (model 4), cord leptin levels (model 5) or prenatal determinants such as maternal BMI, diabetes status and age at the time of delivery (model 6) did not attenuate the association between early childhood leptin and ASD. Analysis using early childhood plasma leptin levels as a continuous variable or categorical variable yielded consistent findings (Supplement table 5). Sensitivity analyses using stringent controls or cases showed similar trends in association between cord, early childhood leptin and ASD risk (Supplemental tables 6 and 7). Results from alternative analyses using Cox proportional hazard regression for birth weight for gestational age, weight gain during infancy, cord and early childhood leptin, and ASD risk (supplemental tables 8 and 9) were consistent in direction and statistical significance.

Early childhood leptin mediating the relationship between weight gain during infancy and ASD risk

A total 476 children had both weight gain during infancy data and early childhood leptin measurements (Table 4). In the unadjusted model that assessed the role of early childhood leptin as a mediator of the relationship between weight gain during infancy and risk of ASD, the total effect of extremely rapid weight gain was statistically significant (OR: 2.80; 95% CI: 1.07, 7.28). Both direct (OR: 2.22; 95% CI: 0.84, 5.87) and indirect effects (OR: 1.26; 95% CI: 0.95, 1.67) were non-significant. In the adjusted model, the total effect attenuated (aOR: 1.80; 95% CI: 0.55, 5.90). However, the indirect effect became significant (aOR: 1.56; 95% CI: 1.01, 2.42), suggesting an indirect-only mediation (Zhao, Lynch, & Chen, 2010) and that the early childhood leptin potentially mediates 76.03% of the total relationship between extreme rapid weight gain and ASD, after adjusting for confounders. Other weight gain categories such as slow and rapid weight gain were not significantly associated with ASD and adjusting for early childhood leptin levels did not alter their association with ASD.

Discussion

In this prospective cohort study, our results showed that extremely rapid weight gain during infancy and elevated early childhood leptin levels measured prior to ASD diagnosis were associated with an increased ASD risk in childhood. Our findings are in line with several studies that have reported that rapid weight gain during infancy is a potential indicator of early autism risk (Chawarska et al., 2011; Dissanayake et al., 2006; Sacco et al., 2007; Suren et al., 2013; Torrey et al., 2004). We extend the previous findings and suggest that the association between rapid weight gain and ASD is potentially mediated, at least indirectly, by early childhood plasma leptin. To our knowledge, this is the first study to assess the interrelationships between birth weight, infancy weight gain and leptin in the context of ASD in a prospective birth cohort.

Conceptual Framework of ASD risk factors from prenatal to early childhood:

Epidemiological studies and animal models have consistently showed that an adverse in-utero environment may lead to altered programming of tissue structure and function, predisposing to later behavioral problems, learning difficulties, abnormal or delayed cognitive development and other conditions (Van den Bergh, 2011; Vickers, 2007). Sub-optimal prenatal environmental influences could induce permanent fetal adaptations that are beneficial for short-term survival, but increases the vulnerability to later pathogenic environmental stimuli (Krechowec, Vickers, Gertler, & Breier, 2006; Vickers & Sloboda, 2012). As illustrated in Figure 2, based on the findings by us and others, postnatal influences such as extremely rapid weight gain and elevated leptin levels may not be isolated stand-alone occurrences during the first year of life; but could rather be a compensatory event to an adverse prenatal condition or deviation in biological mechanism (Courchesne et al., 2003; Karaolis-Danckert et al., 2008; G. Wang, Johnson, et al., 2016). In support of this argument, we observed that children that were exposed to maternal diabetes or overweight/obesity during pregnancy and those that were SGA or early preterm, were more likely to have extremely rapid weight gain during infancy. Further, in line with the existing evidence (Ong, Ahmed, Emmett, Preece, & Dunger, 2000), low concentrations of cord blood leptin were associated with rapid weight gain during the first year of life suggesting that cord leptin could serve as a signal for catch-up growth. Taken together, it can be inferred that the incongruent prenatal (e.g. SGA) and postnatal milieu (rapid catch up growth) associated with endocrinologic alterations (early childhood leptin levels) may have a negative impact on the brain architecture and circuits, which could predispose an individual to adverse neurobehavioral outcomes (Pylipow et al., 2009; Van den Bergh, 2011). Given this context, we further elaborate our findings and discuss how they compare to the previous studies and provide possible explanations.

Many studies, in addition to ours, reported an inconsistent association between fetal growth and ASD (Glasson et al., 2004; Langridge et al., 2013; Larsson et al., 2005; Schendel & Bhasin, 2008). Langridge et al. demonstrated that the percentage of optimal birth weight, a measure of fetal growth (Blair, Liu, de Klerk, & Lawrence, 2005), was not associated with ASD, especially among those with intellectual disability (Langridge et al., 2013). Glasson et al. also showed no association between SGA and ASD (Glasson et al., 2004), while Schnedel et al., noted that the relationship was observed only in girls and not in boys (Schendel & Bhasin, 2008). Similarly, Larrson et al. observed that the association between fetal growth and ASD attenuated after adjusting for other covariates (Larsson et al., 2005). In contrast, a few studies showed that SGA children had elevated risk of ASD (Lampi et al., 2012; Maimburg & Vaeth, 2006; Moore et al., 2012). A possible explanation for the lack of association between fetal growth and ASD is likely due to the heterogeneity in the SGA group related to the timing of onset. Fetal growth restriction may have different clinical manifestation and sequelae depending on whether the onset of growth restriction is early or late during gestation (Dall'Asta, Brunelli, Prefumo, Frusca, & Lees, 2017; Savchev et al., 2014). In our study, considering SGA as a homogenous group could have possibly blurred the association between fetal growth and ASD. We do not have data in the current study to tease apart this association, but can be explored further in future studies. Other potential reasons including methodological differences, lack of control for confounding factors, and

sample size variations could explain some of the inconsistencies (Lampi et al., 2012; Schendel & Bhasin, 2008).

Consistent with our findings, several studies have shown that children who are later diagnosed with ASD have accelerated weight gain during infancy and early childhood (Dissanayake et al., 2006; Mraz, Green, Dumont-Mathieu, Makin, & Fein, 2007; Sacco et al., 2007; Torrey et al., 2004). This accelerated weight gain may not be a distinct morphological feature, but is suggestive of a broader autistic phenotype characterized by rapid increase in head circumference, height and weight (Dissanayake et al., 2006; Fukumoto et al., 2008; Mraz et al., 2007; Sacco, Gabriele, & Persico, 2015; Sacco et al., 2007; van Daalen, Swinkels, Dietz, van Engeland, & Buitelaar, 2007). In support of this hypothesis, studies have shown that head circumference is well correlated with weight and height in ASD children(Dementieva et al., 2005; Mraz et al., 2007; Sacco et al., 2007). Rapid increase in head circumference in children with ASD is one of the most consistent findings that many studies have demonstrated (Chawarska et al., 2011; Courchesne et al., 2003; Dementieva et al., 2005; Dissanayake et al., 2006; Fukumoto et al., 2008; Sacco et al., 2015; Sacco et al., 2007). Although we did not analyze head circumferences due to incomplete data, weight has been shown to be the strongest predictor of head circumference during most of infancy (Mraz et al., 2007). Taken together, our findings support the existing evidence that extremely rapid weight gain during infancy is associated with ASD, possibly indicative of an overall growth dysfunction. There are many speculations about why rapid weight gain is observed in children with ASD. Studies have posited that an abnormality in factors (such as metabolism, growth or neurotrophic factors and hormone levels) may predispose an individual to overall accelerated growth as well as ASD (Dissanayake et al., 2006; Fukumoto et al., 2008; Mraz et al., 2007; Torrey et al., 2004).

Our study showed that early childhood leptin levels were altered in children with ASD. While prior studies assessing this relationship were mainly cross-sectional, our prospective study for the first time showed that elevated leptin levels are observed even prior to ASD diagnosis. Considering the role of leptin in neurocognition, elevated leptin and associated leptin resistance during the critical periods of postnatal brain development may have permanent adverse implications (Glavas et al., 2010; Valleau & Sullivan, 2014). While the mechanism behind leptin resistance is still being understood, it is believed to involve reduced transport of leptin to the brain, poor negative feedback mechanism, endoplasmic reticulum stress and an intracellular leptin signaling system that is saturable (Boeke et al., 2013; Glavas et al., 2010; Mantzoros et al., 2011).

Similar to other studies (Dulloo, 2008; Ong et al., 1999), we noted that low cord leptin levels closely reflected birth weight and also predicted the greatest weight gain during infancy. However, cord blood leptin was not associated with ASD. This finding may be intriguing especially in the context that early childhood leptin is associated with ASD; however, our results are consistent with the existing evidence that cord and early childhood leptin may have different roles to play (Boeke et al., 2013; Zhang et al., 2017).

Cord blood leptin is derived primarily from the fetal tissue and is reflective of fetal adiposity (Catov et al., 2007; Hauguel-de Mouzon, Lepercq, & Catalano, 2006; Mellati et al., 2010;

Tessier, Ferraro, & Gruslin, 2013). While leptin is detectable in the fetus at around 18 weeks, rapid increase in leptin levels are observed after 34 weeks, in tandem with increase in fetal adipose tissues (Grisaru-Granovsky, Samueloff, & Elstein, 2008; Mellati et al., 2010). Perinatal and neonatal periods are considered to be a window of maximum leptin sensitivity with normal neonates having two to three times higher leptin when compared to adults (Bouret, 2012, 2013; Paz-Filho et al., 2008; Valleau & Sullivan, 2014). Neonatal leptin has a different physiological response and promotes hyperphagia and swallowing activity in newborn and may not inhibit growth, food intake or energy expenditure (Alexe, Syridou, & Petridou, 2006; Bouret & Simerly, 2004; El-Haddad, Desai, Gayle, & Ross, 2004; Vickers & Sloboda, 2012). However, leptin sensitivity declines with age (Boeke et al., 2013; Levin, Dunn-Meynell, & Banks, 2004).

After closure of the critical window, higher leptin does not protect against adiposity and some children even develop leptin tolerance (Boeke et al., 2013). Thus, leptin, once positively associated with birth weight and less adiposity during early childhood (Boeke et al., 2013; Karakosta et al., 2011; Mantzoros et al., 2009) no longer possesses the same effect – demonstrating that the effect of leptin in perinatal period is distinct from that of later life (Cottrell et al., 2009). One study that longitudinally measured cord and early childhood leptin showed that while high cord blood leptin was initially shown to be protective against adiposity, it was subsequently associated with weight gain and adiposity at age 7 (Boeke et al., 2013). These age-specific effects of leptin have been linked to developmental changes in leptin receptor expression – which are widely expressed in the central nervous system starting from mid-gestation (Cottrell, Mercer, & Ozanne, 2010). While these findings are related to adiposity, it is plausible to believe that leptin's role may be similar with neurocognitive outcomes.

Leptin as a mediator:

After establishing independent associations between ASD and 1) extremely rapid weight gain during infancy, and 2) early childhood leptin, we showed that children with extremely rapid weight gain during infancy had elevated leptin levels. In support of this, animal models that have shown that rapid catch-up growth in early childhood is associated with leptin resistance and this occurs independent of postnatal diet induced obesity (Coupe, Grit, Hulin, Randuineau, & Parnet, 2012; Krechowec et al., 2006; Yura et al., 2005). It has been hypothesized that proinflammatory cytokines may mediate the relationship between rapid postnatal growth and ASD (Pylipow et al., 2009). As a proof of concept, our study was able to demonstrate the mediating effect of leptin in the association between extremely rapid weight gain and ASD. However, in our dataset, cord leptin did not possess any mediating effects unlike early childhood leptin.

Mechanism of leptin in ASD:

Inflammation is a possible mechanism through which leptin may impact the psychopathology of ASD. Leptin, a pro-inflammatory cytokine may play a role in the pathophysiology of conditions such as schizophrenia (Haupt et al., 2005; Stubbs, Wang, Vancampfort, & Miller, 2016) and ASD (Ashwood et al., 2011; Goines & Ashwood, 2013). A variety of independent studies have linked cytokine dysregulation to ASD (Goines &

Ashwood, 2013). Cytokines act as immune mediators and their imbalance during development and throughout life can adversely impact neural activity and mediate behavioral aspect of the disorder (Goines & Ashwood, 2013). Inflammatory cytokines are implicated in higher neurological functions such as memory and cognition, in addition to being involved in brain development, synaptic functioning including processes of differentiation, migration, proliferation and impairments in behavior (Tonhajzerova et al., 2015). Thus, abnormal inflammatory activity and imbalance of cytokines during development can adversely impact neural activity and could contribute to behavioral and neurological dysfunction in ASD (Goines & Ashwood, 2013; Tonhajzerova et al., 2015).

Altered leptin levels can also impact brain structure and function. For example, leptin levels are increased at the site of inflammation in the post-mortem brain tissue (Ashwood et al., 2008). Leptin deficient and leptin resistant state is associated with lower brain weight, protein content, reduction in brain myelin, neuronal soma size and several synaptic proteins. Reduced brain weight is observed in animals that lacked leptin signaling (Bouret & Simerly, 2004). A study conducted on autopsy tissues showed that there is a marked increase in leptin levels in anterior cingulate gyrus among those that had ASD (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). In a small subset of patients, genetic correlation was observed between ASD and leptin coding (Bochukova et al., 2010). Leptin is involved in long-term potentiation and long-term depression (Bliss, Collingridge, & Morris, 2014) and dysregulation of this function is implicated in ASD (Bliss et al., 2014). Further, leptin is also known to suppress serotonin synthesis, which is reported in ASD, possibly suggesting another biological pathway through which leptin can be involved in ASD (Valleau & Sullivan, 2014).

In our earlier report in the BBC, we showed that maternal obesity and diabetes was associated with increased risk of ASD in offspring (M. Li et al., 2016). Our results, along with consistent findings across diverse populations (Y. M. Li et al., 2016; Nahum Sacks et al., 2016; Xiang et al., 2015; G. Xu, Jing, Bowers, Liu, & Bao, 2014) raised the possibility of early metabolic dysfunction in the development of ASD. Studies have posited that early life manipulations of leptin in animal models alter susceptibility to subsequent obesity and metabolic disorders (Dulloo, 2008; Vickers & Sloboda, 2012). Periods of hypo- or hyperleptinemia may induce metabolic adaptations, which could be the basis of developmental programming (Vickers & Sloboda, 2012). In this context, the role of leptin as a potential mediator of the developmental programming of ASD (Cottrell et al., 2009) may be a novel proposition for ASD, but requires further investigation. Additional research is warranted on the role of other hormones with leptin opposing action, so as to better understand the metabolic milieu involved in ASD. Similarly, future studies should also examine variants in leptin and leptin receptors to better understand the biological pathways of leptin in ASD.

Limitations and Strengths

Although our study stemmed from a rigorously designed prospective birth cohort, the findings may be tempered due to some limitations. First, case and neurotypical development classification of children was based on EMR data and it is possible that there may be

outcome misclassification. However, this misclassification may not be differential given the prospective study design. Second, the relatively small number of cases in our prospective cohort design could have resulted in wide confidence intervals and imprecise estimates. Third, although our models accounted for breastfeeding vs. formula feeding, more research is needed to examine the role of perinatal nutrition and its influences on weight gain, early childhood leptin and ASD. Fourth, we could not directly assess fat mass at the time of leptin measurement and this could have resulted in some residual confounding. Fifth, plasma leptin levels follow a circadian rhythm (Mantzoros et al., 2011) and may be impacted by fasting status; although, the timing of plasma sample collection for leptin measurements was random, the distribution was comparable between ASD and neurotypical groups. Finally, our study population consisted mainly of urban low-income minority populations that were also at high risk for conditions such as SGA and preterm births and thus, the results may not be generalizable to the U.S. population.

Despite these limitations, our study has a number of strengths. This is one of the first longitudinal studies that addressed leptin levels at birth and in early childhood in the context of ASD. Infant weight gain was assessed as part of well-child visit during first year of life, when child's ASD status was not known. By using a sample of children that have weight gain data as well as data on cord and early childhood leptin, we were uniquely poised to examine the inter-relationship of these variables in the development of ASD.

Conclusion

In the BBC, we showed that extremely rapid weight gain during infancy and elevated leptin levels during early childhood were independently associated with greater ASD risk and early childhood plasma leptin levels at least indirectly mediated the relationship between early childhood weight gain and ASD. Furthermore, the prenatal and postnatal risk factors for ASD are interrelated and act along a continuum from prenatal to postnatal periods. An important implication of these findings is that in addition to prenatal factors, pathogenic processes underlying ASD likely continue during the postnatal period, including infancy and possibly extending to early childhood (Sacco et al., 2007). Even though accelerated weight gain in early life, combined with elevated plasma leptin may not be a unique biomarker for ASD, our preliminary findings provide a basis from which to further explore the relationship between prenatal events, infancy rapid weight gain, leptin and ASD under a life course framework (Courchesne et al., 2003). Additional research is needed to understand if a combination of prenatal and early childhood anthropometric, biological, genetic variables and behavioral signs together can accurately predict ASD sooner. If proven to be useful by future studies, this will provide an opportunity to start intervention earlier thereby potentially halting or mitigating the progression towards ASD (Allely, Gillberg, & Wilson, 2014; Courchesne et al., 2003; Dissanayake et al., 2006).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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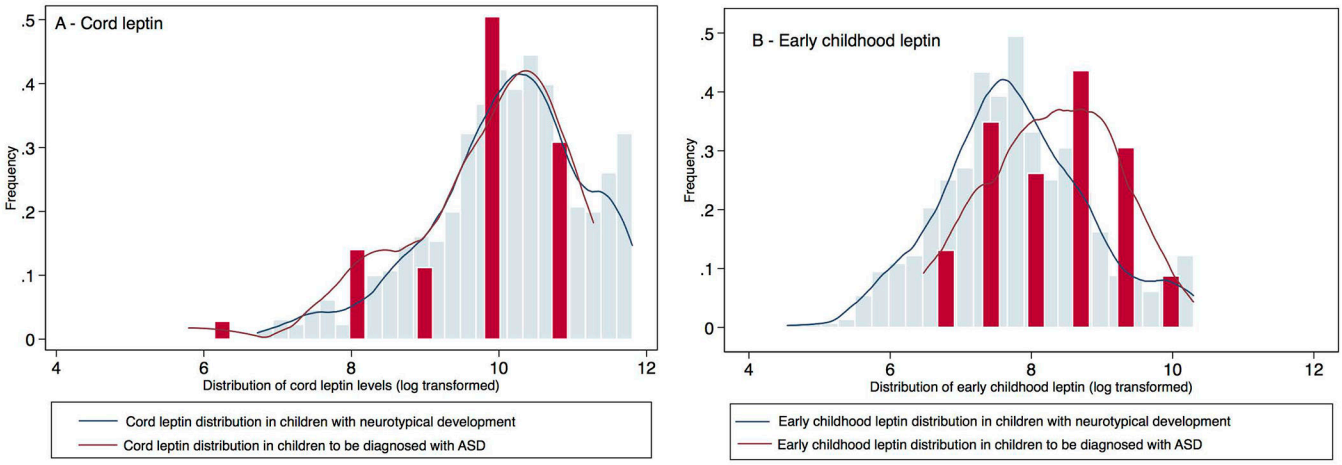

Figure 1:

Distribution of cord and early childhood plasma leptin levels (log transformed) in children categorized by ASD status

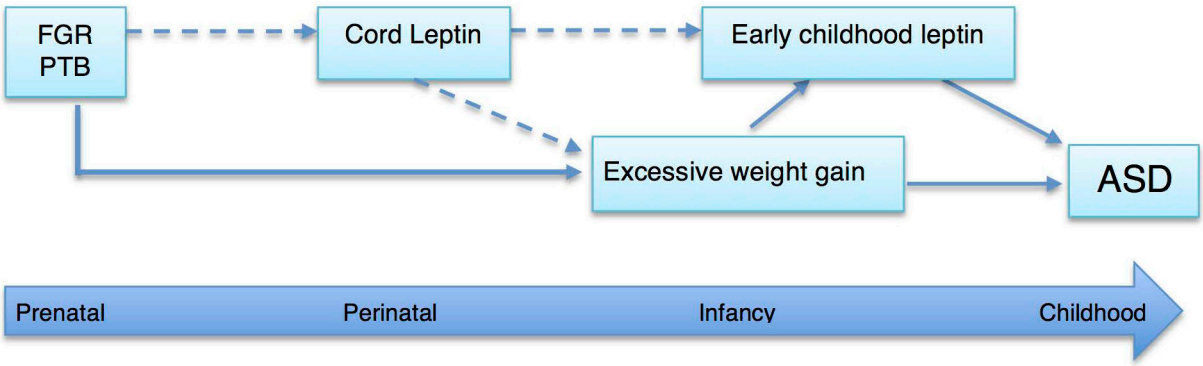

Figure 2:
Illustration of Prenatal, perinatal and early childhood determinants of ASD in a life course framework

Table 1:

Maternal and child characteristics by child's status (neurotypical vs. ASD) in the BBC

	Neurotypical (n=769)	ASD (n=53)	p value
Characteristics			
Mothers			
Age at birth (yrs), mean (SD)	28.21 (6.51)	30.35 (6.28)	0.02
Parity (%)			0.92
0	331 (41.74)	21 (39.62)	
1 or more	447 (58.13)	32 (60.38)	
Missing	1 (0.13)	0 (0.0)	
Mother's education (%)			0.43
High School or less	498 (64.76)	31 (58.49)	
Some college or more	266 (34.59)	21 (39.62)	
Missing	5 (0.65)	1 (1.89)	
Maternal BMI (%)			0.16
Underweight (<18.5) + Normal Weight (≥18.5-<25)	371 (48.24)	19 (35.85)	
Overweight (25–29.9)	235 (30.56)	18 (33.96)	
Obesity (≥30)	163 (21.20)	16 (30.19)	
Diabetes mellitus (%)			0.19
No	688 (89.47)	45 (84.91)	
Gestational	53 (6.89)	3 (5.66)	
Pre-gestational diabetes	27 (3.51)	5 (9.43)	
Missing	1 (0.13)	0 (0.0)	
Smoking during & 3 months prior to pregnancy (%)			0.17
No	659 (85.70)	41 (77.36)	
Yes	105 (13.65)	12 (22.64)	
Missing	5 (0.65)	0 (0.00)	
Offspring			
Sex (%)			<0.001
Male	327 (42.52)	39 (73.58)	
Female	442 (57.48)	14 (26.42)	
Race-ethnicity (%)			0.91
Black	434 (56.44)	32 (60.38)	
White	46 (5.98)	4 (7.55)	
Hispanic	185 (24.06)	11 (20.75)	
Other	99 (12.87)	6 (11.32)	
Missing	5 (0.65)	0 (0.0)	
Gestational age (%)			0.007
Term	579 (75.29)	32 (60.38)	
Late preterm (≥34 - <37 weeks)	126 (16.38)	10 (18.87)	

	Neurotypical (n=769)	ASD (n=53)	p value
Early preterm (<34 weeks)	64 (8.32)	11 (20.75)	
Birthweight (g)	3009.07 (714.09)	2782.26 (886.18)	0.03
Year of birth (%)			0.70
1998–2006	400 (52.02)	29 (54.72)	
2007–2013	369 (46.98)	24 (45.28)	
Birth weight for gestational age (%)[a,b]			0.73
Appropriate for gestational age (AGA)	442 (80.07)	36 (76.60)	
Small for gestational age (SGA)	59 (10.69)	5 (10.64)	
Large for gestational age (LGA)	51 (9.24)	6 (12.77)	
Weight gain during infancy (%)[c, d]			0.06
On target	178 (33.78)	9 (19.57)	
Slow	65 (12.33)	5 (10.87)	
Rapid weight gain	89 (16.89)	6 (13.04)	
Extremely rapid weight gain	195 (37.00)	26 (56.52)	
Cord blood leptin (SD)[e]	38.23 (34.01)	27.37 (19.94)	0.05
Early childhood leptin (SD)[f]	4.22 (5.60)	5.88 (5.68)	0.08
Mode of feeding (%)			0.62
Formula	177 (23.02)	10 (18.87)	
Both	537 (69.83)	37 (69.81)	
Breastfeeding	49 (6.37)	5 (9.43)	
Missing	6 (0.78)	1 (1.89)	

[a] Fetal growth defined as AGA (≥10th – 90th percentile); SGA (<10th percentile), and LGA (>90th percentile)

[b] n =599 (Neurotypical n=552; ASD n=47)

[c] Weight gain *z*-scores during the first year of life were defined as the change in weight-for-age *z*-scores from birth until the target time-point and was categorized into the following groups: slow (weight gain *z*-score <−0.67), on track (−0.67 to 0.67), rapid (>0.67 to 1.28), and extremely rapid (>1.28)

[d] n=573 (Neurotypical n=527; ASD n=46)

[e] n=655 (Neurotypical n=616; ASD n=39)

[f] n=652 (Neurotypical n=616; ASD n=36)

Table 2:

Association between in-utero growth, weight gain during infancy and ASD risk in children in the BBC

	Total n	ASD n	OR	95% CI	p value
Birth weight for gestational age[a]					
Unadjusted					
AGA	478	36	Ref		
SGA	64	5	1.04	0.39, 2.76	0.94
LGA	57	6	1.44	0.58, 3.59	0.43
Model 1					
AGA	478	36	Ref		
SGA	64	5	0.81	0.28, 2.34	0.70
LGA	57	6	1.23	0.44, 3.47	0.69
Model 2					
AGA	478	36	Ref		
SGA	64	5	0.86	0.29, 2.54	0.79
LGA	57	6	1.37	0.48, 3.91	0.55
Weight gain during infancy[b]					
Unadjusted					
On target	187	9	Ref		
Slow	70	5	1.52	0.49, 4.71	0.47
Rapid weight gain	95	6	1.33	0.46, 3.86	0.60
Extremely rapid weight gain	221	26	2.64	1.20, 5.78	0.02
Model 3					
On target	187	9	Ref		
Slow	70	5	1.71	0.53, 5.52	0.37
Rapid weight gain	95	6	1.39	0.43, 4.44	0.58
Extremely rapid weight gain	221	26	3.11	1.37, 7.07	0.007
Model 4					
On target	187	9	Ref		
Slow	70	5	1.55	0.46, 5.24	0.48
Rapid weight gain	95	6	1.50	0.46, 4.88	0.50
Extremely rapid weight gain	221	26	3.33	1.44, 7.72	0.005
Model 5					
On target	187	9	Ref		
Slow	70	5	1.74	0.54, 5.66	0.36
Rapid weight gain	95	6	1.32	0.41, 4.24	0.64
Extremely rapid weight gain	221	26	2.08	0.84, 5.13	0.11
Model 6					
On target	187	9	Ref		

	Total n	ASD n	OR	95% CI	p value
Slow	70	5	1.40	0.40, 4.86	0.59
Over growth	95	6	1.22	0.36, 4.14	0.75
Extremely rapid weight gain	221	26	3.33	1.40, 7.89	0.006

[a] In-utero growth defined as Appropriate for gestational age (≥10th – 90th percentile); Small for gestational age (<10th percentile), and Large for gestational age (>90th percentile)

[b] Weight gain during infancy defined as the change in weight-for-age *z*-scores from birth until the target time-point and was categorized into the following groups: slow (weight gain *z*-score <−0.67), on track (−0.67 to 0.67), rapid (>0.67 to 1.28), and extremely rapid (>1.28)

Model 1: Adjusted for maternal age at delivery, parity, smoking, education, maternal BMI, maternal diabetes status, race, child's sex and follow-up time

Model 2: Adjusted for Model 1 + gestational age

Model 3: Adjusted for child's sex, race, follow-up time and breastfeeding status

Model 4: Adjusted for Model 3 + birth weight for gestational age

Model 5: Adjusted for Model 3 + gestational age

Model 6: Adjusted for Model 3 + maternal age, maternal diabetes status, maternal BMI

Table 3:

Association between cord, early childhood plasma leptin levels and ASD risk in children in the BBC

	Total n	ASD n	OR	95% CI	p value
Cord leptin					
Unadjusted					
Q1	164	10	Ref		
Q2	163	11	1.11	0.46, 2.70	0.81
Q3	164	11	1.11	0.46, 2.68	0.82
Q4	164	7	0.69	0.25, 1.85	0.46
Model 1					
Q1	164	10	Ref		
Q2	163	11	1.44	0.53, 3.87	0.48
Q3	164	11	1.76	0.66, 4.69	0.26
Q4	164	7	0.96	0.31, 2.94	0.94
Model 2					
Q1	164	10	Ref		
Q2	163	11	2.01	0.68, 5.92	0.21
Q3	164	11	2.74	0.90, 8.31	0.08
Q4	164	7	1.40	0.42, 4.66	0.58
Early childhood leptin Unadjusted					
Unadjusted					
Q1	163	3	Ref		
Q2	163	8	2.75	0.72, 10.57	0.14
Q3	163	10	3.49	0.94, 12.91	0.06
Q4	163	15	5.41	1.53, 19.05	0.009
Model 3					
Q1	163	3	Ref		
Q2	163	8	3.32	0.83, 13.37	0.09
Q3	163	10	4.61	1.17, 18.22	0.03
Q4	163	15	7.87	2.06, 30.04	0.003
Model 4					
Q1	163	3	Ref		
Q2	163	8	3.30	0.81, 13.41	0.10
Q3	163	10	4.93	1.23, 19.77	0.02
Q4	163	15	7.89	2.05, 30.44	0.003
Model 5					
Q1	163	3	Ref		
Q2	163	8	3.59	0.68, 18.96	0.13
Q3	163	10	4.18	0.79, 22.19	0.09
Q4	163	15	8.41	1.69, 41.81	0.009

	Total n	ASD n	OR	95% CI	p value
Cord leptin					
Model 6					
Q1	163	3	Ref		
Q2	163	8	3.43	0.84, 13.94	0.09
Q3	163	10	5.09	1.28, 20.21	0.02
Q4	163	15	7.46	1.93, 28.82	0.004

Model 1: Adjusted for maternal characteristics such as maternal age at delivery, parity, smoking, maternal BMI, maternal diabetes status, education, race, child's sex and follow-up time

Model 2: Adjusted for Model 1 + gestational age

Model 3: Adjusted for child's sex, race, age of leptin measurement, follow-up time and breastfeeding status

Model 4: Adjusted for Model 3 + gestational age

Model 5: Adjusted for Model 3 + cord leptin levels

Model 6: Adjusted for Model 3 + maternal age, maternal BMI, maternal diabetes status

Table 4:

Mediation analysis – Leptin as a mediator in the relationship between weight gain during first year of life and ASD risk

	Total Effect, OR (95% CI)	Direct Effect, OR (95% CI)	Indirect effect, OR (95% CI)	Percentage mediated by early childhood leptin (%)
Unadjusted (Total N=476; ASD=32)				
On track	Ref			
Slow	1.92 (0.52, 7.11)	1.93 (0.52, 7.16)	0.99 (0.81, 1.22)	
Rapid weight gain	1.39 (0.38, 5.11)	1.17 (0.32, 4.32)	1.19 (0.93, 1.52)	
Extreme rapid weight gain	2.80 (1.08, 7.28)	2.22 (0.84, 5.87)	1.26 (0.95, 1.67)	
Model 1: Adjusted				
On track	Ref			
Slow	1.80 (0.44, 7.47)	1.81 (0.44, 7.49)	1.00 (0.72, 1.39)	
Rapid weight gain	1.06 (0.23, 4.85)	0.82 (0.18, 3.78)	1.29 (0.89, 1.87)	
Extreme rapid weight gain	1.80 (0.55, 5.90)	1.15 (0.34, 3.88)	1.56 (1.01, 2.42)	76.03

Model 1: Adjusted for child's sex, race, breast-feeding category, age of leptin measurement, follow-up time and gestational age

A causal inference framework was used to estimate ORs and 95% CI for total, direct and indirect effects. A logistic regression model was fit using categorical exposure (weight gain during infancy) and continuous mediator (leptin).