Maternal Pre-pregnancy Body Mass Index and Gestational Weight Gain in Relation to Autism Spectrum Disorder and other Developmental Disorders in Offspring

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Abstract

Most prior studies examining maternal pre-pregnancy body mass index (BMI) in relation to offspring autism spectrum disorders (ASD) have reported an association, though findings are not uniform and few have also examined gestational weight gain (GWG). Therefore, we examined both in the Study to Explore Early Development, a multi-site case–control study of children born in 2003–2006. Children identified from clinics, schools, and birth certificates were enrolled at ages 2–5 year and using standardized developmental evaluations, classified as: ASD, other developmental delays (DD), or population-based controls. Maternal height, weight, and GWG were self-reported during the telephone interview. Three primary weight risk factors were examined: (a) Pre-pregnancy BMI, classified as underweight to obese, (b) GWG continuous and categorized as quintiles, and (c) Institute of Medicine clinical weight-gain recommendations. Odds ratios adjusted (AOR) for sociodemographic and prenatal factors were calculated among term singletons, comparing the ASD ($n = 540$) or DD ($n = 720$) groups to the control group ($n = 776$). The AOR of ASD and maternal obesity was 1.37 (95%CI 0.98–1.92). Associations with higher GWG were stronger (Quintile5 vs. Quintile3 AOR = 1.58, 95%CI 1.08–2.31), and particularly so among overweight/obese women (AOR = 1.90, 95%CI 0.98–3.68). DD was associated with maternal overweight and obesity (obesity AOR = 1.48, 95%CI 1.08–2.02), but not with total GWG or clinical recommendations. High maternal BMI and GWG are risk factors for other pregnancy and child outcomes, and our results suggest they may also represent modifiable risk factors for neurodevelopmental outcomes.

Lay Summary:

In a large, national study, we found that children with autism were more likely than unaffected children to have mothers with higher weight gain during pregnancy; risk of autism may be even stronger if mothers were also overweight before pregnancy. Children with other developmental delays were more likely to have mothers who were overweight or obese before pregnancy, but not who gained more weight during pregnancy. Overweight and weight gain may represent factors that could be modified.

Keywords

autism spectrum disorder; autism; BMI; developmental delay; epidemiology; obesity; gestational weight gain; maternal child health

Introduction

Autism spectrum disorder (ASD) has increased steadily in prevalence (Christensen et al., 2016; Lyall et al., 2017; Rice et al., 2010), with an etiology considered to be multifactorial, involving both genetic and environmental factors (Hallmayer et al., 2011; Lyall et al., 2017; Sandin et al., 2014). The prenatal period is a sensitive window for the development of ASD, with several maternal and obstetric risk factors identified during that time (Dodds et al.,

2011; Gardener, Spiegelman, & Buka, 2009; Lyall et al., 2017; Sandin et al., 2012). Another such factor may be maternal pre-pregnancy weight or body mass index (BMI).

Maternal obesity has been associated with pregnancy complications, adverse effects on infant health, and obesity in offspring (Aune, Saugstad, Henriksen, & Tonstad, 2014; Moss & Chugani, 2014; Schieve et al., 2000). Recently, a number of studies have examined maternal BMI and ASD with several, but not all, reporting increased risk of ASD among heavier mothers (Bilder et al., 2013; Dodds et al., 2011; Gardner et al., 2015; Getz, Anderka, Werler, & Jick, 2016; Krakowiak et al., 2012; Li et al., 2016; Lyall, Pauls, Santangelo, Spiegelman, & Ascherio, 2011; Moss & Chugani, 2014; Suren et al., 2014). In addition, maternal overweight/obesity has been associated with other developmental disabilities in offspring (Hinkle et al., 2012; Hinkle, Sharma, Kim, & Schieve, 2013; Jo et al., 2015; Krakowiak et al., 2012; Rivera, Christiansen, & Sullivan, 2015; Yeung, Sundaram, Ghassabian, Xie, & Buck Louis, 2017), which have also been increasing in prevalence in US children (Boyle et al., 2011; Visser et al., 2014), suggesting possible common mechanisms. Specifically, obesity can lead to systemic inflammation, altered endocrine response, and insulin resistance (de Heredia, Gomez-Martinez, & Marcos, 2012; Denison, Roberts, Barr, & Norman, 2010; Heerwagen, Miller, Barbour, & Friedman, 2010), which have been linked to ASD and other neurodevelopmental disorders (Auyeung et al., 2009; Baron-Cohen et al., 2014; Goines & Van de Water, 2010; Gore, Martien, Gagnidze, & Pfaff, 2014). Excessive weight gain during pregnancy is also associated with pregnancy complications and adverse maternal/fetal outcomes, leading to clinical recommendations for weight gain based on pre-pregnancy BMI (Rasmussen & Yaktine, 2009). Only a few studies have examined this in relation to ASD, using different metrics (Bilder et al., 2013; Dodds et al., 2011; Gardner et al., 2015), thereby leaving a gap in knowledge.

The prevalence of obesity has increased in the last few decades, paralleling increases in ASD and other developmental disorders. At the start of pregnancy, over 20% of the United States women are considered obese and only about half are at a healthy weight (Chu, Kim, & Bish, 2009; Deputy, Dub, & Sharma, 2018; Fisher, Kim, Sharma, Rochat, & Morrow, 2013). Further, a recent study found that 40–50% of women gained an amount of weight during pregnancy that exceeded clinical recommendations (Deputy, Sharma, & Kim, 2015). Given the magnitude of the obesity epidemic and evidence that its impacts may extend beyond the individual, the need to address questions related to the effects on offspring neurodevelopment is pressing.

The study to explore early development (SEED) is a large, multisite case–control study of ASD risk factors (Schendel et al., 2012; Wiggins et al., 2015) that allows us to examine these research questions more comprehensively than many previous studies. Specifically, we sought to examine not only maternal pre-pregnancy BMI, but also gestational weight gain in association with both clinician-confirmed ASD and developmental delay more broadly. Examining multiple dimensions of maternal weight may help provide clues about underlying mechanisms and concurrently examining other developmental delays can inform whether such associations are specific to ASD or impact neurodevelopment more generally.

Methods

Participants and Data Collection

Sample sources.—SEED is a case–control study originally conducted at sites in California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania. Briefly (see Schendel et al., 2012 for more details), for phase 1, children were eligible if they were age 2–5 years old (30–68 months at clinical assessment), born between September 2003 and August 2006 in (and still residing in) one of the study catchment areas, and lived with a caregiver who could communicate in English (all sites) or Spanish (California and Colorado sites only) to complete a computer-assisted telephone interview, in-person clinic assessments and self-administered questionnaires. Children with ASD (cases) or other developmental delays or disorders (DD) were initially identified from multiple clinical and education sources in each catchment area. A third group of children from the general population (POP) were randomly sampled from birth certificates in each area. Institutional review boards at each study site and the Centers for Disease Control and Prevention approved the study and caregivers of enrolled participants provided informed consent.

Outcome ascertainment.—Details of ASD screening and classification procedures are published elsewhere (Wiggins et al., 2015). To summarize, at the invitation call, caregivers of all children were administered the social communication questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003), with a score of 11 or higher considered the cut-point for identifying "at risk" of ASD. Children with an SCQ score below 11, and who did not have a previous ASD diagnosis, received a general developmental assessment during their in-person study visit. Children with (a) a previous ASD diagnosis from the ascertainment source, (b) an SCQ score 11, or (c) ASD symptoms noted by a SEED research clinician during the general in-person assessment, received a full ASD developmental evaluation, including the autism diagnostic interview-revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and autism diagnostic observation schedule (ADOS) (Gotham, Risi, Pickles, & Lord, 2007), which were used in final ASD classification. We further subdivided the ASD group according to whether or not the child had co-occurring intellectual disability (ID), (Mullen early learning composite (ELC) Standard Score 70). All children not meeting ASD case criteria were classified in the "other DD" or POP groups, depending on whether they were originally sampled from schools/health providers or birth certificate files, respectively. Thus, our eligible analytic sample was comprised of the 2600 index children who completed assessments allowing final classification as ASD, DD, or POP (Wiggins et al., 2015).

Data sources.—A wealth of data were collected about children in all study groups and their families, including from an extensive telephone interview with the caregiver about family sociodemographics, child health and if the caregiver was the biological mother (98% of respondents), her reproductive history and information about her pregnancy with the index child, as well as self-administered forms and birth certificates. We excluded 30 children for whom key interview data were missing (relationship of respondent to child and parental race), resulting in 2,570 children—696 ASD, 987 DD, 887 POP.

Weight variables.—We examined three primary measures of maternal body size and weight gain: prepregnancy BMI (hereinafter referred to as BMI), total gestational weight gain (GWG), and adherence to clinical weight gain guidelines based on pre-pregnancy BMI, as recommended by the Institute of Medicine/American College of Obstetricians and Gynecologists (IOM/ACOG) (ACOG, 2013). We had planned to obtain weight variables from medical records, but because such data were missing for nearly 40%, we relied on the telephone interview, which included maternal height, weight before pregnancy, and amount of weight gained (or lost) during pregnancy. We used typical weight and height distributions among US women of reproductive age (20–39) in NHANES (National Center for Health Statistics [NCHS], 2009; NCHS, 2011) as guidelines to identify outliers in our data for additional comparison of height to weight values. If outliers could not be rectified on manual review they were excluded (<1%). Less than 5% of mothers in the analytic sample were missing information for either BMI or GWG.

Pre-pregnancy BMI was calculated as weight/height^2 (kg/m^2), resulting in all values falling within the BMI range of NHANES (14.7–73.4 kg/m^2). BMI was classified as underweight (<18.5 kg/m^2), normal-weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (30 kg/m^2) (Centers for Disease Control and Prevention, 2015). Total GWG was categorized into quintiles based on the distribution in the POP group. The IOM/ACOG recommended weight gain standards (ACOG, 2013), calculated separately for twins and singletons (i.e., for singleton births, among underweight women: 28–40 lbs; normal-weight women: 25–35 lbs; overweight women: 15–25 lbs; obese women: 11–20 lbs) are used to classify weight gain into categories of "Below," "Meets," or "Exceeds" recommended GWG. GWG varies greatly between singleton versus multiple pregnancies and by the length of gestation, so we limited our primary analyses to term, singleton births, resulting in a sample of 2,036—540 ASD (338 with co-occurring ID, 196 without ID, and six missing this information), 720 DD, and 776 POP. The same sample was used for assessing BMI for simplicity of presentation and because initial results for BMI were quite similar whether preterm births were included or not.

Covariate information.—Possible confounders or effect modifiers were identified from the BMI/GWG literature and other SEED analyses. Demographic variables including maternal age, race/ethnicity, and education, and child sex were ascertained during the maternal interview. Maternal smoking and hypertension variables were derived from interview and medical records data. Maternal smoking was categorized as (a) no smoking during (or 3 months before) pregnancy, (2) peri-conceptional smoking (smoking noted only during the 3 months prior to pregnancy and/or the first trimester), or 3) smoking "throughout" pregnancy (e.g., smoking during trimester 2 and/or 3, as well as an earlier time point peri-conceptionally). Hypertension was treated dichotomously based on prior SEED analyses; a woman was categorized as having hypertension if she had any hypertensive disorders active during pregnancy, including preexisting chronic hypertension or pregnancy-induced hypertension. Birth certificate records were the source of gestational age, parity, and plurality variables.

Statistical Analysis

Chi-square tests were used to assess associations between the three weight variables and case status, as well as with possible confounders. Covariates not associated with BMI or recommended weight gain, and case status were not included in models (e.g., child sex).

Crude and adjusted odds ratios (AOR) were calculated by logistic regression in separate models for the three primary risk factors of interest: maternal pre-pregnancy BMI (normal weight as referent), total GWG in quintiles (quintile 3 as the reference, encompassing the median, to examine both higher and lower total weight gain as possible risk factors), and clinically recommended GWG (meets recommendations as reference). Effect estimates were calculated for ASD or DD compared to POP controls from models including maternal age, education, race/ethnicity, parity, and smoking, as well as a sensitivity analysis adding hypertension, which may be on the causal pathway (for BMI at least). For GWG by quintiles, a similar modeling approach was taken but also accounting for BMI by including it in adjusted models, as well as gestational age in an additional sensitivity analysis. We also examined total GWG as a continuous variable (in 5-pound increments) for comparison with prior studies, adjusting for the same covariates as in categorical GWG models. To further assess combined effects of prepregnancy BMI and GWG, we ran interaction models with a dichotomous BMI variable (normal vs. overweight +obese, or "high" BMI) by GWG quintiles. We ran additional analyses to examine possible effect modification of the primary associations by child sex, also calculating interaction terms (with $P < 0.10$ considered suggestive). Lastly, we conducted a sensitivity analysis by re-running primary analyses excluding from the DD group any children with a prior ASD classification or ASD-like traits, but who did not meet study case criteria for ASD ($n = 133$ term singletons), to create a clean "non-ASD DD" group for comparison of results.

Results

Several participant characteristics varied by case status (Table 1), including child sex and maternal characteristics such as parity, education and race/ethnicity. The POP group had the highest proportion of non-Hispanic White mothers (72%), while the ASD group had the highest proportions of non-Hispanic Asian/Other (12%) and non- Hispanic Black mothers (17%) (Table 1). Mothers of children in the POP group were more likely to report not smoking at all during pregnancy (91%) than other mothers (85 and 86%). The distribution of all three maternal weight variables varied significantly across study groups (Table 1). Mothers of children with ASD or DD were more likely to be obese pre-pregnancy (19% and 18%, respectively) than mothers of POP children (13%). Maternal total GWG was higher in the ASD than DD or POP groups (e.g., for the highest quintile (44+ pounds) 25%, 19%, and 20%, respectively); likewise, exceeding clinically recommended GWG occurred in 51%, 45%, and 44% of these groups, respectively.

Participant characteristics also varied by the maternal weight variables, including maternal age, race, education, parity, smoking, and hypertension (Supporting Information Table S1). The weight gain variables we examined overlapped somewhat; among women who exceeded clinical recommendations 80% had GWG in quintiles 4–5, among those below recommendations all had GWG in quintiles 1–2, and among those who met

recommendations about one-third had GWG in quintile 3 and none in quintile 5 (data not shown). Overweight and obese women were more likely to exceed recommended weight gain (~55%) than normal-weight women (~35%), but on average, obese women were not more likely to have greater total GWG (mean 25 pounds for obese vs. 35 for normal BMI, Supporting Information Table S1).

In unadjusted maternal BMI models, ASD was moderately associated with pre-pregnancy overweight (OR = 1.40, 95% CI 1.06–1.84) and obesity (OR = 1.72, 95%CI 1.26–2.37), but adjustment attenuated these associations (overweight: AOR = 1.25, 95%CI 0.94–1.68; obesity AOR = 1.37, 95%CI 0.98–1.92) (Table 2). The adjusted associations were relatively similar for ASD with, or without, ID. Associations of high BMI with DD remained moderately elevated even after adjustment (overweight AOR = 1.43, 95%CI 1.10–1.85; obese AOR = 1.48, 95%CI 1.08–2.02) (Table 2). Results were quite similar when hypertension was added to models.

Gestational weight gain in the upper two quintiles, compared to the middle, was associated with ASD, and adjustment, including for pre-pregnancy BMI, had little effect (35– <44 pounds: AOR = 1.52, 95%CI 1.05–2.22; > = 44 pounds: AOR = 1.58, 95%CI 1.08–2.31) (Table 3). These patterns did not differ substantially by presence or absence of ID among children with ASD, with confidence intervals slightly wider due to smaller sample sizes. In the continuous model of GWG, each 5-pound increase was associated with increased odds of ASD of 6% (AOR = 1.06, 95%CI 1.02–1.10), which did not vary by ASD with or without ID. No association was observed between higher quintiles or continuous GWG and DD. Modest associations of lower GWG (quintile 1) with both ASD and DD were attenuated by adjustment (Table 3). Adding hypertension to the models, or gestational age, yielded nearly identical results.

Exceeding clinically recommended GWG yielded slightly elevated odds of ASD (AOR = 1.29, 95%CI 1.00–1.66) (Table 4), which were very similar for ASD with or without co-occurring ID. Similarly, as for total GWG, DD was slightly associated with below recommended gains in unadjusted models, although not after adjustment (AOR = 1.11, 95%CI 0.80–1.54) and no association was observed with exceeding recommendations.

Examining effect modification by dichotomous prepregnancy BMI, the association of ASD with higher GWG was more apparent in the overweight/obese (high BMI) group than in the normal BMI group, although not statistically significantly (P-interaction = .69) (Fig. 1. and Supporting Information Table S2; in the high BMI group, the 4th GWG quintile AOR = 2.17, 95%CI 1.10–4.29 and the fifth GWG quintile AOR = 1.90, 95%CI 0.98–3.68). We observed a stronger interaction for ASD without ID (P-interaction =.06; AORs = 3.25 and 4.0 for quintiles 4 and 5, respectively, among the high BMI group), but none for ASD with ID (P-interaction = .82). The association of continuous GWG did not vary by BMI for ASD overall (data not shown, interaction P-value = .98), but an interaction was again observed for ASD without ID (P-interaction = .085; AOR = 1.09, 95% CI 1.01–1.17 among high BMI vs. 0.99, 95%CI 0.91–1.07 among normal BMI, per five pound increase), and not for ASD with ID (P-interaction = .25). For DD, a pattern of effect modification was less consistent than for ASD, with greater odds in the high BMI group for GWG in the fourth quintile (AOR =

2.24), but less so in the fifth quintile (AOR = 1.51) (Fig. 2 and Supporting Information Table S2, interaction *P*-value = .15).

Examining effect modification by child sex, the associations for overweight or obese with ASD or DD did not show consistent differences between males and females (Supporting Information Table S3). However, more consistent sex differences were suggested for ASD and greater GWG (Fig. 3, Supporting Information Table S4); odds were increased among male children but not among females at the fourth and fifth GWG quintiles (e.g., fifth quintile AOR in males is 2.16 (95%CI 1.37–3.41) versus 0.63 (95% CI 0.29–1.40) in females, *P*-interaction =.08), and were similar by co-occurring ID, although the interaction term *P*-values varied (*P* = .085 for ASD without ID and 0.23 for ASD with ID). Additionally, the slight association of ASD with exceeding clinically recommended GWG was observed in males only (Supporting Information Table S5, *P*-interaction =.38) and the difference was accentuated in ASD without ID (*P*-interaction =.09).

In the sensitivity analysis among children with DD and no ASD characteristics, results for the primary weight variables were very similar to results for the overall DD group.

Discussion

This is one of the few studies to comprehensively examine the maternal weight-ASD association by assessing both pre-pregnancy BMI and gestational weight gain using several metrics, as well as examining specificity of effects by sub-grouping ASD according to co-occurrence of ID and including children with other developmental disorders. Greater gestational weight gain, examined in quintiles or continuously, was moderately and consistently associated with ASD. There was a slight association of obesity with ASD, and the GWG association appeared stronger among mothers who were overweight or obese pre-pregnancy, suggesting possible potentiation of effects. This was evident primarily in the sub-group of ASD without ID. Maternal pre-pregnancy overweight or obesity was associated with DD and in contrast to the ASD findings, there was no association of greater GWG overall with DD.

There are some limitations to consider in interpreting our results. BMI and GWG were based on self-report of weight or weight gain 3–5 years postnatally. SEED did include some medical record review, so our original intent was to use prenatal records, but a substantial proportion of women were missing necessary information and this varied by demographic characteristics. We compared pre-pregnancy weight by medical record versus interview for those who had both and found high correlation (*r* = .88). Future analyses including additional phases of SEED data collection may allow for comparisons of weight variable data from interview and medical records, by case status, with additional power to make up for missing medical record data in SEED1. Higher functioning children with ASD may be under-represented in SEED due to the age at ascertainment, similar to other studies of this age group (Wiggins et al., 2015). Another limitation is possible selection bias because a substantial number of families targeted from the multiple recruitment sources could not be located or contacted. Analyses from one SEED site with the complete data available to assess nonresponse found it was associated with younger maternal age, lower maternal

education, and non-white race, but not with perinatal factors, such as parity or preterm birth (unpublished analysis). In all analyses, we controlled for these three sociodemographic factors. Although we accounted for a number of confounders, including smoking (and co-occurrence of hypertension), there may still be residual confounding by some unknown or unmeasured factors, such as specific components of maternal diet or genetic predisposition. As both obesity and ASD have genetic components, their overlap should be explored in future studies. We did not have paternal BMI, nor biomarkers of intermediate conditions (inflammation, endocrine alterations) that may help elucidate mechanisms if included in future studies.

Strengths of SEED include the large sample size with detailed clinical and covariate data. A primary strength of the study is the thorough ASD case-classification and sub-grouping possible by ID, based on in-person examination and standardized diagnoses, only available in one other study on this topic (Krakowiak et al., 2012). The DD group provided an additional comparison to examine specificity, although diagnoses were not confirmed by study staff. Further, the detailed data collection provided more information on maternal factors than most previous studies examining these questions. SEED is not limited to one geographic area but includes several regions of the United States.

The existing literature on maternal BMI and GWG in association with ASD is based on studies with a number of methodological differences and some inconsistent results. For example, definition of "pre-pregnancy" BMI could vary from early adult age to prenatal visit measurements and sources of information on weight or weight gain varied from self-report to medical records or birth certificates (which may be self-report for pre-pregnancy BMI). In addition, child autism diagnosis was ascertained in various ways, including maternal-report (usually of physician diagnosis) (Jo et al., 2015; Lyall et al., 2011; Moss & Chugani, 2014), medical records or linkage (primarily) (Bilder et al., 2013; Dodds et al., 2011; Gardner et al., 2015; Getz et al., 2016; Li et al., 2016; Suren et al., 2014), or child evaluation with standardized instruments (Krakowiak et al., 2012 and our current study). The studies of DD include even more heterogeneous endpoints and assessment tools (reviewed in Rivera et al., 2015). This nonspecificity may make it more difficult to identify risk factors or distinguish mechanisms, particularly as some of the children with DD may have autism-like behaviors given the spectrum nature of the condition, though these did not drive our results as indicated by the sensitivity analysis.

Reviewing prior ASD-BMI studies, several investigators reported associations with greater maternal weight or obesity pre-pregnancy, with odds ratios from about 1.5–2.0 (Dodds et al., 2011; Gardner et al., 2015; Krakowiak et al., 2012; Li et al., 2016; Lyall et al., 2011), and J- or U-shaped associations have been reported (Andersen, Thomsen, Nohr, & Lemcke, 2018; Getz et al., 2016). However, others did not observe associations with BMI in final adjusted models (Bilder et al., 2013; Moss & Chugani, 2014; Suren et al., 2014). Two studies reported associations with paternal obesity (one was at age 18), while accounting for maternal BMI status (Gardner et al., 2015; Suren et al., 2014). These results may indicate possible confounding or genetic associations for maternal results. Studies that further sub-divided ASD by co-occurring ID either found little difference (Bilder et al., 2013; Gardner et al., 2015), or in one very small study, a somewhat stronger association in those without ID

(Li et al., 2016), which we did not observe for BMI. One study examining more severe obesity (class II/III or BMI > 35 kg/m^2) reported an association, although with ASD and other DD combined due to very small numbers of ASD (Jo et al., 2015). Our sample size was too small for making conclusions with regard to these sub-classes of obesity among our case groups so this should be examined further in larger studies, including additional phases of SEED.

Only a few of these studies examined some type of GWG variable in relation to ASD, reporting modest associations using different metrics. A Canadian study (Dodds et al., 2011) reported an association of high weight gain (18 kg), which was slightly attenuated when adjusted (RR = 1.2), including for pre-pregnancy weight. In two different samples from Utah (Bilder et al., 2013), odds increased 10–20% (ORs 1.1–1.2) per five-pound weight gain, adjusted for pre-pregnancy BMI. A large study from Sweden examined the IOM clinical recommendations and found slight associations with ASD (ORs 1.1–1.2) for both women who were below or exceeded recommendations (Gardner et al., 2015). Neither study found differences in association within ASD by co-occurring ID. Thus our results have some comparability, supporting an association with greater GWG, even when adjusting for prepregnancy BMI. These prior GWG studies did not report data in a manner we could use for comparison to our result that suggested potentiation of associations of ASD and greater GWG by high pre-pregnancy BMI, for example, an interaction. The somewhat weaker associations we observed for exceeding clinical GWG recommendations compared to total GWG may reflect the rather broad categories; nearly half our sample "exceeded" recommendations. The upper quintiles of GWG in our study represent more extreme cut-points than those for exceeding clinical recommendations among overweight or obese women. While useful clinically, these recommendations are designed for purposes unrelated to ASD risk. We also found that the association of greater GWG and ASD was only apparent in male children, a comparison not previously reported, but limited by smaller sample size for females, especially when sub-classifying by ID status.

We examined other DD primarily to consider specificity of effects, that may reflect potential mechanisms, observing somewhat different results than for ASD. As recently reviewed, numerous studies reported associations of pre-pregnancy obesity and DD, although not entirely consistently across a variety of assessments and endpoints (Rivera et al., 2015; van der Burg et al., 2016). For example, in a national longitudinal study (Hinkle et al., 2012 and 2013), children of severely obese mothers had higher rates of DD that tended to reflect cognitive or learning/behavior endpoints, but no association with motor or physical disabilities. In contrast, in a study of a New York population, maternal obesity was associated with failing the fine motor domain of the ages and stages questionnaire (ASQ), whereas paternal obesity was associated with failing the personal-social domain (Yeung et al., 2017). Children in the SEED DD group have a variety of conditions, the majority being speech delay or other general developmental delay, with some chromosomal, syndromic or other conditions; 24% also had ID (Wiggins et al., 2015). Another study, with a similar design as SEED, reported associations of maternal obesity with both ASD and non-ASD DD (all of whom had ID) (Krakowiak et al., 2012).

Fewer studies have examined GWG and DD, with inconsistent results. Jo et al. (2015) stated that none of the endpoints associated with maternal BMI had independent associations with GWG, consistent with our findings for DD. Rodriguez et al. (2008) reported an increased risk of offspring ADHD with excessive GWG among obese mothers, more consistent with our ASD findings.

There are several mechanistic hypotheses regarding a relationship of excess maternal weight with ASD or neurodevelopment in offspring. The metabolic syndrome, including obesity and related conditions such as hypertension or diabetes, is associated with chronic inflammation; the developing fetus is exposed to higher levels of glucose, triglycerides, leptin and elevated inflammatory cytokine levels (de Heredia et al., 2012; Denison et al., 2010; Rivera et al., 2015). Inflammation and immune dysfunction have been associated with deleterious effects on brain development and with ASD (Goines & Van de Water, 2010; Rivera et al., 2015; Rose et al., 2012; van der Burg et al., 2016). Further, resulting oxidative stress may bring about alterations in myelination and cortical connectivity and cell necrosis (Main, Thomas, Esterman, & Fenech, 2013; Rose et al., 2012), as well as changes in the epigenome, also shown associated with both obesity and ASD (de Heredia et al., 2012; Heerwagen et al., 2010; Herrera, Keildson, & Lindgren, 2011; Ladd-Acosta et al., 2014). The findings with paternal obesity noted in a few studies above may support this pathway, such as through epigenetic alterations in sperm, which should be examined further.

Obesity is also related to endocrine abnormalities, both as a precursor or endpoint (Kokkoris & Pi-Sunyer, 2003). Imbalances in the endocrine system, which is crucial to brain development, have long been considered a factor in autism etiology (Auyeung et al., 2009; Baron-Cohen et al., 2014; Gore et al., 2014; Lyall et al., 2017), leading to efforts to examine sex-specific effects of risk factors. Our suggestive finding of a stronger association of GWG and ASD among male versus female children is interesting in this regard and should be replicated. Fat cells lead to increased hormone production, including estrogens, so it is unclear how this may relate to the higher testosterone levels hypothesized associated with ASD (Auyeung et al., 2009; Kokkoris & Pi-Sunyer, 2003). Additional studies that could be useful for elucidating mechanisms would include metabolomic and/or hormone measurements, or have a large enough sample size to examine the interaction of co-occurring conditions such as hypertension and obesity.

While not as well studied, excessive or rapid weight gain among pregnant women may lead to (or reflect) similar mechanisms, such as inflammation, altered nutritional status, and endocrine dysregulation. Resulting changes in nutrient delivery and demand for oxygen may alter fetal metabolism and growth, thereby affecting brain development (Rasmussen & Yaktine, 2009; Rivera et al., 2015). Excessive weight gain may exacerbate already elevated inflammatory cytokines or changes associated with pre-pregnancy adiposity, explaining the potentiation we observed. However, the mechanisms of obesity and excessive GWG may differ, reflecting effects of differential timing pre-pregnancy versus during fetal development, which could contribute to differences we observed for ASD versus DD. Chronicity of overweight/obese status and timing of weight gain during pregnancy, as well as their interaction, should be explored further.

Animal studies, typically of a maternal gestational high fat diet, support human findings, showing effects on offspring hyperactivity, impairments in social behavior, increased anxiety- and depressive-like symptoms, and diminished cognition (reviewed in Rivera et al., 2015). One study of nonhuman primates on high fat diets for 2–4 years before pregnancy reported perturbations in the serotonergic system of fetal offspring, increased anxiety exhibited by female infants, and increased aggression by males (Sullivan et al., 2010). The high fat diet continued during pregnancy, as well as postnatally in offspring, so timing cannot be separated. Further limiting the usefulness of comparison of animal to epidemiologic studies are the complex causes of obesity in humans, including aspects of diet other than fat, exercise, stress, and genetics.

In summary, this study, with its rigorous case-classification and large sample size, indicates an association of greater GWG with ASD in offspring, but little association with non-ASD DD. Our work adds to only a few existing studies that have examined weight gain during pregnancy. Although this association with ASD was still observed when adjusting for maternal pre-pregnancy BMI, it may be potentiated among women who were overweight or obese pre-pregnancy. The association observed between maternal overweight or obese status and DD confirms several other studies. Importantly, GWG (and BMI) may represent potentially modifiable risk factors, some of the few identified thus far for ASD, and better understanding of these relationships may aid in reducing the impact of this complex developmental condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

American College of Obstetricians and Gynecologists. (2013). ACOG Committee opinion no. 548: Weight gain during pregnancy. Obstetrics & Gynecology, 121(1), 210–212. [PubMed: 23262962]

Andersen CH, Thomsen PH, Nohr EA, & Lemcke S (2018). Maternal body mass index before pregnancy as a risk factor for ADHD and autism in children. European Child & Adolescent Psychiatry, 27(2), 139–148. [PubMed: 28712019]

Aune D, Saugstad OD, Henriksen T, & Tonstad S (2014). Maternal body mass index and the risk of fetal death, stillbirth, and infant death: A systematic review and meta-analysis. JAMA : The Journal of the American Medical Association, 311(15), 1536–1546. [PubMed: 24737366]

Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, & Hackett G (2009). Fetal testosterone and autistic traits. British Journal of Psychology, 100(Pt 1), 1–22. [PubMed: 18547459]

Baron-Cohen S, Auyeung B, Norgaard-Pedersen B, Hougaard DM, Abdallah MW, Melgaard L, … Lombardo MV (2014). Elevated fetal steroidogenic activity in autism. Molecular Psychiatry, 20(3), 369–376. [PubMed: 24888361]

Bilder DA, Bakian AV, Viskochil J, Clark EA, Botts EL, Smith KR, … Coon H (2013). Maternal prenatal weight gain and autism spectrum disorders. Pediatrics, 132(5), e1276–e1283. [PubMed: 24167172]

Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, … Kogan MD (2011). Trends in the prevalence of developmental disabilities in US children, 1997-2008. Pediatrics, 127(6), 1034–1042. [PubMed: 21606152]

Centers for Disease Control and Prevention. (2015). About Adult BMI. Retrieved from https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html.

Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN, … Yeargin-Allsopp KR; Centers for Disease Control and Prevention (CDC). (2016). Prevalence and characteristics of autism spectrum disorder among children aged 8 years--autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveillance Summaries, 65(3), 1–23.

Chu SY, Kim SY, & Bish CL (2009). Prepregnancy obesity prevalence in the United States, 2004-2005. Maternal and Child Health Journal, 13(5), 614–620. [PubMed: 18618231]

de Heredia FP, Gomez-Martinez S, & Marcos A (2012). Obesity, inflammation and the immune system. Proceedings of the Nutrition Society, 71(2), 332–338.

Denison FC, Roberts KA, Barr SM, & Norman JE (2010). Obesity, pregnancy, inflammation, and vascular function. Reproduction, 140(3), 373–385. [PubMed: 20215337]

Deputy NP, Dub B, & Sharma AJ (2018). Prevalence and trends in prepregnancy normal weight - 48 states, New York City, and district of Columbia, 2011-2015. MMWR. Morbidity and Mortality Weekly Report, 66(5152), 1402–1407. [PubMed: 29300720]

Deputy NP, Sharma AJ, & Kim SY (2015). Gestational weight gain - United States, 2012 and 2013. MMWR. Morbidity and Mortality Weekly Report, 64(43), 1215–1220. [PubMed: 26540367]

Dodds L, Fell DB, Shea S, Armson BA, Allen AC, & Bryson S (2011). The role of prenatal, obstetric and neonatal factors in the development of autism. Journal of Autism and Developmental Disorders, 41(7), 891–902. [PubMed: 20922473]

Fisher SC, Kim SY, Sharma AJ, Rochat R, & Morrow B (2013). Is obesity still increasing among pregnant women? Prepregnancy obesity trends in 20 states, 2003-2009. Preventive Medicine, 56(6), 372–378. [PubMed: 23454595]

Gardener H, Spiegelman D, & Buka SL (2009). Prenatal risk factors for autism: comprehensive meta-analysis. British Journal of Psychiatry, 195(1), 7–14.

Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, … Dalman C (2015). Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: Results from a Swedish total population and discordant sibling study. International Journal of Epidemiology, 44(3), 870–883. [PubMed: 26045508]

Getz KD, Anderka MT, Werler MM, & Jick SS (2016). Maternal pre-pregnancy body mass index and autism spectrum disorder among offspring: A population-based case-control study. Paediatric and Perinatal Epidemiology, 30(5), 479–487. [PubMed: 27239935]

Goines P, & Van de Water J (2010). The immune system's role in the biology of autism. Current Opinion in Neurology, 23(2), 111–117. [PubMed: 20160651]

Gore AC, Martien KM, Gagnidze K, & Pfaff D (2014). Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. Endocrine Reviews, 35(6), er20131122.

Gotham K, Risi S, Pickles A, & Lord C (2007). The autism diagnostic observation schedule: Revised algorithms for improved diagnostic validity. Journal of Autism and Developmental Disorders, 37(4), 613–627. [PubMed: 17180459]

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, … Risch N (2011). Genetic heritability and shared environmental factors among twin pairs with autism. Archives of General Psychiatry, 68(11), 1095–1102. [PubMed: 21727249]

Heerwagen MJ, Miller MR, Barbour LA, & Friedman JE (2010). Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 299(3), R711–R722.

Herrera BM, Keildson S, & Lindgren CM (2011). Genetics and epigenetics of obesity. Maturitas, 69(1), 41–49. [PubMed: 21466928]

Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, & Sharma AJ (2012). Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. International Journal of Obesity, 36(10), 1312–1319. [PubMed: 22964791]

Hinkle SN, Sharma AJ, Kim SY, & Schieve LA (2013). Maternal prepregnancy weight status and associations with children's development and disabilities at kindergarten. International Journal of Obesity, 37(10), 1344–1351. [PubMed: 23860335]

Jo H, Schieve LA, Sharma AJ, Hinkle SN, Li R, & Lind JN (2015). Maternal prepregnancy body mass index and child psychosocial development at 6 years of age. Pediatrics, 135(5), e1198–e1209. [PubMed: 25917989]

Kokkoris P, & Pi-Sunyer FX (2003). Obesity and endocrine disease. Endocrinology and Metabolism Clinics of North America, 32(4), 895–914. [PubMed: 14711067]

Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, & Hertz-Picciotto I (2012). Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics, 129(5), e1121–e1128. [PubMed: 22492772]

Ladd-Acosta C, Hansen KD, Briem E, Fallin MD, Kaufmann WE, & Feinberg AP (2014). Common DNA methylation alterations in multiple brain regions in autism. Molecular Psychiatry, 19(8), 862–871. [PubMed: 23999529]

Li M, Fallin MD, Riley A, Landa R, Walker SO, Silverstein M, … Wang X (2016). The association of maternal obesity and diabetes with autism and other developmental disabilities. Pediatrics, 137(2), e2015–e2206.

Lord C, Rutter M, & Le Couteur A (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders, 24(5), 659–685. [PubMed: 7814313]

Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, … Newschaffer C (2017). The changing epidemiology of autism spectrum disorders. Annual Review of Public Health, 38, 81–102.

Lyall K, Pauls DL, Santangelo S, Spiegelman D, & Ascherio A (2011). Maternal early life factors associated with hormone levels and the risk of having a child with an autism spectrum disorder in the Nurses' Health Study II. Journal of Autism and Developmental Disorders, 41(5), 618–627. [PubMed: 20700638]

Main PA, Thomas P, Esterman A, & Fenech MF (2013). Necrosis is increased in lymphoblastoid cell lines from children with autism compared with their non-autistic siblings under conditions of oxidative and nitrosative stress. Mutagenesis, 28(4), 475–484. [PubMed: 23766106]

Moss BG, & Chugani DC (2014). Increased risk of very low birth weight, rapid postnatal growth, and autism in underweight and obese mothers. American Journal of Health Promotion, 28(3), 181–188. [PubMed: 23875984]

National Center for Health Statistics (2009). NHANES 2007–2008 demographics data. Retrieved from https://wwwn.cdc.gov/NCHS/NHANES/Search/DataPage.aspx?Component=Demographics&CycleBeginYear=2007.

National Center for Health Statistics (2011). NHANES 2007–2008 examination data. Retrieved from https://wwwn.cdc.gov/Nchs/Nhanes/Search/DataPage.aspx?Component=Examination&CycleBeginYear=2007.

Rasmussen AL, & Yaktine KM (Eds.) (2009). Institute of medicine (committee to reexamine I. O. M. Pregnancy weight guidelines, food and nutrition board and board on children, youth, and families) In Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academy Press.

Rice C, Nicholas J, Baio J, Pettygrove S, Lee LC, Van Naarden Braun K, … Yeargin-Allsopp M (2010). Changes in autism spectrum disorder prevalence in 4 areas of the United States. Disability and Health Journal, 3(3), 186–201. [PubMed: 21122784]

Rivera HM, Christiansen KJ, & Sullivan EL (2015). The role of maternal obesity in the risk of neuropsychiatric disorders. Frontiers in Neuroscience, 9, 194. [PubMed: 26150767]

Rodriguez A, Miettunen J, Henriksen TB, Olsen J, Obel C, Taanila A, … Järvelin MR (2008). Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. International Journal of Obesity, 32(3), 550–557. [PubMed: 17938639]

Rose S, Melnyk S, Pavliv O, Bai S, Nick TG, Frye RE, & James SJ (2012). Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. Translational Psychiatry, 2, e134. [PubMed: 22781167]

Rutter M, Bailey A, & Lord C (2003). The Social Communication Questionnaire. Los Angeles: Western Psychological Services.

Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, & Reichenberg A (2012). Advancing maternal age is associated with increasing risk for autism: A review and meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry, 51(5), 477–486.e471. [PubMed: 22525954]

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, & Reichenberg A (2014). The familial risk of autism. JAMA : The Journal of the American Medical Association, 311(17), 1770–1777. [PubMed: 24794370]

Schendel DE, Diguiseppi C, Croen LA, Fallin MD, Reed PL, Schieve LA, … Yeargin-Allsopp M (2012). The study to explore early development (SEED): A multisite epidemiologic study of autism by the centers for autism and developmental disabilities research and epidemiology (CADDRE) network. Journal of Autism and Developmental Disorders, 42(10), 2121–2140. [PubMed: 22350336]

Schieve LA, Cogswell ME, Scanlon KS, Perry G, Ferre C, Blackmore-Prince C, … Rosenberg D (2000). Prepregnancy body mass index and pregnancy weight gain: Associations with preterm delivery. The NMIHS collaborative study group. Obstetrics & Gynecology, 96(2), 194–200. [PubMed: 10908762]

Sullivan EL, Grayson B, Takahashi D, Robertson N, Maier A, Bethea CL, … Grove KL (2010). Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring. Journal of Neuroscience, 30(10), 3826–3830. [PubMed: 20220017]

Suren P, Gunnes N, Roth C, Bresnahan M, Hornig M, Hirtz D, … Stoltenberg C (2014). Parental obesity and risk of autism spectrum disorder. Pediatrics, 133(5), e1128–e1138. [PubMed: 24709932]

van der Burg JW, Sen S, Chomitz VR, Seidell JC, Leviton A, & Dammann O (2016). The role of systemic inflammation linking maternal BMI to neurodevelopment in children. Pediatric Research, 79(1–1), 3–12. [PubMed: 26375474]

Visser SN, Danielson ML, Bitsko RH, Holbrook JR, Kogan MD, Ghandour RM, … Blumberg SJ (2014). Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. Journal of the American Academy of Child and Adolescent Psychiatry, 53(1), 34–46.e32. [PubMed: 24342384]

Wiggins LD, Reynolds A, Rice CE, Moody EJ, Bernal P, Blaskey L, … Levy SE (2015). Using standardized diagnostic instruments to classify children with autism in the study to explore early development. Journal of Autism and Developmental Disorders, 45(5), 1271–1280. [PubMed: 25348175]

Yeung EH, Sundaram R, Ghassabian A, Xie Y, & Buck Louis G (2017). Parental Obesity and Early Childhood Development. Pediatrics, 139(2), e20161459. [PubMed: 28044047]

Figure 1.
Interaction of gestational weight gain (GWG) and prepregnancy Body Mass Index (BMI) on the development of autism spectrum disorder (ASD) in offspring, among singleton term births. Figure displays adjusted odds ratios (ORs) (log scale) comparing ASD to the population control group by quintile of weight gain (reference is 30 to <35 pounds or middle quintile), with error bars representing 95% confidence intervals, fully adjusted in logistic regression models for variables used in primary tables; e.g., maternal race/ethnicity, age, education, parity, and prenatal smoking, plus interaction terms. The normal BMI (18.5–24.9 kg/m^2, n = 758) group is indicated by squares, and high BMI (overweight/obese, or 25 kg/m^2, n = 463) group by diamonds.

Figure 2.
Interaction of gestational weight gain (GWG) and prepregnancy body mass index (BMI) on the presence of developmental delays (DD) in offspring, among singleton term births. Figure displays adjusted odds ratios (ORs) (log scale) comparing DD to the population control group by quintile of weight gain (reference is 30 to <35 pounds or middle quintile), with error bars representing 95% confidence intervals, fully adjusted in logistic regression models for variables used in primary tables; e.g., maternal race/ethnicity, age, education, parity, and prenatal smoking, plus interaction terms. The normal BMI (18.5–24.9 kg/m^2, $n = 839$) group is indicated by squares, and high BMI (overweight/obese, or 25 kg/m^2, $n = 547$) group by diamonds.
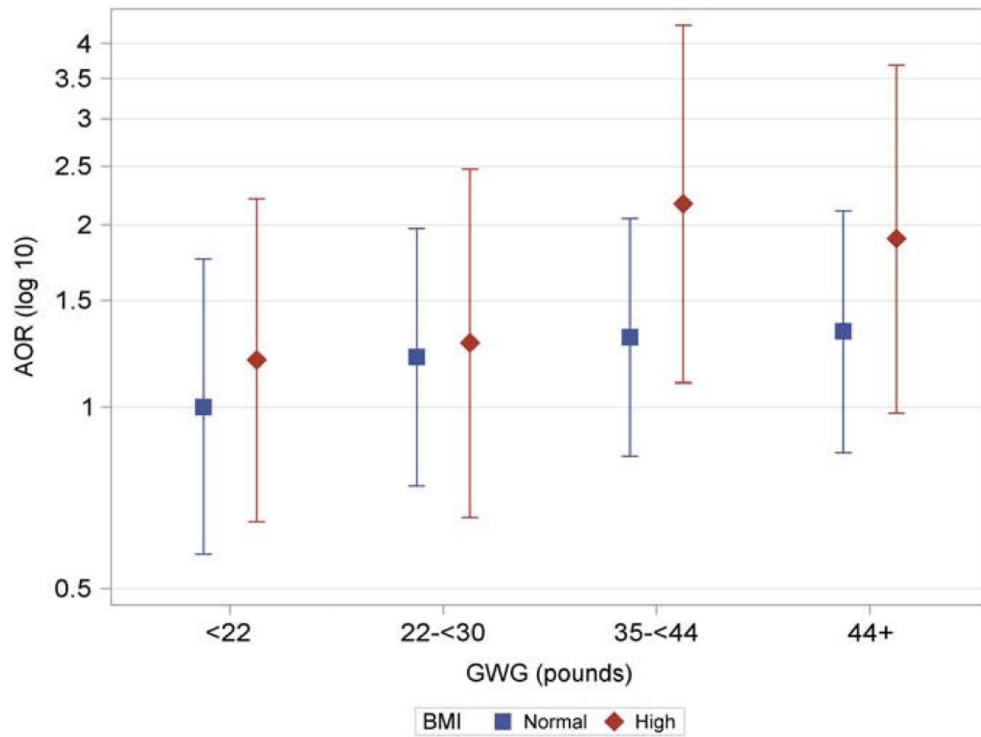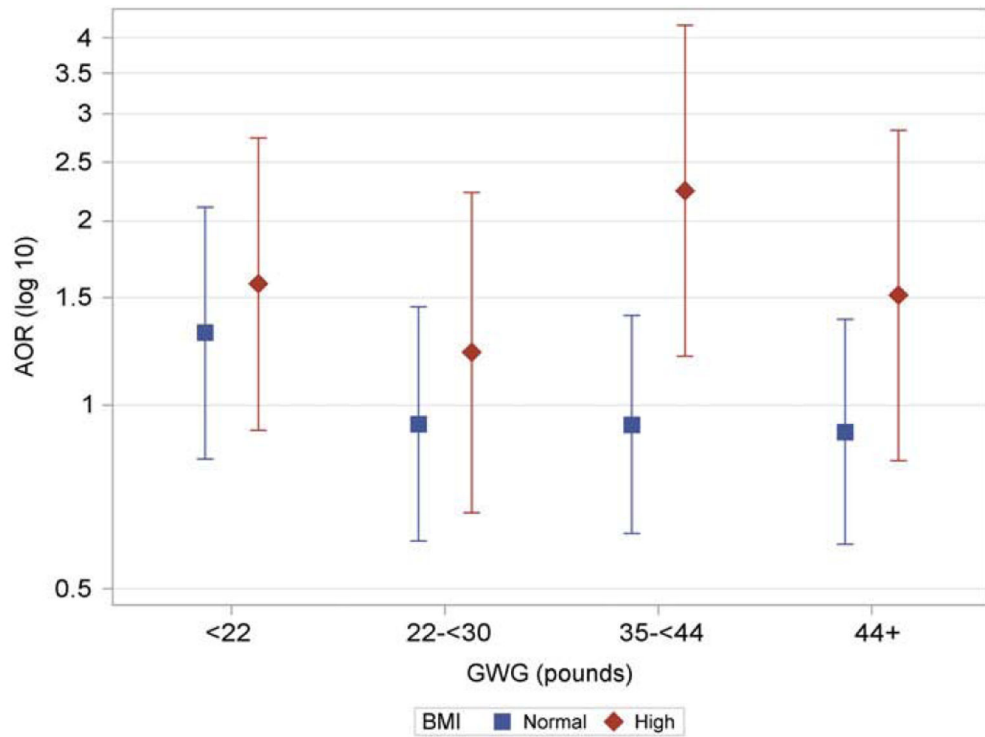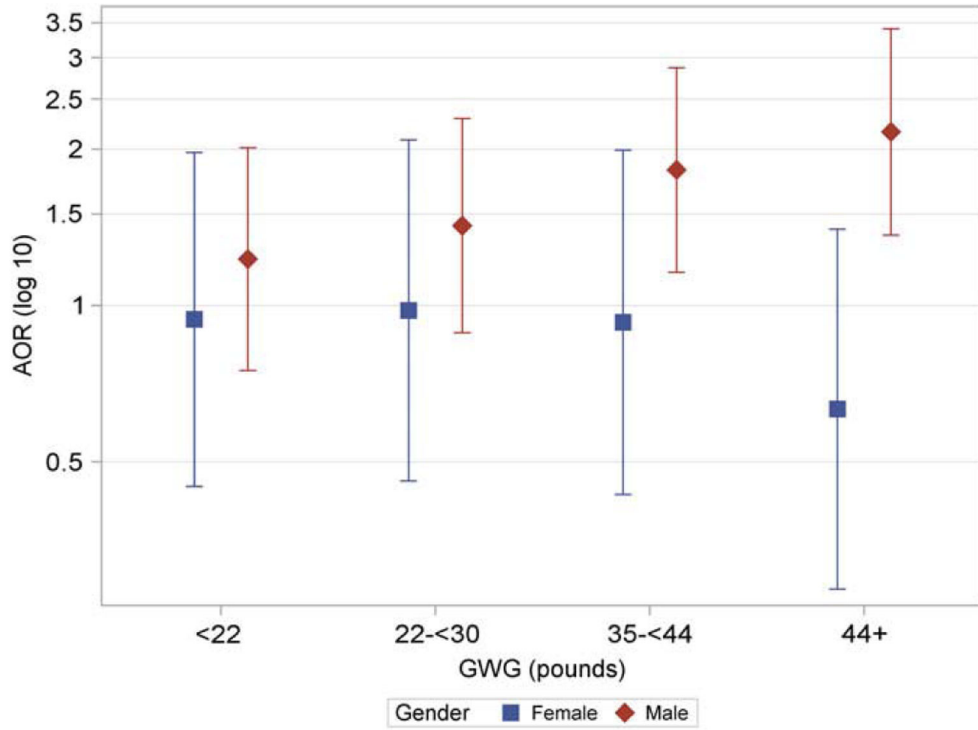
Figure 3.
Interaction of Gestational Weight Gain (GWG) and child sex on development of Autism Spectrum Disorder (ASD) in offspring, among singleton term births. Figure displays adjusted odds ratios (ORs) (log scale) comparing ASD to the population control group by quintile of weight gain (reference is 30 to <35 pounds or middle quintile), with error bars representing 95% confidence intervals, fully adjusted in logistic regression models for variables used in primary tables; e.g., maternal race/ethnicity, age, education, parity, pre-pregnancy Body Mass Index (BMI), and prenatal smoking, plus interaction terms. (n = 446 females indicated by squares and 811 males, indicated by diamonds).

Table 1.

Characteristics of the study population by offspring case status, among singleton, term births

	ASD		DD		POP		
	n (540)	%	n (720)	%	n (776)	%	P-value [1]
Child gender							
Male	442	81.9	489	67.9	410	52.8	<.0001
Female	98	18.2	231	32.1	366	47.2	
Maternal parity (previous livebirths)							
0	258	47.8	292	40.6	358	46.1	.0022
1	180	33.3	255	35.4	290	37.4	
2	102	18.9	173	24.0	128	16.5	
Maternal age at delivery (years)							
< 20	14	2.6	19	2.6	20	2.6	.2251
20–24	55	10.2	76	10.6	58	7.5	
25–29	138	25.7	159	22.1	163	21.0	
30–34	182	33.8	262	36.4	295	38.0	
35	149	27.7	204	28.3	240	30.9	
Maternal race/ethnicity							
Non-hispanic white	314	58.3	445	61.8	557	71.8	<.0001
Non-hispanic black	91	16.9	113	15.7	80	10.3	
Non-hispanic Asian, multiple races, and other	65	12.1	65	9.0	66	8.5	
Hispanic	69	12.8	97	13.5	73	9.4	
Maternal education							
High school or less	84	15.6	125	17.4	69	8.9	<.0001
Some college	170	31.5	187	26.0	180	23.2	
College degree	168	31.2	235	32.7	283	36.5	
Masters or higher	117	21.7	172	23.9	243	31.4	
Maternal smoking							
None during pregnancy	456	85.2	614	86.4	697	90.8	.0006
Any only during 3 months pre-pregnancy or first trimester	50	9.4	46	6.5	49	6.4	
Throughout pregnancy	29	5.4	51	7.2	22	2.9	

	ASD		DD		POP		
	n (540)	%	n (720)	%	n (776)	%	P-value [1]
Maternal hypertension							
Yes (chronic or pregnancy-induced)	73	13.6	92	12.8	79	10.2	.1306
No	465	86.4	625	87.2	695	89.8	
Maternal pre-pregnancy body mass index (kg/m^2)							.0003
Underweight (<18.5)	12	2.3	17	2.4	26	3.4	
"Normal" weight (18.5–24.9)	288	54.7	371	53.1	486	63.6	
Overweight (25–29.9)	129	24.5	188	26.9	156	20.4	
Obese (30)	98	18.6	123	17.6	96	12.6	
Gestational weight gain (quintiles)							.0079
< 22 pounds	103	19.6	176	25.1	142	18.7	
22- <30	92	17.5	121	17.3	149	19.6	
30- <35	77	14.6	121	17.3	152	20.0	
35- <44	123	23.4	151	21.5	163	21.5	
44 pounds	131	24.9	132	18.8	153	20.2	
IOM/ACOG recommended weight gain							.0307
Below	69	13.3	117	17.0	104	13.9	
Meets	185	35.7	262	38.0	316	42.1	
Exceeds	265	51.1	310	45.0	330	44.0	

ASD, autism spectrum disorder; DD, other developmental disorder; POP, population control group; IOM, institute of medicine, ACOG, american college of obstetricians and gynecologists.

[1] P-value for Chi-Square Test of Independence across groups.

Table 2.

Associations of ASD or DD with maternal pre-pregnancy BMI[1] among singleton term births; crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI)

	Model	Underweight (<18.5 kg/m²)		Overweight (25.0–29.9 kg/m²)		Obese (≥30 kg/m²)	
		OR	95% CI	OR	95% CI	OR	95% CI
ASD	Crude	0.78	(0.39–1.57)	1.40	(1.06–1.84)	1.72	(1.26–2.37)
(n = 522)	Adj[2]	0.72	(0.35–1.49)	1.25	(0.94–1.68)	1.37	(0.98–1.92)
ASD with ID	Crude	0.98	(0.45–2.14)	1.48	(1.07–2.03)	1.93	(1.34–2.76)
(n = 322)	Adj[2]	0.92	(0.40–2.08)	1.21	(0.86–1.70)	1.35	(0.91–2.00)
ASD without ID	Crude	0.49	(0.15–1.64)	1.25	(0.85–1.83)	1.37	(0.87–2.15)
(n = 194)	Adj[2]	0.49	(0.14–1.66)	1.27	(0.85–1.91)	1.38	(0.86–2.23)
DD	Crude	0.86	(0.46–1.60)	1.58	(1.23–2.03)	1.68	(1.24–2.26)
(n = 693)	Adj[2]	0.91	(0.48–1.72)	1.43	(1.10–1.85)	1.48	(1.08–2.02)

ASD, autism spectrum disorder; DD, other developmental disorder; ID, intellectual disability (IQ < 70); POP, population-based control group; BMI, body mass index.

[1] Reference is "normal" BMI; ASD or DD compared to POP control group (n = 757). N's shown are for adjusted models.

[2] Adjusted for maternal age (<25, 25–29, 30–34 = ref, ≥35), education (HS or less, some college, college degree = ref, Masters or higher), race/ethnicity (Non-Hispanic White = ref; Non-Hispanic Black; Non-Hispanic Asian; multiple races, or other; Hispanic), parity (0 = ref, ≥1), and smoking (during pre-pregnancy or first trimester, throughout pregnancy, none = ref).

Table 3.

Associations of ASD or DD with maternal gestational weight gain (quintiles of pounds and continuous)[1], among singleton, term births; crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI)

	Model	Q1 (<22 pounds)		Q2 (22–30 pounds)		Q4 (35–44 pounds)		Q5 (44 pounds)		Continuous	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
ASD	Crude	1.43	(0.99–2.08)	1.22	(0.84–1.78)	1.49	(1.04–2.14)	1.69	(1.18–2.42)	1.03	(1.00–1.07)
(n = 514)	Adj[2]	1.05	(0.70–1.57)	1.24	(0.84–1.84)	1.52	(1.05–2.22)	1.58	(1.08–2.31)	1.06	(1.02–1.10)
ASD with ID	Crude	1.46	(0.95–2.26)	1.19	(0.76–1.85)	1.45	(0.95–2.21)	1.58	(1.04–2.41)	1.02	(0.98–1.06)
(n = 317)	Adj[2]	0.87	(0.54–1.41)	1.14	(0.72–1.83)	1.45	(0.92–2.27)	1.55	(0.99–2.43)	1.07	(1.02–1.11)
ASD without ID	Crude	1.26	(0.73–2.19)	1.24	(0.72–2.14)	1.57	(0.93–2.63)	1.81	(1.08–3.02)	1.05	(1.00–1.11)
(n = 191)	Adj[2]	1.20	(0.67–2.14)	1.26	(0.72–2.20)	1.57	(0.92–2.66)	1.64	(0.97–2.79)	1.05	(1.00–1.11)
DD	Crude	1.56	(1.12–2.16)	1.02	(0.73–1.43)	1.16	(0.84–1.61)	1.08	(0.78–1.51)	0.98	(0.95–1.01)
(n = 683)	Adj[2]	1.27	(0.89–1.80)	0.99	(0.70–1.40)	1.24	(0.88–1.73)	1.06	(0.75–1.50)	1.00	(0.97–1.04)

ASD, autism spectrum disorder; DD, other developmental disorder; ID, intellectual disability (IQ 70); POP, population-based control group

[1] Reference is middle Quintile (30 to<35 pounds); continuous is per five pound increase; in ASD or DD compared to POP control group (n = 743). N's shown are for adjusted models.

[2] Adjusted for maternal age (<25, 25–29, 30–34 = ref, 35), education (HS or less, some college, college degree = ref, Masters or higher), race/ethnicity (Non-Hispanic White = ref; Non-Hispanic Black; Non-Hispanic Asian; multiple races, or other; Hispanic), parity (0 = ref, 1), pre-pregnancy BMI (<18.5, 18.5–24.9 = ref, 25–29.9, 30), and smoking (during pre-pregnancy or first trimester, throughout pregnancy, none = ref).

Table 4.

Associations of ASD or DD with IOM/ACOG Recommended Weight Gain[1], among singleton, term births; Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI)

	Model	Below IOM/ACOG Recommendation		Exceeds IOM/ACOG Recommendation	
		OR	95% CI	OR	95% CI
ASD	Crude	1.13	(0.80–1.62)	1.37	(1.08–1.75)
(n = 514)	Adj[2]	0.92	(0.63-1.34)	1.29	(1.00–1.66)
ASD with ID	Crude	1.17	(0.78–1.77)	1.37	(1.03–1.82)
(n = 317)	Adj[2]	0.84	(0.53-1.32)	1.32	(0.98–1.79)
ASD without ID	Crude	1.07	(0.64–1.80)	1.41	(1.00–1.99)
(n = 191)	Adj[2]	1.07	(0.63-1.81)	1.32	(0.93–1.89)
DD	Crude	1.36	(0.99–1.85)	1.13	(0.90–1.42)
(n = 683)	Adj[2]	1.11	(0.80-1.54)	1.08	(0.85–1.36)

ASD, autism spectrum disorder; DD, other developmental, disorder; ID, intellectual disability (IQ   70); POP, population-based control group; IOM, institute of medicine, ACOG, American college of obstetricians and gynecologists

[1]Reference is "Met" recommendation of weight gain per initial BMI; ASD or DD compared to POP control group (n = 743). N's shown are for adjusted models.

[2]Adjusted for maternal age (<25, 25–29, 30–34 = ref,   35), education (HS or less, some college, college degree = ref, Masters or higher), race/ethnicity (Non-Hispanic White = ref; Non-Hispanic Black; Non-Hispanic Asian; multiple races, or other; Hispanic), parity (0 = ref,   1), and smoking (during pre-pregnancy or first trimester, throughout pregnancy, none = ref). N's shown are for adjusted models.